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# Muscle contraction patterns and their associations in the upper third of the face: a clinical and epidemiological study

Padrões de contração muscular e suas associações no terço superior da face: um estudo clínico e epidemiológico

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#### ABSTRACT

**Introduction:** The use of botulinum toxin has become one the essential cosmetic procedures performed in the world.

**Objective:** To identify patterns of muscle contraction of the forehead, glabellar complex, and orbicularis oculi muscle in patients from southern Brazil, establishing their epidemiology and possible associations between them.

**Methods:** One hundred and one patients who sought treatment with botulinum toxin for the forehead, glabella, and periocular lines between 2012 and 2016 were included. Analyzes were made using digital photographs taken during a medical consultation before applying the products., The subjects received different brands of botulinum toxin, according to the patients' or the doctors' preference.

**Results:** The most common contraction patterns were complete frontal, glabellar in converging arrows, and complete periocular. Women represented 94.1% of patients. Most patients were between 31 and 50 years old, with an average of 44.57 years. More frequent patterns in each area were more frequently associated.

**Conclusions:** The study shows the main muscle contraction patterns of the upper third of the face in 101 patients, as well as their clinical characteristics, comparing them with previously published articles. Studies on muscle contraction patterns can assist in the safer and more rational use of the products available, avoiding waste and complications.

Keywords: Muscle contraction; Skin aging; Face; Facial muscles; Botulinum toxins type A

#### RESUMO

**Introdução:** o uso da toxina botulínica tornou-se um dos procedimentos cosméticos mais importantes realizados no mundo.

**Objetivo:** identificar padrões de contração muscular da fronte, complexo glabelar e músculo orbicular dos olhos em pacientes do sul do Brasil, estabelecendo sua epidemiologia e possíveis associações entre eles.

**Métodos:** foram incluídos 101 pacientes que buscaram tratamento com toxina botulínica para fronte, glabela e linhas perioculares entre 2012 e 2016. Análises foram feitas por meio de fotografias digitais tiradas durante consulta médica, antes da aplicação dos produtos. Os pacientes foram tratados com diferentes marcas de toxina botulínica, de acordo com suas preferências ou com as do médico.

**Resultados:** os padrões de contração mais comuns foram frontal completo, glabelar em setas convergentes e periocular completo. Mulheres representaram 94,1% dos pacientes. A maioria tinha idade entre 31 e 50 anos, com média de 44,57 anos. Padrões mais frequentes em cada área individual foram mais frequentemente associados.

**Conclusões:** o estudo mostra os principais padrões de contração muscular do terço superior da face em 101 pacientes, bem como suas características clínicas, e os compara com artigos publicados anteriormente. Estudos sobre padrões de contração muscular podem auxiliar no uso mais seguro e racional dos produtos disponíveis, evitando desperdícios e complicações.

Palavras-chave: Contração muscular; Envelhecimento da pele; Face; Músculos faciais; Toxinas botulínicas tipo A

# **Original Article**

Autores:

Adma Silva de Lima<sup>1</sup> Marina Gubert<sup>2</sup> Thaise Lyra<sup>2</sup> Carolina Fissmer Sardagna<sup>2</sup>

- <sup>1</sup> Private Clinic, Dermatology, Brusque (SC), Brazil.
- <sup>2</sup> Universidade de Blumenau, Department of Medicine, Blumenau (SC), Brazil.

#### Correspondence:

Adma Silva de Lima contato@admalima.com.br / Alternative email: draadmalima@ gmail.com

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#### INTRODUCTION

Botulinum toxin (BT) for therapeutic and aesthetic purposes has constantly increased in recent decades. It has become one of the most critical aesthetic procedures performed in many countries. Obtained from Clostridium botulinum, a bacterium known to cause botulism, this toxin has seven subtypes, of which type A is the most potent.<sup>1–3</sup> BT acts by blocking the release of acetylcholine from the presynaptic terminal of the neuromuscular junction, preventing muscle contraction.<sup>3</sup>

Different authors have described population patterns of glabellar, periocular, and forehead contractions in recent years.<sup>4-7</sup> The description of these patterns contributed to a better understanding of the local anatomy, guiding the rational use of available products, avoiding complications resulting from inadequate applications or dosages, and, finally, optimizing the use in the indicated areas.

The primary objective of this study was to identify the contraction patterns of the forehead, glabellar complex, and orbicularis oculi muscle in a population of patients in southern Brazil. The secondary objectives were to assess possible associations between different contraction patterns and establish an epidemiological profile of this population.

#### MATERIALS AND METHODS

The contraction patterns of muscles located in the upper third of the face – including the frontal muscle, the glabellar region (corrugator supercilii, depressor supercilii, and procerus muscles), and the orbicularis oculi muscle – were evaluated in the present study. The classification patterns described by Trindade et al. for glabellar lines,<sup>4,5</sup> Braz et al. for the frontal muscle,<sup>6</sup> and Tamura et al.<sup>7</sup> for lateral periocular rhytids were applied (Figures 1–7).

Patients who sought medical evaluation to apply botulinum toxin between 2012-2016 for men and 2015-2016 for women were included. All analyzes were performed using digital photographs taken during the medical consultation before product application. Patients were treated with Botox<sup>®</sup> (Allergan,



FIGURE 1: Illustration of frontal contraction patterns



FIGURE 2: Illustration of periorbital contraction patterns



**FIGURE 3:** Illustration of glabelar contraction patterns: omega and inverted omega patterns



FIGURE 4: Illustration of glabellar contraction patterns - U, V and converging arrow patterns

Dublin, Ireland), Dysport<sup>®</sup> (Galderma, Lausanne, Switzerland) or Xeomin<sup>®</sup> (Merz, Frankfurt, Germany) according to their preferences or those of the physician. The same researcher evaluated all patients.

Data were organized into descriptive graphs containing absolute frequencies, relative frequencies, means, standard deviations (SD), and 95% confidence interval (CI) estimates. The independent chi-square test was used to associate the qualitative variables, while the proportion test was chosen to compare the independent proportions. In all cases, statistical significance was considered if p < 0.05.

Data analysis was performed using Microsoft Excel 2016 software and SPSS version 21 software. This study followed the ethical standards based on the Declaration of Helsinki 2000.

#### RESULTS

Tables 1 to 3 represent the univariate analysis of the characteristics assessed in absolute frequency, relative frequency, means, and standard deviations. They also present estimate proportions and the mean at 95% confidence intervals.

Men accounted for 5.9% of the studied patients, while women accounted for 94.1%. For men, the mean age was  $45.33 \pm 14.19$ , ranging between 26 and 69 years. Regarding women, the mean age was  $44.53 \pm 11.24$ , ranging between 28 and 73 years. The global mean age was 44.57 years, with a median of 43 years, a minimum of 26 years, and a maximum of 73 years.

Concerning the age group, most patients (63.24%) were between 31 and 50 years old, and 34.7% of subjects in this study were between 31 and 40 years.



FIGURE 5: Clinical illustrations of frontal contraction patterns. A - full pattern; B - medial pattern and **C** - lateral pattern



FIGURE 6: Clinical illustration of periocular contraction patterns. A - type 1 pattern, also known as full pattern; B - type 2 pattern, also called lower eyelid/upper cheeks pattern and C - type 3 pattern, representing only midlines



illustration of glabellar contraction patterns. A - U pattern; **B** - pattern V; **C** - omega pattern; **D** - inverted omega pattern; E- converging arrows pattern

means, standard deviations and estimates in the confidence intervals				
Characteristics	Ν	CI (95%)		
Gender				
Men	6 (5.9%)	(1.33 - 10.55)		
Women	95 (94.1%)	(89.45 - 98.67)		
Age (years)				
≤ <b>3</b> 0	8 (7.9%)	(2.65 - 13.19)		
31 a 40	35 (34.7%)	(25.37 - 43.93)		
41 to 50	29 (28.7%)	(19.89 - 37.54)		
51 to 60	18 (17.8%)	(10.36 - 25.29)		
> 60	11 (10.9%)	(4.82 - 16.97)		
	(Mean $\pm$ SD)	CI (95%)		
Age (years)	(44.57 ± 11.35)	$(43 \pm 8.5)$		

TABLE 1. Sociodemographic profile of patients with the distribution of absolute frequencies relative frequencies

I - CI: Confidence Interval with 95% confidence; SD: Standard Deviation

TABLE 2: Main measures described in age, years and according to gender						
Age (years)	n	Variation	Mean ± SD	VC	CD   I (95%)	(Mean ± QD)
Men	6	(26 - 69)	(45.33 ± 14.19)	31.30%	(30.44 - 60.22)	$(43 \pm 4.38)$
Women	95	(28 - 73)	(44.53 ± 11.24)	25.24%	(42.27 - 46.79)	$(43 \pm 9)$
Both	101	(26 - 73)	(44.57 ± 11.35)	25.46%	(42.36 - 46.79)	(43 ± 8.5)

I - SD: Standard Deviation; QD: Quartile Deviation; CI: Confidence Interval for mean

According to the Fitzpatrick skin phototype scale, 66.3% of patients were skin phototype III, followed by skin phototype II (21.8%), skin phototype IV (8.9%), and skin phototype I (3%). No patients were skin phototypes V and VI.

We assessed frontal muscle contraction patterns in 100 patients. The complete pattern was the most common, in 62.4% of cases, followed by medial in 14.9%, asymmetric in 13.9%, and lateral in 7.9% of cases.

The glabellar contraction patterns were evaluated in 95 patients. The most frequent was the converging arrow pattern, found in 31.7% of cases, followed by the U pattern in 28.71% of cases. The omega pattern corresponded to 18.8% of the cases, the V pattern to 9.9%, and the inverted omega to 3% of cases. Two patients were considered atypical.

The complete pattern was the most common in the periocular region, present in 62.4% of cases, followed by the medial and lower/upper eyelids patterns, 11.9% of each case. The asymmetric pattern was found in 5.9% of patients.

The most frequently found contraction patterns in both genders were the complete frontal, glabellar in converging arrows, and complete periocular patterns. However, it was not possible to use the chi-square test to assess associations between contraction patterns and gender because more than 25% of the expected frequencies were below 5.

Table 4 depicts these data. Tables 5 to 7 show the associations between the different facial areas and their corresponding muscle contraction patterns.

When associating the patterns of the frontal and periocular regions, the complete frontal pattern and the complete periocular pattern occurred in 41 patients (40.59%). According to the proportion test, this association was statistically significant, with p<0.05.

Comparing the frequencies between the periocular and glabellar patterns, the glabellar converging arrows pattern and the periocular complete pattern were present in 21 patients (20.79%), the glabellar and the periocular complete U pattern occurred in 19 patients (18.81%), and the glabellar omega and the periocular complete patterns were observed in 10 patients (9.9%). According to the proportion test, the glabellar omega, converging arrows, and U patterns were associated with the periocular complete, with p < 0.05.

Regarding the associations between the glabellar and frontal patterns, the omega pattern, with 15 patients (14.85%), converging arrows, with 16 patients (15.84%), and U pattern,

frequencies and	estimates in confidence intervals	
Variables	Ν	CI (95%)
Phototype		
I	3 (3%)	(0 - 6.28)
п	22 (21.8%)	(13.73 - 29.83)
III	67 (66.3%)	(57.12 - 75.55)
IV	9 (8.9%)	(3.35 - 14.47)
Frontal		
Medial	15 (14.9%)	(7.92 - 21.79)
Lateral	8 (7.9%)	(2.65 - 13.19)
Complete	63 (62.4%)	(52.93 - 71.82)
Asymmetric	14 (13.9%)	(7.12 - 20.6)
Not reported	1 (1%)	(0 - 2.92)
Glabellar		
Pattern U	29 (28.71%)	(19.89 - 37.54)
Pattern V	10 (9.9%)	(4.08 - 15.73)
Converging arrows	32 (31.7%)	(22.61 - 40.76)
Omega	19 (18.8%)	(11.19 - 26.43)
Inverted omega	3 (3%)	(0 - 6.28)
Atypical	2 (1.98%)	(0 - 4.7)
Not reported	6 (5.9%)	(1.33 - 10.55)
Periocular		
Medial	12 (11.9%)	(5.57 - 18.19)
Absence	1 (1%)	(0 - 2.92)
Complete	63 (62.4%)	(52.93 - 71.82)
Asymmetric	6 (5.9%)	(1.33 - 10.55)
Lower eyelids/upper cheeks	12 (11.9%)	(5.57 - 18.19)
Not reported	7 (6.9%)	(1.98 - 11.88)

TABLE 3: Analysis of specific variations (contraction patterns) of patients distributed in absolute frequencies, relative
frequencies and estimates in confidence intervals

I - CI: Confidence Interval with 95% confidence; SD: Standard Deviation

with 18 patients (17.82%), were associated with the complete frontal pattern according to the proportion test, with p < 0.05.

Considering the age group, patients between 31 and 50 years more commonly presented complete muscle contraction patterns in the frontal muscle, converging arrows and U patterns in the glabella, and the complete pattern in the periocular region.

#### DISCUSSION

Although the aesthetic use of botulinum toxin started more than 30 years ago, only recently the assessment of muscle contraction patterns in the upper third of the face has been standardized. Previously, the application patterns varied from the use of pre-established injection points to the application based on the muscular contraction of each patient, empirically. Although a standardized approach may be helpful, or even necessary, for purposes of comparative studies, the use of preset injection points may not be suitable for all cases, as a treatment with preset injection points can generate irregular results, with an artificial appearance, or even maintain areas of muscle contraction, not reaching the desired goal with the treatment. Today, the focus of cosmiatrics is to achieve a face that looks beautiful but as natural as possible. Thus, the more individualized a therapy, the better the results obtained.

Regarding the clinical profile of the patients, women predominantly comprised the study. The most common skin phototype was III. The prevalent age group was between 30 and

	Gender	0 00	
Patterns	Women $(n = 95)$	Men (n = 6)	Р
Frontal			
Complete	59 (62.1%)	4 (66.7%)	-
Medial	15 (15.8%)	0 (0%)	
Asymmetric	12 (12.6%)	2 (33.3%)	
Lateral	8 (8.4%)	0 (0%)	
Not reported	1 (1.1%)	0 (0%)	
Glabellar			
Converging arrows	29 (30.5%)	3 (50%)	-
Pattern U	28 (29.5%)	1 (16.7%)	
Omega	19 (20%)	0 (0%)	
Pattern V	10 (10.5%)	0 (0%)	
Inverted omega	3 (3.2%)	0 (0%)	
Atypical	2 (2.2%)	0 (0%)	
Not reported	4 (4.2%)	2 (33.3%)	
Periocular			
Complete	59 (62.1%)	4 (66.7%)	-
Medial	12 (12.6%)	0 (0%)	
Lower eyelids/ upper cheeks	12 (12.6%)	0 (0%)	
Asymmetric	6 (6.3%)	0 (0%)	
Absence	0 (0%)	1 (16.7%)	
Not reported	6 (6.3%)	1 (16.7%)	

#### TABLE 4: The association of contraction patterns regarding gender

I - P: p-value of the chi-square test (non-parametric). If p<0.05, then the association is significant. Note: In the frontal, glabellar and periocular patterns, it was not possible to perform the chi-square test, as more than 25% of the estimated frequencies were below 5.

50, with an overall mean age of 44.57 years, similar to comparative studies.  $^{\rm 5}$ 

The muscles of the glabella region – corrugator supercilii, depressor supercilii, and procerus – generate the lowering of the eyebrow when they are contracted. In this action, the medial fibers of the orbicularis oculi muscle also participate. Paralysis of these muscles leads to reduction or erasure of the vertical and horizontal lines in the glabella.<sup>1–3</sup>

The frontal muscle is the only one responsible for raising the eyebrow. Generally, several injection points are needed for proper treatment. In patients with a complete contraction pattern, the muscle should be treated in multiple areas on the forehead. In contrast, patients with a medial or lateral contraction pattern may need focal treatment in regions with greater hyperkinesia to avoid eyebrow ptosis. In addition, the medial fibers are generally more robust and therefore require larger doses of the product.<sup>3</sup> Correct treatment of the glabellar and frontal muscles is essential to maintain the correct position of the eyebrow.

The orbicularis oculi muscle is a sphincter whose function is to occlude the eye. While the contraction of the medial portion helps while lowering the evebrow, the lateral portion, when contracted, leads to periocular rhytids. In the present article, patients were classified according to the patterns of rhytids they presented when asked to smile and categorized according to a classification system developed by Thamura et al.7 However, other authors also studied periocular lines and found slightly different results. Kane<sup>8</sup> standardized a classification for periocular wrinkles in Caucasian women in a study conducted in 2003. He described four main patterns: periocular complete pattern, lower eyelid/upper cheeks, upper eyelid pattern, and central or lateral corner of the eye pattern. Patients were evaluated through smiling and squinting. In the present study, the rhytids pattern was observed by asking the patient to smile. It is probably why the upper eyelid pattern was not observed in the present study.

The most common contraction patterns in both sexes were the complete frontal, glabellar converging arrows, and

	TABLE 5: The association between the frontal and periocular contraction pattern						
Periocular							
Frontal	Not reported	Asymmetric	Absence	Complete	Lower eyelids/ upper cheeks	Medial	Total
Not reported	0 (0%)	0 (0%)	0 (0%)	1 (0.99%)	0 (0%)	0 (0%)	1 (0.99%)
Asymmetric	1 (0.99%)	1 (0.99%)	1 (0.99%)	9 (8.91%)	0 (0%)	2 (1.98%)	14 (13.86%)
Complete	3 (2.97%)	3 (2.97%)	0 (0%)	41 (40.59%)	7 (6.93%)	9 (8.91%)	63 (62.38%)
Lateral	1 (0.99%)	0 (0%)	0 (0%)	4 (3.96%)	2 (1.98%)	1 (0.99%)	8 (7.92%)
Medial	2 (1.98%)	2 (1.98%)	0 (0%)	8 (7.92%)	3 (2.97%)	0 (0%)	15 (14.85%)
Total	7 (6.93%)	6 (5.94%)	1 (0.99%)	63 (62.38%)	12 (11.88%)	12 (11.88%)	101 (100%)

#### TABLE 6: Association between the glabellar and periocular contraction pattern

Periocular							
Glabellar	Not reported	Asymmetric	Absence	Complete	Lower eyelids/up- per cheeks	Medial	Total
Not reported	1 (0.99%)	0 (0%)	0 (0%)	4 (3.96%)	0 (0%)	1 (0.99%)	6 (5.94%)
Atypical	0 (0%)	0 (0%)	0 (0%)	1 (0.99%)	0 (0%)	1 (0.99%)	3 (2.97%)
Omega	1 (0.99%)	1 (0.99%)	0 (0%)	10 (9.9%)	4 (3.96%)	3 (2.97%)	19 (18.81%)
Inverted omega	0 (0%)	0 (0%)	0 (0%)	2 (1.98%)	0 (0%)	1 (0.99%)	3 (2.97%)
Converging arrows	4 (3.96%)	2 (1.98%)	1 (0.99%)	21 (20.79%)	2 (1.98%)	2 (1.98%)	32 (31.68%)
Pattern U	1 (0.99%)	3 (2.97%)	0 (0%)	19 (18.81%)	3 (2.97%)	3 (2.97%)	29 (28.71%)
Pattern V	0 (0%)	0 (0%)	0 (0%)	6 (5.94%)	3 (2.97%)	1 (0.99%)	10 (9.9%)

#### Table 7: The association between the frontal and glabellar contraction pattern

Glabellar						
Frontal	Not reported	Asymmetric	Complete	Lateral	Medial	Total
Not reported	1 (0.99%)	3 (2.97%)	2 (1.98%)	0 (0%)	0 (0%)	6 (5.94%)
Atypical	0 (0%)	0 (0%)	1 (0.99%)	1 (0.99%)	0 (0%)	3 (2.97%)
Omega	0 (0%)	2 (1.98%)	15 (14.85%)	0 (0%)	2 (1.98%)	19 (18.81%)
Inverted omega	0 (0%)	0 (0%)	3 (2.97%)	0 (0%)	0 (0%)	3 (2.97%)
Converging arrows	0 (0%)	6 (5.94%)	16 (15.84%)	5 (4.95%)	5 (4.95%)	32 (31.68%)
Pattern U	0 (0%)	2 (1.98%)	18 (17.82%)	1 (0.99%)	8 (7.92%)	29 (28.71%)
Pattern V	0 (0%)	1 (0.99%)	8 (7.92%)	1 (0.99%)	0 (0%)	10 (9.9%)
Total	1 (0.99%)	14 (13.86%)	63 (62.38%)	8 (7.92%)	15 (14.85%)	101 (100%)

periocular complete patterns. These data corroborate previous studies published by Braz et al. for frontal muscle contraction, and by Tamura et al. Regarding the lateral portion of the orbicularis oculi muscle contraction, in the glabellar complex, the converging arrows patterns were the most commonly found in this group, followed by the U and omega patterns. In previous studies published by Trindade et al., the V and U patterns were more frequently followed by the convergent arrow pattern. A study in the Chinese population, conducted by Jiang et al.,<sup>9</sup> with more than 400 patients, focused on glabellar contraction patterns and found a classification compatible with the Chinese population, also reporting the converging arrows pattern as the most common.

Despite being studied and classified separately, the glabella, forehead, and periocular region muscles have interrelated fibers, and muscle contraction can influence the borderline muscles contraction to a greater or lesser extent.<sup>7</sup>

For example, the fibers of the orbital part of the orbicularis oculi muscle communicate with the fibers of the frontal muscle.<sup>7</sup> It is not uncommon to ask patients to close their eyes tightly so that we can observe not only the orbicularis oculi muscle contraction, but to a greater or lesser degree, depending on the patient, the involuntary contraction of other muscle fibers located in the forehead, glabella, and even the nasal muscles. These data support the need to treat the entire upper third of the face in a single session, aiming at better results when compared to the treatment of isolated muscle groups. It is because interconnected muscle fibers that have not been appropriately addressed can lead to maintenance of muscle contraction in a specific area, resulting in the persistence of rhytids during movement.

Due to the interposition of muscle fibers and considering the influence of borderline fibers contraction, in this study, we assessed the associations between the different patterns of muscle contraction to verify their relationships and frequency. According to the proportion test, there was a statistically significant association between the periocular complete and frontal complete patterns; between the omega, converging arrows, U patterns for the periocular complete pattern; and the omega, converging arrows, and U patterns for the frontal complete pattern. This study confirmed that the most common patterns were associated with higher frequency. Gender differences can also affect muscle strength. Due to this factor, it is common for men to have greater difficulty and resistance to treating muscles with botulinum toxin when compared to women. However, in the present study, due to the low number of male patients in the studied population, the correlation of contraction patterns and gender was not feasible.

Regarding the age group, patients between 31 and 50 years of age most commonly showed the complete muscle contraction pattern in the frontal muscle, the converging arrows and U-shaped patterns in the glabella area, and the complete pattern in the periocular region. Therefore, these were the patterns most frequently found in the age group that most sought this treatment.

Aesthetic treatments can improve the appearance and cosmetics and contribute to an increase in quality of life, as previously shown. It is, therefore, of paramount importance to understand the kinetics of the muscles involved in the formation of wrinkles to improve care and achieve the best results in patient treatment.<sup>10</sup>

The limitations of this study are its retrospective nature, the fact that it is based on clinical photography, and the low number of men studied. The small number of male patients can be observed in other comparative studies,<sup>5-7</sup> because, as mentioned above, men tend to seek treatment with botulinum toxin less often than women. Prospective studies in different global populations are needed to better understand these muscle contraction patterns.

#### CONCLUSION

The present study shows the main muscle contraction patterns in the upper third of the face in a population of patients in southern Brazil and their clinical characteristics. It compares them to other Brazilian and worldwide studies. It also shows current associations between contractions types in different muscle groups and discusses their likely causes. The study of the contraction pattern aims to provide more accurate and safe treatments, in addition to the rational product use in the most indicated areas and with stronger muscle contraction.

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#### **AUTHORS' CONTRIBUTION:**

Adma Silva de Lima DORCID 0000-0001-9240-4464 Statistical analysis; approval of the final version of the manuscript; study design and planning; active participation in research orientation.

**Marina Gubert** D ORCID 0000-0002-9293-5019 Preparation and writing of the manuscript.

**Thaise Lyra D** ORCID 0000-0002-7125-9576 Preparation and writing of the manuscript.

**Carolina Fissmer Sardagna** D ORCID 0000-0002-2394-494X Preparation and writing of the manuscript.

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# Risk factors correlated with frontal fibrosing alopecia in Criciuma, Santa Catarina: a case-control study

Fatores de risco correlacionados à alopecia frontal fibrosante em Criciúma, Santa Catarina: estudo caso-controle

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#### ABSTRACT

**Introduction:** Fibrosing Frontal Alopecia (FFA) is a form of scarring alopecia, in which patients have an irreversible loss of hair follicles, especially in the frontal and temporoparietal regions. The etiopathogenesis is not fully understood, although hypotheses about genetic, hormonal, and behavioral factors, such as the use of sunscreen and facial moisturizers, have already been described.

**Methods:** A case-control study was conducted using an objective questionnaire with 33 questions. Sixty women were evaluated, 30 diagnosed with FFA, and 30 not affected by the disease.

**Results:** The mean age of the sample was 64 years old. 76.7% of patients with FFA and 23.3% of controls used facial sunscreen and the difference was statistically significant (p<0.001). Also, the use of facial moisturizer was significantly higher in patients with alopecia (63.3%) when compared to controls (33.3%; p=0.038). The frequency of use of regular soap on the face was significantly lower in patients with FFA (46.7%) when compared to the control group (83.3%; p=0.006).

**Conclusion:** Results suggest a possible association between FFA and the use of facial products, such as sunscreen and moisturizer, in this population. All patients were menopausal, reinforcing the hormonal relationship with the disease.

Keywords: Alopecia; Contraceptives oral combined; Finasteride; Menopause; Tamoxifen

#### RESUMO

**Introdução:** A alopecia frontal fibrosante (AFF) é uma forma de alopecia cicatricial, em que os pacientes apresentam perda irreversível dos folículos pilosos, principalmente em região frontal e tempoparietal. Sua etiopatogenia não está totalmente elucidada, embora hipóteses sobre fatores genéticos, hormonais e comportamentais, como o uso de filtro solar e hidratante facial, já tenham sido descritas.

**Métodos:** estudo de caso-controle, realizado com aplicação de um questionário objetivo com 33 perguntas. Foram avaliadas 60 pacientes do sexo feminino, 30 diagnosticadas com AFF e 30 não acometidas pela doença.

**Resultados:** a média de idade da amostra foi de 64 anos ( $\pm$  10,37 para casos e  $\pm$  9,40 para os controles). 76,7% das pacientes com AFF e 23,3% dos controles faziam uso de filtro solar, sendo a diferença estatisticamente significativa (p<0,001). Além disso, o uso de hidratante facial mostrou-se significativamente maior nas pacientes com alopecia (63,3%) quando comparadas aos controles (33,3%; p=0,038). Notou-se a frequência de uso de sabonete comum na face significativamente menor nas pacientes com AFF (46,7%), quando comparada ao grupo controle (83,3%; p=0,006).

**Conclusão:** nossos resultados sugerem uma possível associação entre AFF e uso de produtos faciais, como filtro solar e hidratante. Todas as pacientes eram menopausadas, reforçando a relação hormonal com a doença. **Palavras-chave:** Alopecia; Anticoncepcionais; Finasterida; Menopausa; Tamoxifeno

### **Original Article**

Authors:

Lara Xavier Bazotti<sup>1</sup> Leticia Maoletti Teixeira<sup>1</sup> Ana Paula Naspolini<sup>1</sup>

<sup>1</sup> Universidade do Extremo Sul Catarinense, Medical School, Criciúma (SC), Brazil

**Correspondence:** Lara Xavier Bazotti Email:larabazotti@gmail.com

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#### INTRODUCTION

The term cicatricial alopecia represents a group of diseases characterized by replacing the follicular structure with fibrous tissue.<sup>1,2</sup> Frontal Fibrosing Alopecia (FFA) is a scarring, marginal, and symmetrical alopecia along the frontal hair implantation line. First described by Axel Munthe in 1929,3 FFA may have been sporadic and ignored for more than six decades, until 1994, when Kossard published a series of cases with six women affected by the disease.<sup>4</sup> In this report, the patients were Caucasian and menopausal, with a recess in frontal hair implantation line, associated with perifollicular erythema and complete reduction or loss of eyebrows. Since its discovery, there has been an increase in its incidence worldwide. There is even evidence suggesting that FFA is an evolving epidemic.5 However, it's not known for sure whether this increase in the number of cases is due to better recognition of the disease by dermatologists or if there has been an increase in its incidence, since FFA has also been diagnosed in women in the pre-menopause and, more rarely, in men.6

The etiopathogenesis of FFA is not fully understood, although several hypotheses have been proposed. Among them, the genetic factor is relevant since there are cases in siblings and members of the same family,7 suggesting an autosomal dominant inheritance with incomplete dominance.8 The recent identification of genomic loci strongly associated with lichenoid inflammation and FFA reinforces this idea. The locus of most significant susceptibility appears to be 6p21, located in the HLA region. According to the literature, the risk of developing FFA seems to increase five times with the HLA-B class 07: 029 allele implantation.9 Still, a possible hormonal mechanism has already been raised due to its predominance in postmenopausal women or those using antiandrogenic therapy.<sup>10,11</sup> The gamma peroxisome proliferator-activated receptor (PPAR-y) has intense antifibrotic activity, and its decline may correlate with the FFA fibrogenic inflammatory process. The triggering factors that lead to PPAR-y deficiency and consequent inflammation are still unknown.9 The environmental component can participate as an etiopathogenic factor in the disease, mainly due to the late appearance of symptoms in most cases.<sup>12</sup> Environmental exposure through cosmetic habits using facial moisturizers, face foundation, sunscreens, and hair dyes contains components such as nanoparticles of titanium dioxide, which has also been suggested to favor the development of FFA.13

The diagnosis of FFA can be clinical, guided by trichoscopy findings, such as perifollicular erythema and follicular hyperkeratosis, even before the final and permanent phase of evolution, with scarring alopecia.<sup>14</sup> Histopathological evaluation is necessary in the early stages or cases of diagnostic doubt.<sup>15</sup>

FFA is a chronic condition that requires long-term treatment. Currently, there is no consensus on effective treatments.<sup>16</sup> It is constantly associated with decreased quality of life mainly due to symptoms such as itching and scalp sensitivity, unsightly discomfort, and frustration about the inability to control the course of the disease.<sup>17</sup> Given the importance of this clinical condition, a welldesigned study that evaluates risk factors in patients diagnosed with FFA may help to clarify the characteristics predominantly involved in this pathology in our population. Therefore, this study aims to assess the factors correlated with FFA in patients assisted in private dermatological clinics in the municipality of Criciúma – SC, from July 2019 to April 2020.

#### **METHODS**

The Research and Human Ethics Committee (3,938,659) of the Universidade do Extremo Sul Catarinense (UNESC) approved this study. After studying the agreement and signing the Free and Informed Consent Term, the patients agreed to participate, with their privacy and identification respected.

The present study was a case-control study conducted in 17 private dermatological clinics in the city of Criciúma, Santa Catarina, Brazil.

Sixty women living in the city of Criciuma (SC) were evaluated from July 2019 to April 2020. Thirty patients with clinical or histopathological diagnosis of FFA and thirty not affected by the disease were included in the control group after assessment by experienced dermatologists and pathologists. The inclusion criteria considered age over 18 years, follow-up by a dermatologist, FFA diagnosis in the case group, and not having alopecia in the control group. Patients undergoing chemotherapy, with questionnaires incorrectly filled out, and with pathologies that could present similar clinical symptoms (tinea capitis, seborrheic dermatitis, telogen effluvium, alopecia areata, other cicatricial alopecia, rosacea) were excluded from the study.

#### **Collection instrument**

The research data were collected based on the application of an objective questionnaire composed of 33 questions, developed by the researchers and applied by the attending dermatologist.

The questionnaire was divided into two parts: the first part, directed to the specialist doctor, comprised questions on autoimmune diseases and skin allergies; and the second part, aimed at the patients, included queries to assess sociodemographic and behavioral parameters. The common questions for both groups addressed the frequency of the current use of sunscreen, face foundation, facial moisturizer, anti-residue shampoo, common soap on the face, as well as previous chemotherapy treatment, smoking, vegetarian or high-sugar diet, hair straightening or hair dye.

The hormonal history was evaluated by the presence of menopause, previous hysterectomy, use of tamoxifen, intrauterine device (IUD), or combined oral contraceptive pill (COCP). Regarding FFA, previous symptoms (burning, sensitivity, pruritus), treatments in use and perception of response to them, time between the onset of symptoms and diagnosis and quality of life (whether the patient considers or not to have been affected by the disease).

#### **Statistical analysis**

The data collected were analyzed using the software IBM Statistical Package for the Social Sciences (SPSS) version 21.0. Quantitative variables were expressed using the mean and standard deviation. Qualitative variables were expressed through frequency and percentage.

Statistical tests were performed with a significance level of  $\alpha = 0.05$  and 95% confidence. The distribution of data regarding normality was assessed using the Shapiro-Wilk test.

The comparison of the mean of the quantitative variables between the categories of the dichotomous qualitative variables was performed using the Mann-Whitney U test. The investigation of the existence of an association between qualitative variables was conducted by applying Fisher's exact test and Pearson's-chi-square test, followed by residue analysis when statistical significance was observed. The measure of the association strength used was the Odds Ratio (OR), obtained through binary logistic regression.

#### RESULTS

The total sample comprised 60 women, distributed in 30 cases and 30 controls. Table 1 shows the demographic data.

There was no statistical difference in the assessment of autoimmune diseases, such as hypothyroidism, systemic lupus erythematosus, and scleroderma (p = 0.299; p = 0.492, and p = 0.999 respectively – Table 2). No statistically significant difference was found regarding the presence of allergies, such as contact dermatitis or drug allergies (p = 0.112 and p = 0.999, respectively – Table 2).

According to the evolution of symptoms related to FFA, 66.7% of cases reported their presence, with the most common symptom being pruritus (53.3%), followed by sensitivity (23.3%), and burning (20%). When asked about treatment, 53.3% reported improvement with treatment, 13.3% without improvement, and 33.3% without treatment at the time of assessment. The onset of clinical manifestations until diagnosis occurred between 1 to 5 years in 50% of cases, 6 months to 1 year in 20%, more than 5 years in 16.7%, and less than 6 months in 13.3 %. Still, 53.3% reported changes in quality of life due to FFA (Table 3).

Regarding the use of topical facial products, there was no significant difference between the groups when assessing the current use of facial cosmetics, including the use of sunscreen, facial moisturizer, face foundation (makeup), regular soap on the face or anti-residue shampoo (p = 0.353; p = 0.532; p = 0.602; p = 0.605, and p = 0.254, respectively – Table 4).

When asked about the previous use of the same substances, patients with FFA showed greater use of sunscreen (76.7%) when compared to the control group (23.3%). This difference is statistically significant (p < 0.001 - Table 5). Also, 78.3% of patients with FFA used the product daily. Besides, the use of facial moisturizer also proved to be more present in patients with alopecia (63.3%) when compared to the control group (33.3%), with a statistically significant difference (p = 0.020- Table 5). Also, daily use was more frequent (84.2%) among patients with FFA. On the other hand, when analyzing the use of common soap on the face, a significantly lower use was observed in patients with FFA (46.7%) when compared to the control group

TABLE 1: Demographic data of the sample (n=60)						
Group, Mean ± SD, n (%)						
	FFA*	Control	D Value **			
	n=30	n=30	P value^^			
Age	64.47 ± 10.37	$64.20 \pm 9.40$	0.994			
Race						
White	30 (100.0)	30 (100.0)	-			
Education						
Illiterate	0 (0.0)	1 (3.3)	-			
Fundamental, incomplete	5 (16.7)	8 (26.7)	-			
Fundamental, complete	7 (23.3)	5 (16.7)	-			
Junior High, incomplete	2 (6.7)	1 (3.3)	-			
High school, complete	8 (26.7)	5 (16.7)	-			
College, incomplete	2 (6.7)	2 (6.7)	-			
College, complete	6 (20.0)	1 (3.3)	-			

\*\* Value obtained after applying of Mann-Whitney U test Source: Research data, 2020

\*Patients with frontal fibrosing alopecia

TABLE 2: Progressive medical history of the sample (n=60)							
	Group, n (%)						
	FFA*	Control	DValue ***				
	n=30	n=30	P Value and				
Autoimmune							
Yes	10 (33.3)	4 (13.3)	0.067****				
No	20 (66.7)	26 (86.7)					
Autoimmune diseases							
<u>Hypothyroidism</u>	7 (23.3)	3 (10.0)	0.299****				
SLE**	2 (6.7)	0 (0.0)	0.492****				
SLE** and scleroderma	0 (0.0)	1 (3.3)	0.999****				
Allergy							
Yes	3 (10.0)	8 (26.7)	0.181****				
No	27 (90.0)	22 (73.3)					
Types of allergy							
Contact dermatitis	0 (0.0)	4 (13.3)	0.112****				
Food	1 (3.3)	0 (0.0)	0.999****				
Hydroxychroquine	1 (3.3)	0 (0.0)	0.999****				
Perfume	0 (0.0)	1 (3.3)	0.999****				
Rubber	0 (0.0)	1 (3.3)	0.999****				
Perfume e plastic	1 (3.3)	0 (0.0)	0.999****				
Under investigation	0 (0.0)	2 (6.7)	0.492****				

\*Patients with frontal fibrosing alopecia

\*\*Systemic lupus erythematosus

(83.3%; p = 0.003) – it was again the daily use of the most frequent product (92%). Finally, using an anti-residue shampoo and face foundation in the past has not shown a statistically significant difference between groups (Table 5).

Table 6 shows the assessment of chemotherapy or tamoxifen use, vegetarian or high-sugar diet, straightening or dyeing the hair, as well as IUD or COCP use, smoking, menopause, and hysterectomy. None of the factors analyzed showed any difference in statistics when comparing the two groups.

About the topical treatments used, 30% of patients with FFA used minoxidil, 26.7% used corticosteroids, and 20% used tacrolimus. Finally, as systemic therapy, 20% of patients received hydroxychloroquine and 6.7%, finasteride (Table 7).

#### DISCUSSION

The sample with FFA in the present study obtained, in its entirety, caucasian patients, probably because the southern region of the country has a higher prevalence of this population. According to IBGE,<sup>18</sup> in 2010, about 84% of Santa Catarina's citizens declared themselves white – the largest number in the country. However, it is known that FFA is found in all populations. A clinical review of 20 black patients in South Africa reinforced the scarcity of information on the epidemiology of FFA in this population and the difficulty in establishing a correct differential diagnosis between FFA and traction alopecia.<sup>19</sup>

Regarding age and gender, all study participants are women, with a mean age of 64 years ( $\pm$  10.37 for cases and  $\pm$  9.40 for controls), 90% of them menopausal. In a cross-sectional study of 60 cases, the average age of participants at the presentation of FFA was 64 years.<sup>20</sup> It is suggested that estrogens play an essential role in regulating the capillary cycle, producing a decrease in the growth of the hair strand, thus leading to the induction of the catagen phase prematurely and maintenance of the telogen phase.<sup>21</sup> Thus, the estrogen decrease in menopause can alter the control of the capillary cycle and, in a way, predispose to the development of FFA. The post-menopausal women predominance in FFA, together with the reported efficacy of 5-alpha-reductase inhibitors in disease management, led to several theories about the role of sex hormones in the disease pathogenesis.<sup>16</sup>

In the analysis of the previous hysterectomy, we observed

# TABLE 3: Assessment of symptoms related to frontal fibrosing alopecia (n=30)

	n (%) n=30
Symptoms	
Presence	20 (66,7)
Pruritus	16 (53.3)
Burning	6 (20.0)
Sensibility	7 (23.3)
Scaling	1 (3.3)
Rough skin and pustular lesions	1 (3.3)
Treatment	
Treatment with result*	16 (53.3)
Treatment with no result*	4 (13.3)
No treatment	10 (33.3)
Time between the onset of	
symptoms and diagnosis	
< 6 months	4 (13.3)
6 months - 1 year	6 (20.0)
1 year - 5 years	15 (50.0)
< 5 years	5 (16.7)
Changes in quality of life due to FFA	16 (53.3)

Source: Research data, 2020

\*Result of treatment based on subjective patient analysis

that a considerable number of women underwent the procedure, a finding also described by other authors,<sup>22</sup> where 55 of the 139 patients analyzed reported the previous hysterectomy. Still, there was a sudden decrease in serum estrogen levels in patients undergoing surgical menopause on the hormonal relationship.<sup>22</sup> Although more research is needed on hormonal pathogenesis, it is believed that its imbalance may be the trigger for the FFA inflammatory scar reaction in predisposed patients.<sup>13</sup>

In the present study, we found hypothyroidism in 23.3% and autoimmune diseases in 30% of patients with FFA, similar to the frequency observed in other studies.<sup>20</sup> A systematic review of the literature showed that about 34.4% of the cohort of 1083 patients shared the polyautoimmunity phenomenon.<sup>23</sup> This can be explained by the fact that genetic and environmental factors are similar among autoimmune diseases, which could lead to the development of concomitant autoimmune disorders.<sup>23,24</sup>

Regarding the quality of life, although questionnaires applied and validated are not used to evaluate the same, 53.3% of patients reported changes in quality of life by FFA. As mentioned by other authors,<sup>25,26</sup> alopecia negatively affects the quality of life.

It has been shown that older patients with FFA may be more likely to experience anxiety or depression, and patients with severe alopecia may feel powerless over the disease control.<sup>17</sup>

In the analysis between the clinic onset and diagnosis, 50% of patients reported that it occurred between 1 year and 5 years. Previous studies have found an average presentation time of 3.4 to 5.3 years.<sup>10,20</sup> Eyebrow and eyelash loss may be the first sign of presentation of FFA.<sup>20,27,28</sup> Although the frontal hair implantation line is more commonly affected, body hair may also be involved.<sup>2</sup> The loss of body hair is usually confused or related to age and hardly reported by the patients themselves<sup>28,29,30,</sup> resulting in a delay in seeking medical care and, consequently, in treatment.

About the previous or current treatments for AFF, topical minoxidil, topical corticoid, tacrolimus ointment, hydroxychloroquine, and 5-alpha-reductase inhibitors were the most used by the participants. The literature brings all of these treatments as therapeutic options, but there is no curative treatment, and the lack of randomized clinical trials does not allow definitive conclusions about the most effective treatment.<sup>15</sup>

The analysis of the present study showed that women with FFA made more use of facial sunscreen than controls (Figure 1), a result similar to that demonstrated in a case-control study assessing 664 women and 106 British men.<sup>12</sup> Regarding the sunscreen component, titanium dioxide nanoparticles have already been detected in the hair strand of a patient with FFA. This result was confirmed by another recent study,<sup>28</sup> which also detected titanium dioxide in the hair from 16 of 20 FFA patients. Therefore, it is suspected that this molecule is involved in the pathogenesis of FFA. Because it is present in many of the sunscreens of routine use, it makes them a significant risk factor.<sup>31,32</sup> On the other hand, some authors recognize that sunscreens cannot explain some FFA aspects.<sup>31,21</sup> The fact that individuals in the general population use products with sunscreen and do not develop FFA, as well as patients with FFA do not use sunscreen regularly, and also the occipital involvement of FFA, where sunscreens would not normally be applied. A Brazilian case-control study with 902 participants found low adherence to the use of facial sunscreen in patients diagnosed with FFA, with no association with long-term use.33 Therefore, a true causal relationship between sunscreens and FFA cannot be concluded at this time.

Although the use of sunscreens by patients with FFA has not come close to universality, it is essential to note that many facial moisturizers are related to chemicals for sun protection.<sup>31</sup> In the analysis of the present study, the frequency of isolated use of a facial moisturizer in the past was higher in patients with alopecia when compared to the control group (Figure 1). Similar values have been reported in the previously mentioned literature.<sup>10</sup> Data like this corroborate an idea that facial products seem to be related to FFA.

It is worth mentioning that the greater use of these facial cosmetics (sunscreen and facial moisturizer) by patients with alopecia was not demonstrated when asked about the current

TABLE 4: Current use of topical products (n=60)				
	Group,	n (%)		
	FFA*	Control	D 37-1	
	n=30	n=30	P value	
Facial sunscreen				
Yes	29 (96.7)	26 (89.7)	0.353**	
Daily	26 (89.7)	20 (76.9)		
3 times a week	3 (10.3)	3 (11.5)		
At least once a week	0 (0.0)	3 (11.5)		
No	1 (3.3)	4 (13.3)		
Facial moisturizer				
Yes	25 (83.3)	22 (73.3)	0.532**	
Daily	22 (88.0)	20 (90.9)		
3 times a week	0 (0.0)	1 (4.5)		
At least once a week	3 (12.0)	1 (4.5)		
No	5 (16.7)	8 (26.7)		
Facial foundation				
Yes	12 (40.0)	14 (46.7)	0.602***	
Daily	7 (58.3)	6 (42.9)		
3 times a week	2 (16.7)	1 (7.1)		
At least once a week	3 (25.0)	7 (50.0)		
No	18 (60.0)	16 (53.3)		
Regular soap on the face				
Yes	15 (50.0)	17 (56.7)	0.605***	
Daily	15 (100.0)	16 (94.1)		
3 times a week	0 (0.0)	1 (5.9)		
At least once a week	0 (0.0)	0 (0.0)		
No	15 (50.0)	13 (43.3)		
Anti-residue shampoo				
Yes	6 (20.0)	2 (6.7)	0.254**	
Daily	1 (16.7)	0 (0.0)		
3 times a week	1 (16.7)	1 (50.0)		
At least once a week	4 (66.7)	1 (50.0)		
No	24 (80.0)	28 (93.3)		

★Patients with frontal fibrosing alopecia

**\*\***Values obtained after applying the Fisher exact test

\*\*\* Values obtained after applying the Pearson Chi-Square test;

Source: Research data, 2020

use, that is, after FFA diagnosis (Figure 2). It is suggested that the decrease in use would be related to a typical response among patients with hair loss, as they relate the use of these products to hair loss, either through lay knowledge, through research, or

even speeches by the health professional.<sup>31</sup> The same reasoning may explain the lower adherence of FFA patients due to hair procedures and greater use of anti-residue shampoo by this group after the FFA diagnosis. In this case, the use of shampoo

TABLE 5: Use of topical products in the past (n=60)					
	Group	o, n (%)			
	FFA*	Control	DValue	OR	
	n=30	n=30	P value	(IC95%)	
Facial sunscreen					
Yes	23 (76,7)**	7 (23,3)	<0,001****	10,80 (3,26-35,72)	
Daily	18 (78,3)	7 (100,0)			
5 times a week	0 (0,0)	0 (0,0)			
3 times a week	3 (13,0)	0 (0,0)			
At least once a week	2 (8,7)	0 (0,0)			
No	7 (23,3)	23 (76,7)**			
Facial moisturizer					
Yes	19 (63,3)**	10 (33,3)	0,020****	3,45 (1,19-9,99)	
Daily	16 (84,2)	7 (70,0)			
5 times a week	0 (0,0)	0 (0,0)			
3 times a week	1 (5,3)	2 (20,0)			
At least once a week	2 (10,5)	1 (10,0)			
No	11 (36,7)	20 (66,7)**			
Facial foundation					
Yes	11 (36,7)	6 (20,0)	0,252***		
Daily	5 (45,5)	3 (50,0)			
5 times a week	1 (9,1)	0 (0,0)			
3 times a week	3 (27,3)	1 (16,7)			
At least once a week	2 (18,2)	2 (33,3)			
No	19 (63,3)	24 (80,0)			
Regular soap on the face					
Yes	14 (46,7)	25 (83,3)**	0,003****	0,25 (0,08-0,74)	
Daily	14 (100,0)	23 (92,0)			
3 times a week	0 (0,0)	1 (4,0)			
At least once a week	0 (0,0)	1 (4,0)			
No	16 (53,3)**	5 (16,7)			
Anti-residue shampoo					
Yes	3 (10,0)	0 (0,0)	0,237***		
Daily	0 (0,0)	0 (0,0)			
3 times a week	0 (0,0)	0 (0,0)			
At least once a week	3 (100,0)	0 (0,0)			
No	27 (90,0)	30 (100,0)			

\*Patients with frontal fibrosing alopecia

**\*\***Statistic significant values after residue analysis

**\*\*\*** Values obtained after applying the Fisher exact test

**\*\*\*** Values obtained after applying the Pearson Chi-Square test;

Source: Research data, 2020

	TABLE 6: Social history and habits of t	he sample (n=60)				
	Group, n (%)					
	FFA*	Control	D Value			
	n=30	n=30	1 Value			
Chemotherapy						
Yes	2 (6.7)	1 (3.3)	0.999**			
No	28 (93.3)	29 (96.7)				
Smoking						
Yes	1 (3.7)	2 (7.1)	0.999**			
No	26 (96.3)	29 (92.9)				
Has already smoked	3	2				
Vegetarian diet						
Yes	1 (3.3)	1 (3.3)	0.999**			
No	29 (96.3)	29 (96.3)				
Sugar-rich diet						
Yes	5 (16.7)	5 (16.7)	0.999***			
No	25 (83.5)	25 (83.5)				
Hair straightening						
Yes	2 (8.3)	3 (14.3)	0.652**			
No	22 (91.7)	18 (85.7)				
Has already don	6	9				
Hair dye						
Yes	23 (76.7)	23 (76.7)	0.999***			
No	7 (23.3)	7 (23.3)				
Menopause						
Yes	27 (90.0)	29 (96.7)	0.612**			
No	3 (10.0)	1 (3.3)				
Tamoxifen						
Yes	2 (6.7)	0 (0.0)	0.429**			
No	28 (93.3)	30 (100.0)				
IUD						
Yes	3 (10.0)	2 (6.7)	0.999**			
No	27 (90.0)	28 (93.3)				
COCP						
Yes	21 (70.0)	19 (63.3)	0.584***			
No	9 (30.0)	11 (36.7)				
Hysterectomy						
Yes	8 (26.7)	6 (20.0)	0.542***			
No	22 (73.3)	24 (80.0)				

#### TABLE 7: Previous or current treatments of FFA \*

	n (%)
	n=30
Minoxidil	9 (30.0)
Topical corticosteroid	8 (26.7)
Tacrolimus ointment	6 (20.0)
Hydroxychloroquine	6 (20.0)
Chloroquine	1 (3.3)
Finasteride	2 (6.7)
Dutasteride	1 (3.3)
Doxycycline	1 (3.3)
Hair MMP <b>**</b>	1 (3.3)

\*Patients with frontal fibrosing alopecia

**\*\****Technique of micro infusion of medicines into the skin with* 

Dutasteride 1 mg/ml, Tracolimus 0.1%, BFGF/IGF/VEGF/

COOPER PEP 1.2%, Lidocaine HCL 10 mg/ml

would be a typical response to the fact that patients relate the fall to the accumulated capillary waste, a fact also observed in our sample. These results show the importance of knowledge about the fundamental known risk factors for FFA, minimizing stressors, and investing in products with low effectiveness. Other environmental factors were also analyzed, such as the diet followed by the patients. Only one of the patients with FFA followed a vegetarian diet. Some studies have already demonstrated the absence of a relationship between FFA and a diet rich in soy and its derivatives.<sup>13</sup> However, a recent study<sup>32</sup> demonstrated a possible relationship between the emergence of FFA and a diet rich in wheat and corn. Therefore, further studies are needed to confirm the causal relationship between dietary elements and the pathophysiology of FFA.

Regarding the use of tamoxifen, a study with 100 FFA patients raised the hypothesis that tamoxifen use may cause a loss of the estrogenic effect on regulation fibrosis and immunity.<sup>10</sup> However, in our sample, only two patients with FFA used the previous one.

On the other hand, some literature suggests three protective factors for developing FFA, such as previous use of IUD,<sup>10</sup> COCP,<sup>31</sup> and previous or current smoking.<sup>33</sup> These studies justified that the use is more commonly reported in patients not affected by the disease and a possible hormonal relationship related to their exposure. Also, a greater use of regular soap by the control group (83.3%) was observed in our study when compared to the case group (46 %) (Figure 1). Thus, it was not yet demonstrated in other studies, which can be understood as a protective factor since it would indicate greater facial hygiene, helping to remove topical products deposited in the follicle over the years.<sup>34</sup> Therefore, more studies about the possible protective factors are needed.



**Figure 1:** Use of facial products in the past





#### CONCLUSION

The issues raised by the present study bring the need to conduct a well-designed multicenter study with a larger number of patients through long-term follow-up. The substantial result found in the use of facial products highlights the importance of

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studies that investigate the specific component of each one and its relationship with the disease. Still, the application of validated quality of life questionnaires could quantify the impact of the disease on the patients' lives.

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#### **AUTHORS' CONTRIBUTION:**

#### Lara Xavier Bazotti D ORCID 0000-0002-1607-9257

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review.

#### Leticia Maoletti Teixeira D ORCID 0000-0002-6307-933X

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation.

#### Ana Paula Naspolini D ORCID 0000-0002-7201-5709

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.

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# Microneedling and epidermal growth factor (EGF) as strategies for the acne scars treatment

Microagulhamento e fator de crescimento epidérmico (EGF) como estratégias para o tratamento de cicatrizes de acne

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#### ABSTRACT

**Background:** The microneedling technique and the transdermal drug delivery are indicated to treat acne scars.

**Objective:** Evaluation of the microneedling technique associated with the drug delivery of the epidermal growth factor (EGF).

**Methods:** Randomized double-blind clinical trial of 30 patients divided into two groups: (1) - two microneedling sessions with a 30-day interval, (2) - two microneedling sessions with the same interval but associated with EGF drug delivery. The patients were evaluated clinically (global acne scarring grading system - Goodman and Baron) global acne scarring grading system via multispectral image and through self-perception questionnaires. The statistical analysis (Student T-test, SNK test, analysis of variance) was performed with the SisVar software (UFLA, 1996).

**Results:** The groups were homogeneous regarding age, gender, and phototype. Clinical assessments showed a reduction in severity scores for both groups. The multispectral analysis revealed a decrease in porphyrins (p = 0.0296) and an improvement in skin texture in group two subjects.

**Conclusion:** Microneedling therapy was effective and safe for the acne scars treatment, and EGF demonstrated to be a promising strategy as well.

Keywords: Acne vulgaris; Cicatrix; Skin

#### RESUMO

**Introdução:** a técnica de microagulhamento e aplicação de drug delivery transdérmico é indicada para o tratamento das cicatrizes de acne.

**Objetivos:** avaliar a técnica de microagulhamento associada a aplicação de fator de crescimento epidérmico (EGF) em drug delivery.

**Métodos:** ensaio clínico duplo-cego randomizado, com seleção de 30 pacientes, divididos em dois grupos: (1) duas sessões de microagulhamento com intervalo de 30 dias e (2) duas sessões de microagulhamento com mesmo intervalo e associação de drug delivery de EGF. Os pacientes foram submetidos à avaliação clínica (escala global de cicatriz de acne - Goodman e Baron, 2006), a avaliação por imagem multiespectral e por questionários de autopercepção. A avaliação estatística (Teste T Student, Teste SNK, análise de variância) foi realizada com o software estatístico SisVar (UFLA, 1996).

**Resultados:** os grupos foram homogêneos quanto à idade, sexo e fototipo. Na avaliação clínica, houve redução dos escores de gravidade para ambos os grupos. A análise multiespectral revelou redução das porfirinas (p=0,0296) e melhora da textura da pele, ambas para o grupo 2.

**Conclusão:** a terapia com microagulhamento foi eficaz e segura para o tratamento de cicatrizes de acne, e o EGF demonstrou ser um ativo promissor.

Palavras-chave: Acne vulgar; Cicatriz; Pele

# **Original article**

#### **Authors:**

- Mônica Albuquerque Costa<sup>1</sup> Érika Santos Freire<sup>1</sup> Maria Cristina Vieira Andrade<sup>1</sup> Marcio Roberto Silva<sup>2</sup> Maria Christina Marques Nogueira Castañon<sup>3</sup> Nádia Rezende Barbosa Raposo<sup>1</sup>
- <sup>1</sup> Universidade Federal de Juiz de Fora, Center for Health Science Research and Innovation, Juiz de Fora (MG), Brazil.
- <sup>2</sup> Embrapa, Research and Development, Juiz de Fora (MG), Brazil.
- <sup>3</sup> Universidade Federal de Juiz de Fora, Microbiology Sector and Department of Morphology, Juiz de Fora (MG), Brazil.

#### Correspondence:

Mônica Albuquerque Costa Email: monica\_dealbuquerque@ hotmail.com / Alternative email: monica\_dealbuquerque@hotmail. com

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#### INTRODUCTION

Acne is an inflammatory disorder, and its primary complication is the development of scars.<sup>1</sup> These can occur at any stage of the disease, but early intervention in the treatment of acne is believed to be the most effective way to prevent them.<sup>2</sup> They cause a negative aesthetic impact and generate psychosocial damage, reducing the quality of life of affected patients.<sup>3</sup> The treatment of acne scars still represents a challenge and instigates the search for other therapies and/or safer and more effective procedures.

The microneedling technique, also known as percutaneous collagen induction,<sup>4</sup> is considered a minimally invasive procedure, where a device pierces the skin, physically breaking up compact bands of collagen in the superficial layer of the dermis, leading to the formation of microchannels, thus allowing the transdermal administration of substances (drug delivery).<sup>5</sup> This technique can induce an inflammatory response and stimulate neovascularization and formation of type III collagen, later replaced by type I collagen.<sup>6</sup> Also, it promotes the release of transforming growth factors (TGF) alpha and beta, connective tissue growth factors (CTGF), platelet-derived growth factors (PDGF), and fibroblast-derived growth factors (bFGF), as well as epidermal growth factor (EGF).<sup>7</sup>

EGF decreases sebum production by suppressing lipogenesis. It also demonstrates an anti-inflammatory effect, modulating the expression of cytokines in keratinocytes, inducing changes in the differentiation and maturation of suprabasal keratinocytes, and promoting downregulation of pro-fibrotic factors such as TGF beta-<sup>1.8</sup> These effects suggest that its use is effective and that it is a promising therapeutic option for acne scars.

It is the first clinical trial that assessed the influence of EGF in drug delivery associated with microneedling technique, simultaneously comparing these strategies through multispectral analysis of skin conditions and acne scar assessment tools: global acne scarring grading system (Goodman, Baron, 2006), quality of life assessment questionnaires – Dermatology Quality of Life Index (DLQI), and adapted Cardiff Acne Disability Index (CADI).

#### **METHODS**

It was a randomized, double-blind, experimental clinical study with a quantitative research model, conducted in a group of patients with acne scars who underwent two microneedling sessions associated or not with EGF drug delivery, performed by a dermatologist. The Ethics Committee in Research with Human Beings of the Federal University of Juiz de Fora approved this study under protocol number 2,702,622. Informed consent was obtained from all participants included in the study.

We performed randomization using Excel software, allocating patients randomly and equally (n=15) into group one (intervention = two microneedling sessions) or group two (intervention = two microneedling sessions associated with drug

delivery of EGF), with subsequent loss to follow-up of two patients, one from each group.

The study design was entirely randomized, with responses repeated over time. The criteria analyzed to obtain the results were: analysis of the parameters obtained in the technological device (VISIA<sup>®</sup>) that performs multispectral analysis of skin conditions; responses obtained through the adapted CADI and DLQI questionnaires; and the values obtained in the Goodman and Baron's (2006) global acne scarring grading system. The groups analyzed over time were formed by a combination of treatments (one and two) and sex (woman and man), constituting four groups.

We included patients with a clinical diagnosis of acne scars, of both sexes, aged between 18-45 years, Fitzpatrick's skin phototype IV, and who did not use any type of systemic and/ or topical dermatological or aesthetic treatment in the last six months in the face. We excluded individuals who were pregnant/lactating, who presented photosensitivity, immunosuppression, active infection (such as herpes simplex, impetigo, among others), severe types of acne (acne conglobata and fulminant), predisposition to keloid formation, presence of cutaneous malignancies, self-declared allergy to EGF and/or anesthetic, and those who did not complete all stages of the study.

In group one, two microneedling sessions were performed as a single strategy and with an interval of 30 days between sessions, and in group two, in addition to the two microneedling sessions of the same interval, application of 1 ml of epidermal growth factor (EPIfactor<sup>®</sup> in 30g of vehicle – 4000 ng/g) after the procedure. Only the use of sunscreen was indicated for home care.

The disposable manual device used was a dermaroller (DrRoller MTS Roller, MiRoll, Korea), containing a mobile cylinder with eight rows of 2 mm stainless steel needles, totaling 192 needles.

The facial skin surface was sanitized with 70% ethanol, and then an anesthetic block was performed using 2% lidocaine and 4% lidocaine cream (topical) to minimize discomfort.

Each facial region was pierced eight times in different directions (vertical, up and down, horizontal, right and left, and both diagonal directions) to achieve the endpoint of uniform petechiae and purpura across the entire face. We did not conduct skin preparation with retinoid derivatives or depigmenting agents to avoid confounding bias in the study.

At time zero (T0), we perform the clinical assessment and classification of acne scars using the Goodman and Baron scale (2006), multispectral skin analysis, and quality of life assessment using the adapted DLQI and CADI questionnaires. At time one (T1), corresponding to three to seven days after T0, we performed the first session of microneedling alone or associated with EGF. We conducted the second microneedling session, multispectral imaging assessment, clinical assessment, and quality of life assessment at time two (T2 – 30 days after T1). At time three

(T3 - 60 days after T1) and time four (T4 - 90 days after T1), we performed multispectral analysis and clinical evaluation. The last quality of life assessment was performed applying the described questionnaires at time five (T5 - 180 days after T1). The same investigator conducted all these instruments for each volunteer.

For the statistical analysis, the transformation of the mean values and the tests were conducted: T-Test (to compare the groups between the proposed treatments) and SNK Test (to compare the treatments over the study period).

The simple stratified sampling method with stratification defined for four groups, aiming to meet the analysis domains established for the study (treatment strategies: one [microneedling] and two [microneedling associated with EGF drug delivery], in addition to gender [man and woman]), was used as a strategy to reduce the coefficient of variation and, thus, allow intragroup and intergroup comparisons over time. Therefore, each individual became his or her control over time.

#### RESULTS

Demographic characteristics

There were no statistically significant differences regarding the demographic characteristics (age, sex, and skin type) of the patients between the two treatment groups (Table 1). Regarding the clinical pattern of acne scar classification, all patients had a combination of atrophic scar subtypes in the studied period: icepick, boxcar, and rolling.

#### **Clinical assessment**

The classification of acne scars severity by Goodman and Baron (2006) global acne scarring grading system scores four grades that classify them into grade one (macular scar); grade two (mild), grade three (moderate), and grade four (severe). Before performing any treatment strategy (time zero or baseline), two (7.1%) patients were classified as grade two (mild) and 26 (92.8%) as grade three (moderate), considering the studied population (n=28). At the end of treatment (90 days - T4), 10 (35.71%) patients were classified as mild and 18 (64.28%) as moderate, considering the population studied. Table 2 summarizes the results regarding the stratification by groups, and no statistically significant differences were found between the initial and final scores for both strategies employed (p=0.25 for group one and p=0.12 for group two).

#### **Multispectral analysis**

There was a reduction in porphyrin means, which may reflect a reduction in bacterial colonization by Cutibacterium acnes (C. acnes) (p=0.0296). Porphyrins means in group one in both sexes did not change significantly over time, but for treatment group two, they tended to decrease at time 60 (men) and time 30 (women). At time 60, the porphyrin means in both groups was significantly different for men, with a higher mean for group one than for group two, indicating that the use of EGF in group two was important to control the proliferation of C. acnes and thus reduce the total amount of porphyrins on the face (Table 3 and Figures 1A and 1B).

For the variables pores, wrinkles, red area, and spots on the entire face, the comparison of means between the times and treatments performed did not show a statistically significant difference (p>0.05). However, regarding texture in the frontal region, the overall analysis without stratification by sex and skin phototype showed a trend towards improved skin quality (p=0.059) for the treatment effect. Regarding the texture in the lateral area, when performing stratification by sex and skin phototype, a slight increase in the mean values of this parameter was observed, which clinically translates into a skin improvement (Chart 1) without, however, being statistically significant (p=0.18). In figure 2, it is possible to notice the improvement in the skin texture of patients belonging to the proposed treatments.

TABLE 1: Demographic characteristics of the population studied as a function of the treatment strategies	
used for acne scars.	

	Trea		
	Microneedling (%)	Microneedling + EGF (%)	Total (%)
Age (mean) ±SD	28.3±5.2	$27.4 \pm 4.8$	$27.9 \pm 4.9$
Gender			
Women	57.14	61.2	60.7
Men	42.8	35.7	39.2
Fitzpatrick Skin Phototype			
II	14.2	7.14	10.7
III	64.2	57.1	60.7
IV	21.4	35.7	28.5
Total of participants	14	14	28

Caption: EGF = epidermal growth factor; SD = standard deviation

TABLE 2: Grading of severity of acne scars by Goodman and Baron (2006) between treatment groups.				
		<b>Clinical Evaluation</b>		
	Microneedling		Microneedling + EGF	
Baseline (T0)	Grade 2: 14.2% (2/14)	Baseline (T0)	Grade 2:0	
	Grade 3: 85.7% (12/14)		Grade 3: 100% (14/14)	
T4 (90 days)	Grade 2: 42.8% (6/14)	$T_{4}(00 - 1_{})$	Grade 2: 28.5% (4/14)	
	Grade 3: 57.1% (8/14)	14 (90 days)	Grade 3:71.4% (10/14)	

*Caption:* EGF = epidermal growth factor

# TABLE 3: Mean score for the presence of porphyrins obtained by multispectral analysis of facial skin (laterals: right and left) over time for participants submitted to the proposed treatments and stratified by sex.

Time (days) / Porphyrin (mean score)	0	30	60	90
Treatment 1	2537.6	2133.8	2706.6	2567
Men	Aa	Aa	B*a	Aa
Treatment 1	1637.75	1265.5	1575	1975.5
Women	Aa	Aa	AB*a*	Aab*
Treatment 2	1656	1590	718.6	1291
Men	Ab	Ab	Aa*	Ab
Treatment 2	1777.6	1072.8	1455.8	1436.2
Women	Ab	Aa	AB*ab*	Aab

**Caption:** Capital letters (A, B) compare treatments (1 and 2) within the same time, and lowercase letters (a, b) compare the times within the same treatment (1 or 2). Analysis with root transformation. Tests performed to compare the means: T and SNK test. Markings with the symbol (\*) refer to different means (p<0.05)



**FIGURE 1:** Image showing the reduction in the presence of porphyrins in the treatment group: microneedling with drug delivery of EGF. **A** = microneedling.

- B = microneedling + EGF
- 1 = start of treatment Time o/baseline
- **2** = end of treatment Time 4/90 days



**CHART 1:** Texture score assessed on patients' faces over time



**FIGURE 2:** Comparative image of skin conditions of patients in treatment groups 1 and 2 at baseline and end of follow-up.

A = microneedling.
B = microneedling + EGF
1 = start of treatment - Time o/baseline
2 = end of treatment - Time 4/90 days

#### Self-perception assessment

DLQI is a questionnaire that assesses skin diseases in general and grades them according to the following score: 1 (0-1 point) the skin disease does not interfere with the patient's quality of life; 2 (2-5 points), the skin disease interferes little with the quality of life; 3 (6-10 points), the interference is moderate; 4 (11-20 points), there is a lot of interference in the quality of life; and 5 (21-30 points), there is huge interference in the quality of life of those affected. The results showed no significant differences in the total variation of scores (final score - initial score) for both treatments used (p=0.25 for treatment one and p=0.12 for treatment two). Before the intervention (time zero or baseline), of the 28 patients who participated of the study, 7 (25%) were classified as score 1; 12 (42.85%) as score 2; 4 (14, 28%) patients as score 3; 5 (17.85%) as score 4; and no patient was classified as score 5 (n=28). Based on the stratification of the groups by treatment, in treatment one (microneedling), 3 (21.42%) patients were classified as grade 1; 8 (57.14%) as grade 2; 1 (7.14%) as grade 3; and 2 (14.28%) as grade 4 (n=14). For treatment two (microneedling associated with drug delivery of EGF), 4 patients (25.57%) were classified as grade 1; 4 (25.57%) as grade 2; 3 (21.42%) as grade 3; and 3 (21, 42%) as grade 4 (n=14). At the end of the treatment, 7 (25%) patients scored 1; 19 (67.85%) scored 2; 3 (10.71%) scored 3; and no patients scored 4 and 5, considering the population studied (n=28). Based on the stratification of the groups by treatments, in treatment one (microneedling), 5 (35.71%) patients were classified as grade 1; 7 (50%) as grade 2; and 2 (14.28%) as grade 3 (n =14). For treatment two (microneedling associated with drug delivery of EGF), 2 (14.28%) patients were classified as grade 1 and 12 (85.71%) as grade 2 (n=14) (Chart 2).

The score obtained in the CADI questionnaire grades acne as mild (1) when the sum of the points obtained in the questionnaire varies from 0-5; moderate (2), when the sum varies from 6-10; and severe (3), when this sum varies from 11-15 points. Before conducting the intervention (time 0 or baseline), 15 (53.57%) patients were ranked as mild; 12 (42.85%) as moderate; and 1 (3.57%) as severe. In the last period of evaluation (time 5/180 days), 26 (92.85%) patients were graded as mild,



and 2 (7.14%) as moderate (n=28). In treatment group one (time 0 or baseline), 8 (57.14%) patients were classified as mild, 5 (35.71%) as moderate, and 1 patient (7.14%) as severe. At the end of the study (time 5/180 days), 13 (92.85%) patients were graded as mild and only 1 (7.14%) as moderate (p=0.062). For treatment group two, 7 (50%) patients were ranked as mild and 7 as moderate, at time 0-baseline. At the end of treatment (time 5/180 days), 13 (92.85%) patients were classified as mild and only 1 (7.14%) as moderate (p = 0.12) (Chart 3).

#### DISCUSSION

Acne scar management has been a challenging task and a focus of interest for dermatologists. Skin microneedling is a modality for remodeling acne scars, with minimal damage to the epidermis, few adverse events, and shorter recovery time after the procedure, compared to other methods with the same purpose.<sup>10,5,11</sup> Regarding patient selection, the literature presents several clinical trials with microneedling treatment for acne scars in young patients of both sexes. As verified by Harris et al. (2015), the average number of microneedling sessions needed to achieve satisfactory results was three sessions with mean intervals of four weeks (two to eight weeks), chiefly using 1.5 mm needles (1 mm to 3 mm) in length.<sup>12</sup> In agreement with most of the studies analyzed, we selected 30 patients with acne scars, with a mean age of 27.9  $\pm$  4.9 years, skin phototypes IV, of both sexes. After the loss to follow-up (n=2), 17 women and 11 men completed the study (n=28). Two microneedling sessions were performed using a 2 mm needle at an interval of four weeks between them.

Kalil, Frainer *et al.* (2015) selected 10 patients aged 20-40 years, of both sexes, with atrophic acne scars, who underwent three sessions of microneedling using a 2mm needle. The study used anatomopathological analysis and digital photographs.<sup>13</sup> There was application drug delivery of growth factors (EGF, IGF, TGF-beta3) using masks. The authors did not find improvement in icepick scars, but they did notice an overall improvement in skin texture and a slight improvement in acne scars. In our study,

we also observed an overall improvement in skin texture, especially in those patients who had EGF drug delivery after two microneedling sessions. Additionally, icepick scars slightly improved with shallowing of their depths.

The literature describes that EGF decreases sebum production and has an anti-inflammatory effect, reducing follicular hyperkeratosis. In addition to acting on active acne, it also stimulates the production of dermal matrix constituents, stimulating the production of organized collagen, downregulating TGF-beta1, which has a pro-fibrotic action. With its application in drug delivery, it is expected not only improvement of acne scars but also an enhancement in those patients who have associated active acne (Kim, Yeo, Li *et al.*, 2014; Draelos, 2016; Lian and Li, 2016).<sup>8,14,15</sup>

Based on these data, applying EGF in drug delivery after microneedling is justified due to its direct effect on the pathogenesis of acne and acne scars and its anti-inflammatory action, which can be beneficial for a more efficient repair of the lesion caused by the procedure.

Al Qarqaz et al. (2018) evaluated 48 patients with skin phototypes III-VI treated with microneedling (Dermastamp® electronic device) and noticed a statistically significant improvement when comparing the treatment scores (before and after) obtained by the Goodman and Baron scales and the post-acne hyperpigmentation index (PAHPI).<sup>16</sup> Our study also used different methods to assess the effectiveness of the procedure: Goodman and Baron's global acne scarring grading system, digital photographs, and adapted generic (DLQI) and specific (CADI) self-perception questionnaires. The generic questionnaires assess the quality of life outside the clinical context (Halioua, Beumont, and Lunel, 2000).<sup>17</sup> The specific ones, in turn, are used for a particular disease and, considering that they are manifestations of a determined clinical condition, they are more sensitive when compared to generics. Also, our study demonstrated a reduction in the global acne scarring grading system when comparing the scores before and after treatment, but without statistically significant



Chart 3: Distribution of the study sample (n=14/treatment), according to the classification obtained by the assessment of self-perception using the CADI questionnaire, over time for the proposed treatments

differences between the grades obtained at the beginning and the end of the treatment.

A literature review performed in consultation with PubMed from 1946-2015 and Embase from 1947-2015, by Harris *et al.* (2015)<sup>12</sup>, for microneedling research to treat acne scars, assessed the effectiveness of the procedure alone, combined with other therapies, histological changes, and adverse events. When assessing the technique in isolation, all studies showed improvement with treatment with a reduction in scar severity, based on the Goodman and Baron scale, one of which decreased from 11.7 points to 6.5. Our study showed a reduction in the means with this same assessment instrument in both treatment groups and for both sexes. However, this difference between the beginning (baseline, time zero) in which 7.1% of the patients were classified as grade 2 (mild), and 92.8% as grade 3 (moderate), and the end of the follow-up (90 days, time four) where 35.7% of

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patients were classified as grade 2 (mild) and 64.2% as grade 3 (moderate), was not statistically significant. However, it is worth noting that the 28.6% reduction in cases classified as grade 3 in both groups may translate into clinical improvement.

#### CONCLUSION

Microneedling therapy was effective and safe for treating acne scars, with minimal adverse events and short recovery time. The clinical response, expressed through the variation of the global acne scarring grading system, showed that all patients improved to varying degrees. EGF, used in drug delivery, proved to be a promising active pharmaceutical ingredient as an adjuvant in the acne scars treatment and most patients presented an improvement in quality of life, expressed by the reduction of the values obtained in the adapted DLQI and CADI questionnaires when compared to the initial values. •

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#### AUTHORS' CONTRIBUTION:

#### Mônica Albuquerque Costa D ORCID 0000-0002-7254-4379

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Érika Santos Freire D ORCID 0000-0002-2106-2310

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Maria Cristina Vieira Andrade D ORCID 0000-0002-4205-0618

Author's contribution: Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Marcio Roberto Silva (D ORCID 0000-0002-0755-4415

Statistical analysis; approval of the final version of the manuscript; study design and planning; active participation in research orientation.

#### Maria Christina Marques Nogueira Castañon 🝺 ORCID 0000-0002-2995-1761

Approval of the final version of the manuscript; preparation and writing of the manuscript; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Nádia Rezende Barbosa Raposo iD ORCID 0000-0001-5271-1048

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

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# Clinical characteristics of actinic keratoses and their histological correlations: suggestion for a clinical severity scale

Características clínicas das queratoses actínicas e suas correlações histológicas: sugestão de escala de gravidade clínica

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#### ABSTRACT

**Introduction:** Actinic keratoses are premalignant lesions with a risk of transformation to invasive squamous cell carcinoma. There is no identified correlation between clinical classification and histological grade of these lesions.

**Objectives:** To correlate the clinical characteristics of actinic keratoses of the forearms and back of the hands with the degree of histological atypia (Keratinocyte Intraepidermal Neoplasia); to develop and validate a clinical severity scale correlated with the histological grade of actinic keratoses.

**Methods:** Cross-sectional study with 162 actinic keratoses clinically evaluated for diameter, erythema, infiltration, hyperkeratosis, and exulceration and 34 lesions with different patterns were biopsied. Clinical features were correlated with the degree of histological atypia and p53 and Ki-67 expression.

**Results:** Only the diameter of the lesions was significantly correlated with the degree of atypia (p=0.04), and only the erythema, hyperkeratosis, and the diameter linked with the immunohistochemical markings. A clinical score including diameter, hyperkeratosis, and exulceration was developed, which associated significantly with the degree of atypia (Spearman's Rho=0.43; p=0.01).

**Conclusions:** A score composed of diameter, hyperkeratosis, and exulceration correlated with the histological grade of actinic keratoses of the upper limbs was developed.

Keywords: Carcinoma in situ; Carcinoma squamous cell; Keratosis actinic; Skin diseases

#### RESUMO

**Introdução**: as queratoses actínicas são lesões pré-malignas com risco de transformação para carcinoma espinocelular invasivo. Não há correlação identificada entre classificação clínica e grau histológico destas lesões.

**Objetivos:** correlacionar as características clínicas das queratoses actínicas dos antebraços e dorso das mãos com o grau de atipia histológica (Keratinocyte Intraepidermal Neoplasia); desenvolver e validar uma escala de gravidade clínica correlacionada ao grau histológico das queratoses actínicas.

**Métodos:** estudo transversal com 162 queratoses actínicas avaliadas clinicamente quanto a diâmetro, eritema, infiltração, hiperqueratose e exulceração; biopsiadas 34 lesões com diferentes padrões. As características clínicas foram correlacionadas com o grau de atipia histológica e a expressão de p53 e Ki-67.

**Resultados:** apenas o diâmetro das lesões correlacionou-se significativamente com o grau de atipia (p=0,04), e apenas o eritema, a hiperqueratose e o diâmetro correlacionaram-se com as marcações imuno-histoquímicas. Foi desenvolvido um escore clínico incluindo o diâmetro, a hiperqueratose e a exulceração, o qual se correlacionou significativamente com o grau de atipia (Rho de Spearman=0,43; p=0,01).

**Conclusões**: desenvolveu-se um escore composto por diâmetro, hiperqueratose e exulceração correlacionado com o grau histológico das queratoses actínicas dos membros superiores.

Palavras-chave: Carcinoma de Células Escamosas; Carcinoma In Situ; Queratose Actínica; Neoplasias

# **Original article**

Authors:

Guilherme de Oliveira Arruda<sup>1</sup> Anna Carolina Miola<sup>1</sup> Hélio Amante Miot<sup>1</sup> Juliano Vilaverde Schmitt<sup>1</sup>

Universidade Estadual Paulista, Division of Dermatology and Radiotherapy, Botucatu (SP), Brazil.

Correspondence: Anna Carolina Miola Email: anna.c.miola@unesp.br

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#### INTRODUCTION

Actinic keratoses (AKs) are the most frequent pre-malignant lesions in the human race. They are clinically described as slow-growing, dry, erythematous-scaly plaques, with mild or no infiltration of the base, located mainly in photoexposed areas, such as the scalp, face, cervical region, upper torso, and extremities.<sup>1</sup>

In 1999, Yantsos proposed a histological classification for AKs, based on the proportion of intraepithelial cell atypia observed. Due to the continuous progression of keratinocyte AKs atypia, similar to the progression of cervical intraepithelial neoplasia (CIN) associated with human papillomavirus (HPV), an analogous term was proposed to classify the histological grade of AKs – keratinocyte intraepidermal neoplasia (KIN).<sup>2</sup>

KIN 1 lesions, considered of low histological grade, present atypia only in the lower third of the epidermis and, theoretically, have a low probability of malignant transformation. On the other hand, KIN 2 and KIN 3 lesions, considered to be of high histological grade, have, respectively, atypia in the lower two-thirds and throughout the epidermis and would have a greater chance of malignancy.<sup>2</sup>

Regarding the clinical classification of AKs, the best known is the Olsen classification, which divides the lesions into three different grades according to their thickness and hyperkeratosis. However, there is still no clinical classification that sought to correlate the histological grade of AKs according to KIN.<sup>3,4</sup>

The present study assessed the correlation between the clinical AKs characteristics and the atypia degree in the histopathological examination, as well as the combined effect of the clinical features in the development of a clinical classification with the better correlation between clinical and the degree of histological atypia of the AKs of the superiors limbs.

#### **METHODS**

It is a cross-sectional study conducted from February 2019 to May 2019 at the Oncological Dermatology Outpatient Clinic. Nine patients diagnosed with AKs on the forearms and back of the hands were evaluated, and 34 lesions with distinct clinical characteristics were biopsied. Biopsies were performed by elliptical excision with 2 mm margins after marking their clinical limits. The Research Ethics Committee of the Faculty of Medicine of Botucatu – UNESP approved this study (N. 1,874,384).

We included patients aged over 18 years; lesions clinically compatible with AKs on the forearms and back of the hands; absence of lesions that generate diagnostic doubt with squamous cell carcinoma (SCC) in situ (Bowen's disease) or with invasive carcinomas; and the presence of up to 20 AKs per anatomical region examined. Also, we excluded individuals with any genodermatosis, immunosuppressed patients, previous users of systemic retinoids, those previously submitted to radiotherapy or any clinical treatment for AKs within less than six months.

Two dermatologists independently evaluated five clinical features: diameter in millimeters, erythema, infiltration, hyperkeratosis, and exulceration. Table 1 details the clinical grading used, and Figure 1 illustrates it with photographs.

A total of 162 lesions were clinically examined. Of these, 34 lesions with different clinical characteristics underwent excision.

Biopsies were fixed in 10% buffered formalin, embedded in paraffin blocks, submitted to 4  $\mu$ m cross-sectional histological sections in the center of the lesion, and subsequently stained with hematoxylin & eosin. After confirming the histopathological diagnosis of the AKs, two qualified dermatologists graded them all according to the KIN score.

TABLE 1: Clinical characteristics evaluated in each actinic keratosis lesion			
Clinical characteristic	Clinical grading		
Diameter	Assessed in millimeters, with ruler. The largest diameter of each lesion was considered		
Erythema	Grade 1. Absent or light pink Grade 2. Live erythema		
Infiltration	Grade 1. Flat lesion, without signs of infiltration Grade 2. Raised plaque or papule		
Hyperkeratosis	<ul> <li>Grade 1. Absent or slightly rough lesion on palpation (peeling is more palpable than visible)</li> <li>Grade 2. Evident scaly appearance</li> <li>Grade 3. Compact keratin adhered to the surface of the lesion</li> </ul>		
Exulceration	<b>Grade 1.</b> Absent <b>Grade 2.</b> Present (including areas with blood crust)		



Figure 1: \* A - Grade 1 erythema, Grade 1 infiltration. Grade 1 hyperkeratosis, Grade 1 exulceration. B - Grade 1 ervthema. Grade 1 infiltration, Grade 2 hyperkeratosis, Grade 1 ulceration. **C** - Grade 1 erythema, Grade 2 infiltration. Grade 3 hyperkeratosis. Grade 1 exulceration. D - Grade 1 erythema, Grade 2 infiltration, Grade 3 hyperkeratosis, Grade 1 exulceration (bleeding area is due to anesthetic injection). E - Grade 2 erythema, grade 1 infiltration, grade 1 hyperkeratosis, grade 2 exulceration.

For immunohistochemistry, 4µn-thick histological sections were mounted on salinized slides (Sigma Chemical Corporation, Saint Louis, MO, USA) and stained for Ki-67 and p53 detection using the immunoperoxidase technique and avidin-biotin-peroxidase. For the p53 protein, the murine anti-human p53 monoclonal antibody, clone D0-7 (Dako, code no M7001, CA, USA), was used at a 1/30 dilution. For Ki-67, the murine anti-human Ki-67 monoclonal antibody, clone MIB-1 (Dako, code F7268, CA, USA), was used at a titer of 1/30. Immunohistochemical expression was considered positive when labeled nuclei stained brown. In the absence of the primary antibody, the negative control was tested, and histological sections of mammary carcinoma were used as a positive control.

Two qualified dermatologists assessed the nuclear expression of protein p53 and Ki-67 of keratinocytes in the lesional and perilesional epithelium in a semi-quantitative manner. Numbers from zero to three are assigned, according to the percentage of nuclei labeled as follows: (0) negative immunohistochemical reaction; (1) <30% labeled nuclei; (2) 30-60% labeled nuclei; (3) >60% labeled nuclei; and according to the intensity of the reaction: (0) negative immunohistochemical reaction; (1) weak reaction; (2) moderate reaction; (3) strong reaction. The final immunohistochemistry score was calculated by adding the number assigned to the percentage of labeled nuclei and the intensity of the reaction, with a minimum value of zero and a maximum of six.<sup>5,6</sup>

Categorical variables were represented by absolute, proportional, or percentage values. Continuous variables were described regarding central tendency by the mean and standard deviation or median and first and third quartiles, depending on the normality of the distributions analyzed by the Shapiro-Wilk test.

Inter-rater agreement regarding clinical characteristics was assessed using the intraclass correlation coefficient, single measures.

For statistical analysis, the diameter was also classified into three categories: up to 5 mm (inclusive); between 5 and 10 mm (inclusive); and above 10 mm.

The statistical correlation between the clinical characteristics, the histological grade, and the nuclear expression of lesional and perilesional p53 and Ki-67 was estimated by the Spearman correlation coefficient and chi-square test for trend analysis.

The coefficients of generalized linear models estimated the weight of each clinical characteristic to create the final severity scale.

The sample size was calculated expecting a correlation greater than 0.5 (alpha 0.05 and power of 90%) between the severity score and the histological and immunohistochemical indices.

Data were tabulated in MS Excel, and all analyzes were performed in IBM SPSS 24.0 software. A  $p \le 0.05$ , the two-tailed value was considered significant.

#### RESULTS

In total, 162 lesions distributed on the forearms and dorsum of the hands of nine patients were examined: five women and four men, aged between 44 and 89 years, mean age of 67.6 years (standard deviation: 13 years). Each patient had, on average, 18 AKs. According to the Fitzpatrick classification, eight patients were skin phototype II, and one patient was skin phototype III.

Table 2 shows the frequency of the clinical characteristics of the lesions examined and biopsied, where there is a predominance of small lesions (median diameter = 5 [p25-p75: 4-8] millimeters), absent or mild erythema (grade 1), flat lesion (grade 1), evident desquamation (grade 2), and no exulceration (grade 1).

Histological evaluation of 34 lesions identified five KIN 1 lesions (14.7%), 21 KIN 2 lesions (61.7%), and eight KIN 3 lesions (23.6%). Regarding the predominant histological type, 23 were hypertrophic, 6 were atrophic, 1 was acantholytic, and 4 were lichenoid lesions. Inflammatory infiltrate was absent or

mild in 14 lesions, moderate in 16 lesions, and intense in 4 lesions.

Table 3 illustrates the correlation between clinical variables and the KIN score, where a significant correlation is observed only with the categorized diameter (Spearman's Rho = 0.31; p=0.04). The inflammatory infiltrate intensity did not correlate significantly with the clinical features of erythema, hyperkeratosis, infiltration, diameter, and exulceration (Spearman's Rho = 0.31; p>0.4).

Table 4 illustrates the association between clinical features and immunohistochemical markers. There was a significant correlation between hyperkeratosis and the lesional and perilesional expression of Ki-67 (p<0.01); an inverse correlation between erythema and perilesional expression of Ki-67 (p=0.05); and an inverse correlation between diameter and perilesional p53 expression (p=0.04).

Table 5 shows an inverse correlation between histological grade (KIN) and perilesional p53 expression.

TABLE 2: Frequency of each clinical characteristic of actinic keratoses examined and biopsied				
Clinical characteristic	Clinical grading	Total CAs examined	Total CAs biopsied	
		N=162(%)	N=34(%)	
	Up to 5	89 (55)	14 (41)	
Diameter in millimeters	6 to 10	59 (36)	17 (50)	
	Higher to 10	14 (9)	3 (9)	
	Grade 1	143 (88)	27 (80)	
Erytnema	Grade 2	19 (12)	7 (20)	
X (1)	Grade 1	135 (83)	19 (56)	
Innitration	Grade 2	27 (17)	15 (54)	
	Grade 1	39 (24)	5 (15)	
Hyperkeratosis	Grade 2	90 (56)	15 (44)	
	Grade 3	33 (20)	14 (41)	
Employmetics	Grade 1	154 (95)	31 (91)	
Exulceration	Grade 2	8 (5)	3 (9)	

TABLE 3: Correlation between clinical features of actinic keratoses and grade of keratinocyte intraepithelial neoplasia (KIN)					
Characteristic	Coefficient	р			
Erythema *	0.12	0.73			
Hyperkeratosis <b>*</b>	2.96	0.09			
Infiltration $\star$	0.18	0.67			
Exulceration <b>*</b>	0.19	0.66			
Diameter (millimeters)**	0.31	0.08			
Diameter (categorized)*	4.1	0.04			

\* Chi-square test trend analysis

**\*\*** Spearman's Rho

TABLE 4: Correlation between the clinical features of actinic keratoses and the epithelial expression of p53 and Ki-67								
		Lesional				Perilesional		
	p53*	р	Ki-67*	р	p53*	р	Ki-67*	р
Erythema	0.01	0.96	-0.01	0.94	-0.12	0.52	-0.34	0.05
Hyperkeratosis	-0.15	0.42	0.47	< 0.01	0.13	0.46	0.38	0.03
Infiltration	0.08	0.66	-0.21	0.24	-0.08	0.67	-0.02	0.93
Exulceration	0.12	0.51	-0.09	0.6	-0.01	0.98	-0.05	0.77
Diameter (mm)	0.08	0.66	0.12	0.49	-0.37	0.04	-0.07	0.69
Diameter (cat.)	0.02	0.90	-0.02	0.91	-0.34	0.06	-0.18	0.32

★ Spearman's Rho

Significance level:  $p \le 0.05$ 

TABLE 5: Correlation between the grade of keratinocyte intraepithelial neoplasia (KIN) and the epithelial expression of p53 and Ki-67				
Characteristic	Spearman' Rho	р		
p53 lesional	-0.26	0.15		
p53 perilesional	-0.36	0.04		
Ki-67 lesional	0.18	0.31		
Ki-67 perilesional	-0.08	0.66		

TABLE 6: Final generalized linear model regarding the relationship between clinical features and grade of keratinocyte intraepithelial neoplasia (KIN)				
Characteristic	Coefficient	CI 95%	р	
Hyperkeratosis	0.28	0.03 a 0.53	0.03	
Diameter (categorized)	0.26	-0.01 a 0.52	0.06	
Ulceration	0.25	-0.22 a 0.72	0.3	

P (final model) = 0.05; deviance = 0.34.

For the combined assessment of the correlation of clinical characteristics with the KIN, they were submitted to a regression model with adjustment through the "backward-ste-pwise" process, including all variables in the initial model and, later, leaving only those with  $p \le 0.3$  in the final model (Table 6).

We defined a score with the sum of the characteristics of diameter, hyperkeratosis, and exulceration, with the score a ttributed to each grade (Table 7). The intraclass correlation coefficient (ICC) for the clinical score between the two evaluators was 0.71 (CI 95 %: 0.59 to 0.79).

From the ROC curve developed for the identification of lesions with KIN 3, we obtained a sensitivity of 75%, a specificity of 77%, and an accuracy of 76% for the identification of the-

se lesions when using a cut-off value  $\geq 3$  points. The correlation between the clinical score and the KIN was 0.43 (Spearman's Rho p=0.01). The agreement between the evaluators regarding the identification of lesions with a score  $\geq 3$  (indicative of KIN 3) was 0.69 (Cohen's Kappa).

#### DISCUSSION

In the present study, we found, in general, a low correlation between the clinical characteristics and the histological grade of the AKs, with a significant association only with the diameter of the lesions.

Jiyad *et al.* already demonstrated the importance of lesion size in developing SCCs in 2017. The author identified a

TABLE 7: Clinical actinic keratoses severity scale - AKSS			
Characteristic	Description	Points	
Diameter	0 a 5mm	0	
	6 a 10mm	1	
	Higher than 10mm	2	
Hyperkeratosis	Absent or slightly rough lesion on palpation (scaling is more palpable than visible)	0	
	Evident scaly appearance	1	
	Compact keratin adhered to the surface of the lesion	2	
Exulceration	Absent	0	
	Present	1	

fourfold increased risk of kidney transplant recipients developing SCCs in areas of the skin that had at least one AK with an area of 1cm2.<sup>7,8,9</sup>

On the other hand, the KIN assessment proposed by Yantsos *et al.* in 1999 recommends considering the area of greatest atypia as the one that represents the entire lesion. Thus, due to a probabilistic factor, lesions with a larger diameter would be more likely to present higher degrees of KIN.<sup>2</sup>

We found an inverse relationship between lesion size and KIN grade and perilesional p53 expression (p=0.04). The reduction of the p53 protein around the larger diameter lesions suggests the high activity of the adjacent cancerization field due to the lower antitumor effect of this protein. Loss of p53 function in animal studies has led to aneuploidy and accumulation of mutations in tumors.<sup>5,9,10</sup>

Corroborating the findings of Marinescu *et al.* (2016), we did not identify a correlation between the degrees of KIN and the expression of lesional p53 or Ki-67 (p=0.15; p=0.31, respectively). In a 2016 study, Herfordt *et al.* also demonstrated

no relationship between the degree of epidermis atypia in AKs and the expression of the p53 protein.<sup>11,12</sup>

There was a significant association between clinically evaluated hyperkeratosis and lesional and perilesional Ki-67 expression (p<0.01 and p=0.03, respectively), indicating high proliferative activity of the hyperkeratotic lesion. Consistently, in a 2013 study, Pimentel *et al.* identified invasive SCCs associated only with AKs histologically classified as common or hypertrophic, suggesting hyperkeratosis as a marker for the invasive evolution of the lesions.<sup>5,13</sup>

Despite the low clinical-pathological correlation, the study allowed the definition of a clinical score of the AKs of the forearms with the categorization of the diameter, the hyperkeratosis in three degrees, and the presence or absence of exulceration moderately correlated with the histological degree. As in the analysis of pre-malignant cervical lesions, clinical prediction of the atypia level of AKs can guide more or less aggressive therapies and, when analyzed together, scale the activity of the field cancerization in the region.

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#### AUTHORS' CONTRIBUTION:

#### Guilherme de Oliveira Arruda D ORCID 0000-0001-7721-1920

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review.

#### Anna Carolina Miola D ORCID 000-0001-8926-734X

Approval of the final version of the manuscript; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.

#### Hélio Amante Miot D ORCID 0000-0002-2596-9294

Statistical analysis; approval of the final version of the manuscript; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.

#### Juliano Vilaverde Schmitt D ORCID 0000-0002-7975-2429

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; critical literature review; critical revision of the manuscript.

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## Translation and transcultural validation of a quality of life questionnaire to assess facial cosmetics procedures: a Brazilian Portuguese version

Tradução e validação transcultural de um questionário de qualidade de vida para avaliar procedimentos cosmiátricos faciais: versão para a língua portuguesa falada no Brasilhipertróficas

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#### ABSTRACT

**Background:** The increased demand for cosmetic facial treatments is a universal reality, and Brazil is the second country with the most procedures. Quality of life questionnaires can help assess results objectively and reveal data not yet explored in the scientific literature. Thus, the process of translation, adaptation, and validation of questionnaires is necessary for data universalization.

**Objective:** To translate, adapt and validate a specific questionnaire to assess facial cosmetics procedures in Brazilian Portuguese.

**Methods:** After choosing the Skin Rejuvenation Outcome Evaluation (SROE) questionnaire, the translation process started. A literal translation was performed, with the subsequent synthesis of the versions. Then, a team of experts conducted the reverse translation and final validation. The data obtained were statistically analyzed for validation.

**Results:** The final version was called "Avaliação dos Resultados de Rejuvenescimento da Pele" (ARRP). The Cronbach's resulted in values above 0.70, showing good internal consistency. The Intraclass Correlation Coefficient was 0.995 (p<0.001).

**Conclusions:** The values obtained validate the ARRP questionnaire, translated into the Brazilian language and culture, aiming to evaluate the results and impact on the quality of life of facial cosmetics procedures.

Keywords: Cross-cultural comparison; Quality of life; Patient health questionnaire

#### RESUMO

**Introdução:** O aumento da demanda por tratamentos cosméticos faciais é uma realidade universal, sendo o Brasil o segundo país no mundo que mais os realiza. Questionários de qualidade de vida podem ajudar a avaliar os resultados de forma mais objetiva e revelar dados ainda não explorados na literatura científica. O processo de tradução, adaptação e validação de questionários é necessário para universalização dos dados.

**Objetivo:** Traduzir, adaptar e validar un questionário específico para avaliação de procedimentos cosmiátricos faciais para a língua portuguesa falada no Brasil.

**Métodos:** Iniciou-se o processo de tradução do questionário SROE (Skin Rejuvenation Outcome Evaluation). Foi realizada a tradução literal, com posterior síntese das versões, seguido à tradução reversa e à validação final por equipe de especialistas. Os dados obtidos foram analisados estatisticamente para validação.

**Resultados:** A versão final foi denominada "Avaliação dos Resultados de Rejuvenescimento da Pele" (ARRP). O a de Cronbach obteve valores acima de 0,70, evidenciando boa consistência interna. O Coeficiente de Correlação Intraclasse foi de 0,995 (p<0,001).

**Conclusões:** Os valores obtidos validam o questionário ARRP, traduzido para língua e cultura brasileiras, que tem como objetivo avaliar os resultados e o impacto na qualidade de vida dos procedimentos faciais em cosmiatria. **Palavras-chave:** Comparação transcultural; Qualidade de vida; Questionário de saúde do paciente

### **Original Article**

Authors:

- Jaqueline Barbeito de Vasconcellos<sup>1</sup> Daniela Alves Pereira Antelo<sup>1</sup> Rosane Orofino-Costa<sup>1</sup>
- <sup>1</sup> Hospital Universitário Pedro Ernesto, Dermatology Service, Rio de Janeiro (RJ), Brazil.

#### **Correspondence:**

Jaqueline Barbeito de Vasconcellos Email: jaqueline\_vasconcellos@ hotmail.com

Alternative email: jaquelinebvasconcellos@gmail.com

#### Financial support: None. Conflict of interest: None.

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#### INTRODUCTION

Brazil is the second country in the world with the most aesthetic dermatological procedures, according to the most recent data from the International Society of Aesthetic Plastic Surgery (ISAPS, 2019), only after the United States.<sup>1</sup> ISAPS statistics for the same year showed that the demand for surgical procedures has been decreasing (-0.6% compared to the previous year), while for non-surgical procedures has been increasing (+12%). An American Society for Dermatologic Surgery research (ASDS, 2019) indicated that the dermatologist is the most sought professional after the five main non-surgical procedures (botulinum toxin, hyaluronic acid filling, laser treatments, intense pulsed light, and peels).

Historically, the desire for facial rejuvenation and beautification procedures has been attributed to psychological disorders and narcissism. However, well-being, quality of life, and social and professional insertion are the main motivations nowadays. Maisel *et al.* demonstrated, through a multicenter study, that the number of patients who underwent a procedure motivated by internal desires driven by self-confidence was higher than those who did it to please others.<sup>3</sup>

The expectations and results of these procedures go beyond the clinical analysis of the aesthetic component, considering the patient's perception, the impact on quality of life (QOL), and their social relationships.<sup>4</sup>

The international literature, including the World Health Organization (WHO), has been exploring the challenging development of tools to measure an individual's QOL through questionnaires applied to patients. Tools such as the whoqol-100 and whoqol-bref.<sup>5-7</sup> QOL questionnaires can help assess the results of dermatological procedures more objectively and reveal data not yet explored in medical research and scientific literature, thus improving techniques and outcomes in cosmiatry.<sup>8</sup>

The use of instruments that already exist in other languages to assess outcomes and QOL does not depend on a simple literal translation and application to the patient. Several research groups and experts in QOL measurement have studied the process and indicate that it must follow sequential and specific steps to respect the essential psychometric parameters for this evaluation.<sup>6,9</sup>

Clinical research in national cosmitatrics lacks instruments that evaluate the repercussion of cosmetic procedures, although there are national and international scientific journals aimed only at publishing these techniques.

This study aims to translate, cross-cultural adapt, and validate a quality of life questionnaire in Brazilian Portuguese to assess cosmetic procedures.

#### METHODS

This study was submitted to the Research Ethics Committee (REC) of the Hospital Universitário XXXX, and approved on February 28, 2019, under CAAE 02792818.3.0000.5259, and conducted in the Corrective Dermatology Sector of the same hospital.

#### 1 - Questionnaires

Selection – We selected the Skin Rejuvenation Outcome Evaluation (SROE) questionnaire, which already exists in American English because it is comprehensive, easy to understand, and has a short execution time (Box 1). It was created and validated to assess the results of patients undergoing facial rejuvenation procedures.<sup>10,11</sup> Its author, the North American plastic surgeon Ramsay Alsarraff, granted authorization by e-mail for the translation and cultural adaptation into Brazilian Portuguese.

Translation and cultural validation - We conducted the translations and cultural validation through proposed methods already applied in several questionnaires translated and published in Brazilian literature,<sup>6,9</sup> according to the flowchart shown in figure 1. Briefly, it consists of six steps: Step 1, translation, literary translation of the questionnaire from English to Portuguese, by translator 1 (T1) and translator 2 (T2), one layperson and one from the health area; Step 2, synthesis, assessment of the T1 and T2 Portuguese versions of the questionnaires by the project author together with the translators of Step 1 to verify divergences and prepare an intermediate consensual version, called T-12; Stage 3, pre-pilot test, application of the intermediate version (T-12) to at least ten patients selected from the target audience, aiming at assessing the clarity of the language - each patient answers the T-12 version individually and, when delivering the completed questionnaire, the physician asks about doubts in the patient's understanding and interpretation; Step 4, synthesis and reformulation, review of translated items based on the answers and observations made by the first ten patients - this phase comprises some minor changes, but keeping the semantics; Step 5, reverse translation, submission of the revised T-12 version to a reverse translation, from Portuguese into English, by a professional translator, who was not part of any of the initial translations, and preferably a native English speaker, for the reverse translation (RT) version; finally, Step 6, submission to an expert committee, examination of the latest English version (TR) by an "expert committee", composed of bilingual experts, in this case bilingual dermatologists, and by the author of the original questionnaire, Ramsey Alsarraff, with suggested adaptations being made as many times as necessary, to compare with the original version of the questionnaire and be accepted by the expert committee and by the author of the original questionnaire. In the end, there is the final translated and adapted version of the questionnaire.

We chose another general QOL questionnaire to statistically evaluate the correlation between it and the SROE: the Dermatology Life Quality Index (DLQI),<sup>12</sup> in its translated and validated Brazilian Portuguese version, because this version is already known in the dermatological environment.<sup>13</sup>

#### 2 - Sample size

The sample size regarding the minimum size of a sample for conducting factor analysis, according to Crocker and Algina,<sup>14</sup> is based on the general rule of using 10 subjects per variable, with a minimum of 100 subjects in the total sample. Therefore, as the score studied has six items, it was calculated

Box 1: Skin Rejuvenation Outcome Evaluation (SROE) questionnaire. <sup>10</sup>					
	Skin Rejuvenation Outcomes Evaluation (SROE)				
This questionnaire is designed to assist your surgeon in determining the best patient outcomes following skin resurfacing. Your comments are confidential and may be used to refine resurfacing procedures for future patients. Please circle the number that best characterizes you current opinion regarding the following questions:					
1 - I	How well do you like the	appearance and conditi	on of your facial skin		
No at all	Somewhat	Moderately	Very Much	Completely	
0	1	2	3	4	
2	- How much do your cu	rrent facial lines and wi	rinkles bother you?		
No at all	Somewhat	Moderately	Very Much	Completely	
0	1	2	3	0	
3 - Do you thin	nk the current appearanc	e of your facial skin ma	kes you look old in oth	ners' eyes?	
No at all	Somewhat	Moderately	Very Much	Completely	
0	1	2	3	0	
4 - Do you th	ink the condition of your	r facial skin limits your	social or professional a	ctivities?	
Always	Usually	Sometimes	Rarely	Never	
0	1	2	3	4	
5 - How confident are you that the appearance of your facial skin is the best that it can be?					
No at all	Somewhat	Moderately	Very Much	Completely	
0	1	2	3	4	
6 - Would you like to alter the appearance and condition of your facial skin?					
Definitely	Most likely	Possibly	Probably not	No	
0	1	2	3	4	

ETAPA 1	• TRADUÇÃO EM DUAS VERSÕES -> T1 e T2	
ΕΤΑΡΑ 2	• SÍNTESE DAS VERSÕES -> T-12	
ΕΤΑΡΑ 3	• TESTE PRÉ-PILOTO -> PÚBLICO ALVO	
ΕΤΑΡΑ 4	SÍNTESE E REFORMULAÇÃO	
ΕΤΑΡΑ 5	• TRADUÇÃO REVERSA -> TR	
ΕΤΑΡΑ 6	SUBMISSÃO AO COMITÊ ESPECIALISTA	

**FIGURE 1:** Flowchart of the methodology for the translation of a quality of life questionnaire, according to Beaton *et al.*, 2000.<sup>9</sup>

Box 2: Word change in the translation of the OOL questionnaire after the synthesis and

reformulation step				
٢	Version T-12 Version T-12 after pre-pilot test			pilot test
Item 4: Do you think th social or	the state of your facial skin limits your Item 4: Do you think the appearance of your facial s r professional activities? your social or professional activities?		of your facial skin limits activities?	
Box 3: Translati	on of the Assessment of S Avaliação dos Resulta	kin Rejuvenation Outc Idos de Rejuvenescime	omes (SROE) into Brazilia ento da Pele (ARRP)	n Portuguese:
	Avaliação dos Resulta	dos de Rejuvenescimen	ito da Pele (ARRP)	
Este quest os pacient ser usad futuro. Por favor,	ionário foi desenhado para a es submetidos ao rejuvenesci os para refinar os procedimen circule o número que melho	uxiliar seu médico a de imento da pele. Seus con ntos de rejuvenesciment or caracteriza a sua opin	terminar os melhores resulta nentários são confidenciais o de pele para outros pacier ião atual a respeito das segu	dos para e podem ites no intes perguntas:
1 - O q	uão satisfeito(a) você esta	á com a aparência e o	condição da pele do seu	rosto?
Nem um pouco	Um pouco	Moderadamente	Muito	Completamente
0	1	2	3	4
2 - O quão inc	comodado(a) você está co	om as linhas de expre	essão e rugas do seu roste	o atualmente
Nem um pouco	Um pouco	Moderadamente	Muito	Completamente
4	3	2	1	0
3 - Você acre	edita que a aparência da <sub>l</sub> a	pele do seu rosto faz os olhos dos outros?	com que você pareça ma	ais velho(a)
Nem um pouco	Um pouco	Moderadamente	Muito	Completamente
4	3	2	1	0
4 - Você acha	que a aparência da pele o	do seu rosto limita su	as atividades sociais ou j	profissionais?
Sempre	Geralmente	Algumas vezes	Raramente	Nunca
0	1	2	3	4
5 - O quanto você está confiante que a aparência da pele do seu rosto está na melhor condição possível?				
Nem um pouco	Um pouco	Moderadamente	Muito	Completamente
0	1	2	3	4
6 - Você gostaria de alterar a aparência e condição da pele do seu rosto?				
Definitivamente	Provavelmente sim	Possivelmente	Provavelmente não	Não
0	1	2	3	4
	Escore final (0 a 100) = Soma dos pontos / $24 \ge 100$			

that a sample of 60 subjects would be sufficient and 100 would be ideal for carrying out this analysis. Regarding the test-retest, it is necessary to evaluate 16 patients to detect a difference of 50% of the standard deviation between the assessments, considering a power of 90%, an  $\alpha$  of 0.05, and a correlation between the measurements of 0.8. This calculation was performed using the WINPEPI 11.65 program.^{15}

#### 3 - Casuistry

Patients treated at the XXX Corrective Dermatology Outpatient Clinic between August 2019 and June 2021 (from March to August 2020, activities were suspended due to the Covid-19 pandemic), of any sex and gender, over 18 years of age, and who had an indication of some facial aesthetic procedure were invited to participate in the study. After signing the informed consent form (ICF), the SROE questionnaire in its final translated version and also the DLQI, in that order, were delivered to each patient individually in a closed and quiet environment, where they could respond calmly and without external interferences.

#### 4 - Statistical analysis

The data were entered in the Excel program and later exported to the SPSS v. 20.0 for statistical analysis. The values of the questions and the total score were described by the mean, median, standard deviation, 25th, and 75th percentiles, and minimum and maximum. We used Cronbach's alpha to assess the internal consistency and Exploratory Factor analysis to describe the behavior of the scale in the sample considered. Also, we included the six items of the score to perform Factor Analysis, and the factor extraction method was the Varimax orthogonal rotation. The correlation between ARRP and DLQI was performed using Pearson's correlation coefficient and the test-retest by comparing pre and post-data by Student's t-test for paired samples and the intraclass correlation coefficient between measurements. A significance level of 5% was considered statistically significant.

#### RESULTS

The translation process followed the six steps described in the methods, using a private translation agency with native, non-native, and sworn translators. We applied the T-12 consensus version to ten patients at the XXX Corrective Dermatology outpatient clinic to assess language clarity. Two patients had doubts in only one word from one SROE item (questionnaire item 4), and it was replaced by a synonym without any damage to the semantics of the sentence (Chart 2). The expert committee was composed of the authors of this article, and the author of the original questionnaire, Ramsey Alsarraff, approved the TR version.

Sixteen patients participated in the test-retest stage. This assessment found good temporal stability in the measurements. The intraclass correlation coefficient (ICC) between the measurements was 0.995 (p<0.001). There was no statistically significant difference in the scores obtained between the test and the retest.

Thus, we concluded the final translated and adapted version of a specific questionnaire to evaluate the outcomes and quality of life in patients with indications for cosmetic procedures. This questionnaire was called "Assessment of Skin Rejuvenation Results" (Avaliação dos Resultados de Rejuvenescimento da Pele - ARRP), and Table 3 shows its ready-to-use translation. In addition to the first ten patients who entered the initial translation process, 107 patients were included in this study, with a mean age of 53.9 years (standard deviation of 14.5), 95.3% of which were women.

The individual analysis of the questions measured by Cronbach's alpha was above 0.70 in each item, and the total value between the questions was 0.79, indicating good internal consistency of the scale.

The DLQI score also showed good internal consistency (Cronbach's  $\alpha$ =0.86) in the same sample. We found a strong and inverse, statistically significant correlation between the ARRP and DLQI scores (r= -0.67, p<0.001), that is, as the ARRP increases, the DLQI score decreases (Chart 1).

#### DISCUSSION

Translating and adapting validated QOL questionnaires into other languages is probably more important than creating new assessment instruments. The advantage is to allow results to be compared consistently across different countries and cultures. Thus, there must be standardization in the translation and adaptation of the questionnaires.<sup>9</sup>

The DLQI (Dermatology Life Quality Index), in its translated and adapted version into Portuguese, has been used in studies of the most prevalent dermatoses that impact the patient's QOL, such as psoriasis and atopic dermatitis.<sup>12,13</sup> It is especially valid for chronic and symptomatic diseases, is directed to symptoms, and has general questions. Therefore, it is not suitable for aesthetic complaints.

In this context, for a more detailed and individualized analysis of several other dermatoses, specific questionnaires were created, such as MelasQol for melasma, RosaQol for rosacea, Acne-QoL for acne, and VitiQoL for vitiligo, among others. They were later translated and adapted to our language and culture.<sup>16-19</sup> Consequently, a more specific evaluation concerning aesthetic complaints was gaining space in the literature, and specific questionnaires were also developed to assess procedures, most North Americans and a few still in the process of translation and adaptation to our language and culture.<sup>20</sup>

Kosowski *et al.*, in 2009, in a systematic review, found 442 publications of questionnaires answered by patients, 47 regarding the evaluation of facial cosmetic procedures. Of these, only nine publications met the validation criteria. In English, these specific questionnaires validated for assessing QOL before and after performing cosmetic procedures vary according to the number of items, the complexity of understanding, and score calculations.<sup>20</sup> Almost all of them have plastic surgeons' patients as their target audience and not dermatologists. For example, the FACE–-Q – satisfaction with appearance scale questionnaire, recently translated into Brazilian Portuguese in a journal, is a little more extensive and complex because it assesses other aspects of patient dissatisfaction/satisfaction, including relationships with the clinic staff, adverse events of surgical procedures, and financial cost, among others. Also, there are separate questions for each





location on the face, such as nose, mouth, and eyes, providing a segmented overview of the analysis.<sup>21,22</sup>

SROE was published and validated by Ramsay Alsarraff, a plastic surgeon, between 2000 and 2002, in American English, aimed at evaluating the results and impact on quality of life in patients undergoing facial rejuvenation procedures. In the same period, Alsarraff also published three other specific questionnaires intended for evaluating techniques related to the rhinoplasty, the Rhinoplasty Outcomes Evaluation (ROE), the facelift, the Facelift Outcomes Evaluation (FOE), and blepharoplasty, the Blepharoplasty Outcomes Evaluation (BOE). These, already used in several other publications and international research,<sup>23,24</sup> and the FOE have already gone through transcultural translation into Brazilian Portuguese.<sup>8</sup>

SROE is a questionnaire comprising only six items, is easy to understand, and has a short execution time. These characteristics were essential for our choice of questionnaire to translate and validate. The instrument displays the answer options on a Likert-type scale, which scores from zero to four points. The final score of the ARRP questionnaire (the translated SROE questionnaire) is calculated through the simple sum of the points of the answers marked by the patient, divided by 24 and multiplied by 100, generating a score that varies from 0 to 100 (Figure 2). The higher this score, the better the individual's QOL.

A Brazilian study evidenced the positive impact on the quality of life of patients undergoing cosmetic procedures, using the WHOQOL-bref (Portuguese version of the WHO Quality



FIGURE 2: Calculation of the final score of the ARRP questionnaire (SROE)

of Life Assessment Instrument). It is a wellness and general health questionnaire with no specific questions about complaints and aesthetic evaluations.<sup>25</sup>

Specific questionnaires have been gaining more and more space for a more reliable and detailed analysis of results and impact on QOL. In the case of questionnaires in cosmiatry, the items created address the patient's aesthetic complaint, but preserve three essential characteristics for any psychometric analysis: reliability, which translates into the ability to produce consistent and reproducible scores; validity, which is the ability to measure what is intended, and responsiveness, which is the sensitivity in detecting a difference.<sup>26</sup>

#### CONCLUSION

This study makes public and available the ARRP questionnaire (SROE), translated and validated for the Brazilian language and culture, aimed at evaluating outcomes and the impact on the quality of life of facial procedures in cosmiatry.

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#### **AUTHORS' CONTRIBUTION:**

#### Jaqueline Barbeito de Vasconcellos D ORCID 0000-0002-9726-0719

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Daniela Alves Pereira Antelo D ORCID 0000-0001-8203-1772

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Rosane Orofino-Costa D ORCID 0000-0002-1603-418X

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

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# Evaluation of an educational intervention on skin cancer in the context of the covid-19 pandemic

Avaliação de uma intervenção educativa sobre câncer de pele realizada no contexto da pandemia da covid-19

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#### ABSTRACT

**Introduction**: Skin cancer is one of the most prevalent neoplasms, and melanoma is its most aggressive form. It is responsible for most deaths due to its high metastatic potential. The early diagnosis affects the patients' prognosis and can be encouraged by educating the population regarding self-examination of the skin and recognition of salient characteristics of the lesions.

**Objectives:** To evaluate the impact of an educational video intervention on skin cancer with the application of a questionnaire before and after the intervention.

**Methods:** Prospective quasi-experimental study that included patients assisted in the dermatology service of a public hospital in Belo Horizonte.

**Results:** 196 patients were included. Although most participants recognized the importance of monitoring with a dermatologist (81.1%), most were unaware of melanoma (70.9%). There was a significant change in knowledge about skin neoplasms, especially regarding the ABCDE mnemonic (P<0.01). Conclusions: The educational intervention contributed to increasing significantly the participants' knowledge about skin cancer. With the contact restrictions imposed by the COVID-19 pandemic, actions that disseminate information and encourage self-examination of the skin become even more essential for early diagnosis.

Keywords: Knowledge; Dermatology; Education; Melanoma; Skin neoplasms

#### RESUMO

**Introdução:** o câncer de pele é uma das neoplasias prevalentes, e o melanoma consiste em sua forma mais agressiva por ser responsável pela maioria das mortes devido ao seu alto potencial metastático. O diagnóstico precoce afeta o prognóstico do paciente e pode ser estimulado educando-se a população quanto à realização do autoexame da pele e ao reconhecimento de características marcantes das lesões.

**Objetivos:** avaliar o impacto de uma intervenção educativa em vídeo sobre câncer de pele com a aplicação de questionário antes e após a intervenção.

**Métodos:** estudo prospectivo quase-experimental que incluiu os pacientes assistidos no Serviço de Dermatologia de um hospital público de Belo Horizonte.

**Resultados:** 196 pacientes foram incluídos. Apesar de a maioria dos participantes reconhecer a importância do acompanhamento com o médico dermatologista (81,1%), a maior parte desconhecia o melanoma (70,9%). Houve significativa mudança no conhecimento sobre neoplasias de pele, principalmente no que diz respeito ao mnemônico do ABCDE (p<0,01). **Conclusões:** a intervenção educativa contribuiu para aumentar significativamente o conhecimento do sparticipantes acerca do câncer de pele. Com as restrições de contato impostas pela pandemia da COVID-19, ações que disseminem informações e estimulem o autoexame da pele se tornam ainda mais essenciais visando ao diagnóstico precoce.

Palavras-chave: Conhecimento; Dermatologia; Educação; Melanoma; Neoplasias cutâneas.

## **Original Article**

#### Authors:

Gabriela Souza Diniz Ricardo<sup>1</sup> Luciana Monteiro Gontijo<sup>1</sup> Mariana Azevedo Santa Bárbara<sup>1</sup> Rafaella Morés Artifon<sup>1</sup> Gláucia Vianna<sup>1</sup>

<sup>1</sup> Faculdade Ciências Médicas de Minas Gerais, Belo Horizonte (MG), Brazil.

Correspondence:

Gabriela Souza Diniz Ricardo Email: gabrielasouzadr@gmail.com

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#### INTRODUCTION

Skin cancer is one of the most prevalent neoplasms, and non-melanoma is the most frequent in both sexes. In Brazil, the National Cancer Institute José Alencar Gomes da Silva/Ministry of Health (INCA/MS) estimated 177,000 new cases for each year of the 2020-2022 triennium, with 83,770 cases in men and 93,160 in women. Regarding melanoma skin cancer, an estimated 4,200 new cases in men and 4,250 in women are estimated.<sup>1</sup>

Although less prevalent, the incidence of primary cutaneous melanoma is increasing. It is the most aggressive form of skin cancer, accounting for most deaths due to its high metastatic potential. Its treatment is usually curative if there is early detection of the disease. Thus, it is necessary to recognize a potentially malignant lesion to reduce the number of cases, increase the chances of cure, and lessen expenses with the various treatments the patient must undergo.<sup>2</sup>

Early diagnosis of melanoma is essential for treatment success. Thus, doctors and patients must be familiar with the disease. Knowledge of risk factors, including skin phototypes I and II, age over 40 years, positive family history of skin cancer, and prolonged sun exposure, especially in childhood and adolescence, is essential.<sup>3,4</sup>

Skin self-examination facilitates early detection of melanoma. It should be performed periodically and is represented by the ABCDE mnemonic, created to assist in the early diagnosis of the disease and stimulate the search for a dermatologist in case of clinical suspicion.

In this context, basic health education actions in places with a large circulation of the Public Healthcare System (Sistema Unico de Saúde – SUS) users are responsible to raise awareness and encourage attitudes and behaviors that favor health care. University extension programs show their importance in the relationship between institutions and society. This type of initiative makes it possible to bring together and exchange knowledge and experiences between teachers, students, and the population.<sup>5,6</sup>

Due to this demand, the Academic League of Dermatology of a teaching institution in Belo Horizonte developed the extension project "Look at your skin". The program brings the community dermatological information related to skin cancer and photoprotection, encouraging skin self-examination and, consequently, early detection of potentially malignant lesions.

This study aims to assess the population's knowledge and habits regarding skin cancer and sun exposure, promoting greater discussion and analysis on this subject, in addition to evaluating the effectiveness of an educational action promoted by the Academic League, adapted to the context of the COVID-19 pandemic.

#### **METHODS**

It is a prospective study with a quasi-experimental design, with analysis in two phases (before and after an educational intervention). We used convenience sampling based on the acceptance to participate in the research. Quasi-experimental research, before and after type, involves manipulating a variable (educational intervention), where the individual is the control. Thus, data are collected both before and after an intervention.

The study intended to answer the research question: "What is the effectiveness of an educational intervention on skin cancer in a population treated at a reference hospital in Brazil?". The research took place between March 2020 and January 2021. In total, 196 patients treated at a tertiary care center in Dermatology of a public hospital located in Belo Horizonte, Minas Gerais, participated in the investigation.

People over 18 years of age, literate, regardless of sex and race, and who had been or were patients at the institution were included in the research. Likewise, individuals under 18 years of age, illiterate, or who refused to respond to the questionnaire were excluded from the study.

Data were obtained through a questionnaire developed by the authors based on the scientific literature and adapted for the online format since the face-to-face approach became impossible due to the social isolation imposed by the COVID-19 pandemic. All participants were informed about the ethical aspects involved in the research by reading the Free and Informed Consent Form (ICF) present in the first part of the report and could only proceed with the online questionnaire after indicating that they agreed to participate.

The questionnaire presented two steps: the first step included questions about the characterization of the sample, comprising sociodemographic characteristics of the volunteers (age, sex, education), family income, skin phototypes (skin phototype I: very light skin, burns easily, never tans; II: fair skin, burns easily, tans very little; III: light brown skin, burns moderately and tans moderately; IV: moderate brown skin, burns little, tans easily; V: dark brown skin, burns rarely, tans a lot;VI: black skin, never burns, always tans), and skin cancer history in the family. The second step of the questionnaire included closed questions regarding the participants' knowledge on skin cancer, such as its prevalence and the main characteristics possibly found in potentially malignant lesions. In addition, to assess the participants' visual recognition of skin cancer, we included five images at the end of the questionnaire, three of potentially malignant lesions.

To assess the knowledge acquisition, the participants answered the questionnaire in two moments: at the beginning of the research (including stages one and two) and after the intervention, which consisted of a video prepared by the team containing the main information regarding skin cancer, when they answered again the step two. Then, the participants evaluated the importance of the information and, based on them, whether they would pay more attention and change their skincare.

Categorical variables were presented as absolute and relative frequencies and numerical variables as mean  $\pm$  standard deviation and median (1st quartile – 3rd quartile). The comparison between paired categorical variables was performed using the McNemar and Multinomial tests, when appropriate. The analyzes were performed using the R software version 4.0.3 and a significance level of 5% was considered. We assessed a total of 196 participants, of which 124 (63.3%) were women.

The Research Ethics Committee of the institutions involved approved this research under the numbers 25805319.6.0000.5134 and 25805319.6.3001.5138.

#### RESULTS

The sample consisted of 196 patients, 124 women (63.3%). The mean age found among the participants was 43.1 years ( $\pm$  10.8). Concerning the level of education, the 196 subjects had some level of education, with 10.2% (n=20) with incomplete primary education and 11.2% (n=22) with complete higher education.

Regarding monthly family income, 5.6% (n=11) of the participants received up to 1 minimum wage; 27% (n=53) received between 1 and 3 minimum wages; 29.1% (n=57) received from 3 to 6 minimum wages; 20.9% (n=41) received from 6 to 9 minimum wages; 13.3% (n=26) received from 9 to 12 minimum wages; and 4.1% (n=8) received between 12 and 15 minimum wages.

Concerning the skin phototype, 9.7% of the individuals declared themselves as skin phototype I (n=19); 18.4% (n=36) as skin phototype II; 21.4% (n=42) as skin phototype III; 19.9% (n=39) as skin phototype IV; 20.4% (n=40) as skin phototype V; and 10.2% (n=20) as skin phototype VI.

When asked about their sun protection measures (Table 1), 29.1% (n=57) of participants declared they did not use any protection; 45.9% (n=90) wore clothes to cover more skin; 36.2% (n=71) avoided sunbathing between 10 am and 4 pm; 32.1% (n=63) wore hats or caps; 24% (n=47) used sunscreen; 3.6% (n=7) used parasols as sun protection. Adding the sun protection measures used, one subject used the five measures questioned; 19.9% of respondents (n=39) used one of the sun protection measures; 35.2% (n=69) used two measures; 12.2% (n=24) used three measures; and 3.1% (n=6) used four sun protection measures. As for the use of sunscreen, 76% (n=149) said they did not use it.

Regarding knowledge of skin cancers, 70.9% (n=139) had never heard about melanoma; 97.4% (n=191) had never heard about squamous cell carcinoma; and 94.4% (n=185) had never heard about basal cell carcinoma.

When comparing the rates of correct answers to the questions before and after the intervention, we observed that 30 participants (15.3% of the total) answered the question "What is the most common type of cancer among Brazilians?" correctly. After the intervention, 195 participants (99.5%) answered the same question correctly. When asked "Does family history (family members who had or have skin cancer) increase the chances of having skin cancer?", 117 subjects (59.7%) answered it correctly before the intervention and 193 participants (98.5%) answered it correctly after the intervention.

#### **TABLE 1: Sun protection measures**

	Statistic
What sun protection measures do	you use?
Don't use any measures	57 (29.1)
Clothes that cover the more skin	90 (45.9)
Avoid sunbathing between $10 \text{ am} - 4$	71 (36.2)
pm	
Hats or caps	63 (32.1)
Sunscreen	47 (24.0)
Parasols	7 (3.6)
Number of sun protection measur	es used
0	57 (29.1)
1	39 (19.9)
2	69 (35.2)
3	24 (12.2)
4	6 (3.1)
5	1 (0.5)
Do you use sunscreen?	
Yes	47 (24.0)
No	149 (76.0)
Have you ever heard of melanoma	?
Yes	57 (29.1)
No	139 (70.9)
Have you ever heard of squamous carcinoma (SCC)?	cell
Yes	5 (2.6)
No	191 (97.4)
Have you ever heard of basal cell of	carcinoma (BCC)?
Yes	11 (5.6)
No	185 (94.4)

Regarding the statement: "It is extremely important that everyone follow up their 'spots' with dermatologists to avoid skin cancer", the correct answers went from 81.1% in the pre--intervention (n=159) up to 100% in the post-intervention.

Concerning the questions that requested participants to indicate the meaning of the mnemonic "ABCDE" (Table 2), in the pre-test, 15.3% (n=30) could indicate what A meant; 36.7% (n=72) could say the meaning of B; 37.8% (n=74) got the meaning of C right; 23% (n=45) answered the meaning of D correctly; and 23% (n=45) knew the meaning of E. After the intervention, no question was answered correctly by all participants. The question about A reached 73.5% (n=144) of correct answers; B, 93.9% (n=184); C, 89.8% (n=176); D, 65.3% (n=128); and E, 90.3% (n=77) of correct answers.

Table 2. Comparison between skin cancer answers before and after the intervention				
	<b>Pre-intervention</b>	Post-intervention	P-Value	
What is the most common	n type of cancer among Brazilians	s?	<0.001M	
Colon and rectum	23 (11.7)	0 (0.0)		
Mama	45 (23.0)	1 (0.5)		
Skin	30 (15.3)	195 (99.5)		
Prostate	74 (37.8)	0 (0.0)		
Lung	24 (12.2)	0 (0.0)		
Does family history (famil getting skin cancer?	ly members who have had or have	e skin cancer) increase the chances of	<0.001N	
Yes	117 (59.7)	193 (98.5)		
No	79 (40.3)	3 (1.5)		
Do you know the ABCDE	of melanoma?		<0.001N	
Yes	23 (11.7)	192 (98.0)		
No	173 (88.3)	4 (2.0)		
It is extremely important cancer. Is it true?	that everyone follow up their "spo	ots" with dermatologists to avoid skin	<0.001N	
Yes	159 (81.1)	196 (100.0)		
No	37 (18.9)	0 (0.0)		
Considering that the ABC $- C - D - E$ ) and that these	DE consists of 5 lesion characteri se indicate malignancy, indicate w	stics, beginning with these letters (A – B hat you believe the letter A means	<0.001N	
Altitude	61 (31.1)	6 (3.1)		
Area	74 (37.8)	32 (16.3)		
Arrangement	31 (15.8)	14 (7.1)		
Asymmetry	30 (15.3)	144 (73.5)		
Indicate what you believe	the letter B means		<0.001M	
Blister	54 (27.6)	9 (4.6)		
Borders	72 (36.7)	184 (93.9)		
Bleach	37 (18.9)	2 (1.0)		
Bright	33 (16.8)	1 (0.5)		
Indicate what you believe	the letter C means		<0.001N	
Cilium	21 (10.7)	1 (0.5)		
Color	74 (37.8)	176 (89.8)		
Consistency	57 (29.1)	8 (4.1)		
Crust	44 (22.4)	11 (5.6)		
Indicate what you believe	the letter D means		<0.001N	
Density	48 (24.5)	10 (5.1)		
Diameter	45 (23.0)	128 (65.3)		
Distension	65 (33.2)	39 (19.9)		
Distribution	38 (19.4)	19 (9.7)		
Indicate what you believe the letter E means			<0.001M	
Elasticity	28 (14.3)	0 (0.0)		
Elevation	45 (23.0)	10 (5.1)		
Enlargement	56 (28.6)	9 (4.6)		

Evolving	67 (34.2)	177 (90.3)	
Please indicate below which	lesions you believe are at great	er risk of progressing to skin cance	r, melanoma or
non-melanoma			
1	125 (63.8)	196 (100.0)	<0.001N
2	74 (37.8)	159 (81.1)	<0.001N
3	59 (30.1)	0 (0.0)	<0.001N
4	117 (59.7)	24 (12.2)	<0.001N
5	70 (35.7)	191 (97.4)	<0.001N
1, 2 and 5	6 (3.1)	139 (70.9)	<0.001N

(M) Multinomial Test; (N) McNemar test

In the questions using images of skin lesions (Figure 1) and asking which ones had the highest risk of evolving to skin cancer, melanoma, or non-melanoma, the pre-intervention test had only 3.1% (n=6) of correct answers regarding the right combination of images (1, 2 and 5), and, after the intervention, this percentage rose to 70.9% (n=139).<sup>7</sup>

At the end of the questionnaire, all participants judged the information as important (Table 3); 99.5% stated that they would pass this information on to other people; 96.9% stated that they would change their skincare after learning from the research.

#### DISCUSSION

The extension project "Look at your skin", developed by the Academic League of Dermatology of a teaching institution in Belo Horizonte, is an action for the primary prevention of skin cancer that uses the informative booklet of the Brazilian Society of Dermatology as a tool for information. The intervention is conducted in public spaces in Belo Horizonte – Minas Gerais, such as parks and squares, and the academics involved are responsible for guiding the participants on the association between the sun and skin cancer, applying sunscreen, using appropriate clothing, wearing hats and sunglasses, staying in the shade, and limiting sun exposure. They are also responsible for expanding knowledge about the most frequent skin neoplasms (melanoma, squamous cell carcinoma, and basal cell carcinoma), reinforcing the most striking characteristics of each one of them, encouraging the skin self-examination and periodic follow-up with a dermatologist to contribute to the early diagnosis of these skin lesions.

However, in 2019, the outbreak of the SARS-CoV-2 virus occurred in China, culminating in a global pandemic, requiring the adoption of severe preventive measures, including home isolation, one of the measures adopted to contain the spread of the virus and prevent its main complication, the severe acute respiratory syndrome. From this perspective, most outpatient procedures and dermatological treatments were postponed, except for emergency consultations and cancer patients. Given the



FIGURE 1: Images used to assess the participant's recognition of potentially malignant lesions

Table 3: Importance of information			
Statistic			
Do you think the information received is important?			
Yes	196 (100.0)		
No	0 (0.0)		
Will you pass this information on to others?			
Yes	195 (99.5)		
No 1 (0.5)			
Will you change your skin care?			
Yes	190 (96.9)		
No 6 (3.1)			

evolution of this health crisis, dermatologists have adopted the use of telemedicine as the best solution for the imposed social distance. Nevertheless, although it is a way of treating patients more safely, it limits the performance of a complete skin examination and the evaluation of pigmented lesions.<sup>7,8</sup>

A delay in diagnosing and treating skin cancer, especially melanoma, can lead to an increase in morbidity, mortality, and costs to the health system. Thus, initiatives related to population education and skin cancer screening, including the project "Look at your skin", developed by the Academic League, should be adapted to alternative models of prevention campaigns based on the same original principles, but exploring the various information services currently available that allow people to connect remotely.

A randomized clinical trial conducted at a California Department of Dermatology compared the effectiveness of written and video educational materials on individuals' understanding of melanoma. The results provided evidence that online videos are a more effective tool than written materials, that is, information leaflets. The population studied rated the video intervention as being more attractive and could perform better in the evaluative questionnaire applied by the team of researchers.<sup>9</sup>

Our project, conducted through the delivery of informative booklets, had to undergo modifications so that the intervention could continue to benefit the local community and disseminate information about skin cancer, even with the limitations imposed by the pandemic. The solution found was to transform the approach into a video and assess the retention of information through a self-administered online questionnaire in a population served at a Dermatology referral service.

Regarding the predominance of women among the study participants (63.3%), it is related to the fact that, based on the bibliographic review conducted by the researchers, there is a greater predominance of women in dermatological consultations, suggesting greater gender care concerning aesthetics and skin protection against the harmful effects caused by sun exposure. Also, some studies revealed a prevalence of skin neoplasms in women, which could arouse the interest of this group in receiving more information on the subject.<sup>10,11</sup>

The mean age found was 43.1 years, showing that the sample is composed of relatively young individuals located in the economically productive age group and who use more the means of communication currently available.

Regarding the frequency of sunscreen use by the respondents, we observed that about 76% of participants do not use sunscreen. This data highlights the need to conduct initiatives that reinforce the importance of its use in preventing skin neoplasms associated with educating the population on its correct use. The disuse of this sunscreen may be related to the high cost it represents in the population's budget and to the fact that it does not belong to the list of medicines provided by the Public Healthcare System (SUS), since 61.6% of the participants declared a monthly family income between one and six minimum wages. In this context, it is also necessary to encourage the recurrent use of physical sun protection, such as hats, shirts that cover the skin, and parasols, as they are more affordable and durable items.<sup>12</sup>

Another worrying factor found in the present study is related to the participants' level of prior knowledge about skin cancer. Approximately 70% of patients had never heard about melanoma. This prevalence worsens when analyzing the level of knowledge of non-melanoma skin cancers: more than 95% were unaware of these lesions.

The lack of knowledge on skin neoplasms may be related to the low level of education of the participants, considering that 68.3% of them had, at most, completed high school. Factors related to increased risk of skin cancer include low socioeconomic status and lower education.<sup>13,14</sup>

The evaluation of the educational approach was based on the participants' knowledge of the aspects that characterize the identification of melanoma using the acronym of the screening criteria in the visual examination of pigmented skin lesions, the ABCDE mnemonic (asymmetry, irregular borders, color variation, diameter >6 mm, and lesion evolution). We also used images of pigmented skin lesions to assess whether participants would be able to identify in practice the aspects that visually characterize melanoma. We could observe that the ability to recognize malignant skin neoplasms improved significantly after the intervention.

A randomized clinical trial conducted in Chicago recruited 100 volunteers, selected from those who met the inclusion criteria of having no prior history of counseling on how to perform skin self-examination. Volunteers participated in the educational intervention, and pre-assessment and post-assessment questionnaires were administered before and after the approach to evaluate the retention of transmitted information. The study concluded that determining the presence of the ABCDE criterion is a challenging skill. However, the intervention significantly contributed to improve the participants' ability to perform skin self-examination and identify potentially malignant lesions.<sup>15</sup> Likewise, our study sought to assess the participants' degree of knowledge on aspects involving the identification of potentially malignant pigmented skin lesions before and after an educational intervention, seeking to improve skills related to skin self-examination.

The questionnaire applied before the educational approach represented the first contact of research participants with information about skin neoplasms and how to perform skin self-examination. Regarding the assessment of knowledge on the aspects involving the ABCDE mnemonic and the recognition of potentially malignant lesions, it was evident that most participants did not know the information necessary to identify melanoma correctly. Only 11.7% declared knowing the method before the educational intervention. Similarly, it was possible to observe a significant discrepancy in the aspects that make up the identification of these lesions, such as asymmetry, irregular edges, color variation, diameter, and evolution. Only 3.1% of the participants could identify the correct combination of images corresponding to malignant melanocytic lesions.

The questionnaire applied after the intervention showed a significant increase in the correct answers than the questionnaire applied after the intervention. The right combination of images corresponding to malignant melanocytic lesions increased to 70.09%. It shows that educational actions, such as those conducted by the Academic League, seem to be efficient for raising awareness of the population about skin neoplasms, such as performing self-examination and how to use sun protection measures correctly.

A study based on 3,187 cases of melanoma skin cancer in the state of São Paulo showed the total cost and the unit cost of treating the neoplasm based on its staging. Stage 0 melanomas, which are lesions in situ, represented, at the time, a unit cost for the SUS of R 382.84. For the treatment of advanced stage melanomas, III and IV, the cost was R 30,969.67 and R32,054.23, respectively.<sup>16,17</sup>

The difference between the cost of treating early-stage and advanced-stage melanoma is significant. More than 95% of treatment costs are destined for the most advanced stages, increasing the importance of awareness and prevention campaigns. The recognition of potentially neoplastic lesions allows the patient to seek medical help early, reducing the chances of metastases and the need for prolonged treatments, with onerous costs for the SUS. Thus, educational campaigns in the video can educate the population to seek care in the disease's early stages and protect themselves from harmful sun exposure.

The main limitation of this study is its design in two phases, before and after an educational intervention. The fact that it is not a randomized clinical trial prevents the impact observed on the factors studied from being exclusively attributed to the educational intervention performed. Another aspect is that only literate individuals with access to the internet and mobile communication media were included, considering that illiteracy would prevent them from responding to the self-administered questionnaire. Also, it is noteworthy that the study was conducted in a public reference center, which makes the sample directed to a population with a lower socioeconomic level, limiting the generalization of the results.

#### CONCLUSION

Due to the low cost of production, the ease of distribution, and the accessible language, using a video proved to be an effective communication tool in the study. The high costs necessary to treat an advanced neoplasm justify the implementation of educational campaigns, in the video, to raise awareness of the population about sun protection and potentially neoplastic skin manifestations. This way, individuals can seek specialized medical care when recognizing potentially malignant lesions and effectively protect themselves from ultraviolet radiation.

Also, educational actions involving the recognition of potentially neoplastic skin lesions that encourage the self-examination need to be encouraged, especially during the COVID-19 pandemic, which limited the patients' contact with the dermatologists. Through these initiatives, it is possible to draw the patients' attention to the warning signs of the disease, boosting the immediate search for a specialist in view of the recognition of the characteristics that surround it.

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#### **AUTHORS' CONTRIBUTION:**

**Gabriela Souza Diniz Ricardo** ORCID 0000-0003-3596-4558 Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review; critical revision of the manuscript

#### Luciana Monteiro Gontijo 🝺 ORCID 0000-0002-7173-6379

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; critical literature review.

### Mariana Azevedo Santa Bárbara 问 ORCID 0000-0002-9870-3892

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review; critical revision of the manuscript.

### Rafaella Morés Artifon 🝺 ORCID 0000-0003-2996-1131

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review; critical revision of the manuscript.

#### Gláucia Vianna D ORCID 0000-0003-2070-3750

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; critical literature review; critical revision of the manuscript.

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### Skin cancer awareness campaign in Southern Brazil: A retrospective cohort study

Campanha de prevenção ao câncer de pele no Sul do Brasil: uma coorte retrospectiva

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#### ABSTRACT

**Introduction:** Skin cancer is the most frequent malignant neoplasm in Brazil. Its prognosis is directly related to early diagnosis and institution of adequate treatment. The Skin Cancer National Awareness Campaign (SCNAC) is an essential tool to prevent and detect malignant skin lesions.

**Objectives:** To investigate the incidence of skin cancer and the accuracy of dermoscopy in patients assessed at the SCNAC.

**Methods:** We conducted a retrospective cohort study using directly the data collected from the population assisted at the SCNAC day in 2016, 2017, and 2018 at Clinical Center of the Universidade de Caxias do Sul (CECLIN-UCS).

**Results:** Of the 634 patients included, 105 were referred for biopsy with histopathological study of the lesion. Dermoscopy was suggestive of a malignant lesion in 55 cases. Biopsy diagnosed malignant lesions in 43 patients and benign lesions in 32 patients. Thus, the sensitivity and specificity of the test were 86% and 50%, respectively. The accuracy of dermoscopy in identifying malignant lesions over the three years of the campaign was around 70%.

**Conclusions:** Dermoscopy in SCNAC has a good level of sensitivity and specificity when correlated with final histopathological results.

Keywords: Dermatology; Dermoscopy; Observational study; Skin neoplasms; Health promotion

#### RESUMO

**Introdução:** o prognóstico do câncer de pele está diretamente relacionado ao diagnóstico precoce. As campanhas nacionais de prevenção ao câncer de pele (CNPCPs) consistem em um importante veículo de prevenção e detecção das lesões malignas de pele.

**Objetivos:** investigar a incidência do câncer de pele e a acurácia da dermatoscopia em pacientes atendidos na CNPCP. **Métodos:** um estudo de coorte retrospectiva foi realizado utilizando diretamente os dados coletados da população atendida no dia da CNPCP dos anos de 2016, 2017 e 2018 no Centro Clínico da Universidade de Caxias do Sul (CECLIN-UCS).

**Resultados:** dos 634 pacientes incluídos no estudo, 105 foram encaminhados para realização de biópsia com estudo histopatológico da lesão. A dermatoscopia foi sugestiva de lesão maligna em 55 casos. A biópsia diagnosticou lesões malignas em 43 pacientes e lesões benignas em 32 pacientes. Sendo assim, no estudo, a sensibilidade e a especificidade do exame foram de, respectivamente, 86 e 50%. Pode-se concluir que a acurácia da dermatoscopia na identificação de lesões malignas ao longo dos três anos de campanha foi de cerca de 70%.

**Conclusões:** a dermatoscopia nas CNPCPs apresenta um bom nível de sensibilidade e especificidade quando correlacionada aos resultados finais de exame histopatológico.

Palavras-chave: Dermatologia; Dermoscopia; Estudo Observacional; Neoplasias Cutâneas; Promoção da Saúde.

### **Original Article**

**Authors:** 

Grasiela Cassia Monteiro<sup>1</sup> Carolina Matté-Dagostini<sup>2</sup> Pedro Henrique Lodi<sup>2</sup> Samantha Lia Ziotti-Bohn-Gonçalves-Soares<sup>2</sup> Fernando De-Marco-Dos-Santos<sup>1</sup>

- <sup>1</sup> Universidade de Caxias do Sul, Medical School, Caxias do Sul (RS), Brazil.
- <sup>2</sup> Universidade de Caxias do Sul, Medical School, Caxias do Sul (RS), Brazil

#### Correspondence:

Grasiela Cassia Monteiro Email: gcmonteiro@hotmail.com

Financial support: None Conflict of interest: None

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#### INTRODUCTION

Melanoma and non-melanoma skin cancer (squamous cell carcinoma and basal cell carcinoma) are the most frequent neoplasm in Brazil, corresponding to 27% of all malignant tumors.<sup>1</sup> It is estimated that the number of new cases will increase in the coming years, with a higher incidence in Santa Catarina (SC) and Rio Grande do Sul (RS) in the southern region of Brazil.1 Current evidence indicates that early diagnosis with dermoscopic evaluation and timely treatment reduces skin cancer mortality and morbidity.<sup>2,3</sup>

Dermoscopy is a non-invasive test to assess skin lesions.<sup>4</sup> However, histopathological examination is necessary for diagnostic confirmation.<sup>2</sup> Previous studies suggest that dermoscopy increases the diagnostic accuracy of skin neoplasms compared to the naked eye examination.<sup>5-7</sup> Previous meta-analysis indicated that the sensitivity of dermoscopy associated with clinical examination for the diagnosis of melanoma was 90% (95% CI 80-95) with a specificity of 90% (95%CI 57-98).<sup>8</sup>

Primary and secondary prevention of skin cancer in the adult population through interventions in skin cancer awareness campaigns has been proven to improve the diagnostic rate and can reduce the mortality of these neoplasms.<sup>9-11</sup> Thus, the Brazilian Society of Dermatology (Sociedade Brasileira de Dermatologia – SBD) has promoted, since 1999, the National Skin Cancer Awareness Campaign (NSCAC). It consists of a day in December reserved for a free examination of the population by dermatologists, through dermoscopy and biopsies, associated with guidelines on sun exposure habits and skin cancer prevention.

The data collected at the NSCAC can be analyzed to present an overview of the prevention and detection of skin cancer in this population. Therefore, this study aims to investigate the incidence of skin cancer and the accuracy of dermoscopy of patients treated in the National Skin Cancer Awareness Campaign held at the University of Caxias do Sul (RS) during the years 2016, 2017, and 2018.

#### METHODS Study design

A multidisciplinary team of dermatologists, clinicians, surgeons, pathologists, nurses, and academics from the Medical School develops the National Skin Cancer Prevention Campaign, promoted by the Brazilian Society of Dermatology. It takes place annually at the Clinical Center of the University of Caxias do Sul (CECLIN-UCS) in Caxias do Sul (RS), Brazil. The campaign encompasses dermatological examination, histopathological diagnosis, clinical and surgical treatment, guidance, and patients' follow-up.

The evaluators are responsible for filling out a standard form for each patient seen on the day of the campaign and, later, forwarding it to the Brazilian Society of Dermatology.

We conducted a retrospective cohort study using the data collected from the population assisted on the NSCAC day in 2016, 2017, and 2018 at CECLIN-UCS. The information obtai-

ned from the standard forms completed on the days of the campaigns was transcribed into a Microsoft Excel spreadsheet. The anatomopathological examinations were transcribed by consulting the medical records of patients undergoing skin biopsies.

# Standard form of the National Skin Cancer Prevention Campaign

The standard form presented a table for recording age, biological sex, and skin phototype according to the Fitzpatrick classification; participant's degree of sun exposure; the presence of previous pathological history, family history, or risk factors for the development of skin cancer; how the individual learned about the campaign; clinical hypothesis according to dermoscopy; evolution time or location if lesion present; treatment conducted from the first service in the campaign; histopathological result after biopsy of a suspicious lesion.

#### **Research Ethics Committee**

The Research Ethics Committee of the University of Caxias do Sul (CEP-UCS) previously approved this study under the number 24951659.3.0000.5.341. The principles of the Declaration of Helsinki were followed.

#### **Population studied**

To be included, patients had to: (1) be participating in the NSCAC of the respective year; (2) be  $\geq 18$  years of age. Incomplete forms were excluded from the analysis. In total, 634 patients were included in the study.

#### Endpoints

The primary endpoint was the accuracy of dermoscopy for the diagnosis of skin lesions. Secondary endpoints were: (1) skin cancer incidence by type; (2) analysis of the epidemiological characteristics of the participants of the NSCAC.

#### **Statistical analysis**

The authors used IBM's SPSS version 23.0 for Microsoft Windows. Frequency and accuracy measurements were obtained.

#### RESULTS

Table 1 shows the sample variables. The study included 634 patients, 62.1% women and 37.9% men. In the consultations, the responsible dermatologist classified all individuals according to their skin phototypes following the Fitzpatrick classification. Skin phototype II represented 48.1% of the sample, and it was the most identified, followed by: skin phototype III (37.9%), I (9.5%), IV (7.6%), V (2.8%), and VI (2%). Only 8.4% of patients reported not exposing to the sun. About 62.3% of the subjects usually exposed to the sun without sun protection, and only 29.2% exposed to the sun using protection. Of the participants, 11.8% had a previous pathological history of skin cancer, and 21.3% had a positive family history of skin cancer.

TABLE 1: Proportions of variables found in the sample			
Variables analyzed in the sample	Proportion of the variable in the sample (%)		
Men	38		
Women	62		
Skin phototype by Fitzpatrick classification	III - 37.9		
	I - 9.5		
	IV- 7.6		
	V - 2.8		
	VI - 2		
Sun exposure	Exposure without sun protection - 62.3 Exposure with sun protection - 29.2		
	Don't expose to the sun $-8.4$		
Personal history of skin cancer	11.8		
Family history of skin cancer	21.3		
Presence of risk factors for skin cancer	70		
Presence of skin lesions	97.95		
Location of the skin lesion	Head and neck - 40		
	Trunk – 17		
	Limbs - 16		

Thus, approximately 70% of the sample was classified as having recognized risk factors for malignant skin neoplasms.

g **DISCUSSION** 

We expected the participants to have skin lesions and seek clarification, guidance, and conduct about them when necessary. This demand was present in 98% of the sample. We asked the patients about the evolution time of their main lesion: 30.4%reported  $\leq 1$  year; 31.4%, between 1 and 2 years; and 30.4%,  $\geq 3$ years. Of the total sample, the examining physician did not describe the lesion site in 52 patients. Of those who did, 40% of lesions were located in the head, 17% in the trunk, and about 16% in the limbs.

Of the 634 patients included in the research, 105 were referred for biopsy with the histopathological study of the lesion. Among these, we had access to the results of 75 patients, which represents 71% of the sample. Dermoscopy was suggestive of a malignant lesion in 55 cases and non-suggestive in 20 cases. Biopsy diagnosed malignant lesions in 43 patients and benign lesions in 32 patients. Thus, in the study, the sensitivity and specificity of the test were 86% and 50%, respectively. The positive and negative predictive values were 69% and 72%, respectively. We concluded that the accuracy of dermoscopy in identifying malignant lesions over the three years of the campaign was around 70%. In this context, table 2 demonstrates the correlation between dermoscopy and histopathological study in identifying malignant skin lesions.

NSCACs are essential for early diagnosis as they enable better monitoring of skin lesions and greater adherence to health promotion. Consequently, it is suggested that they act to reduce morbidity and mortality and trigger a more favorable prognosis.

The number of exams performed each year shows a growing trend, indicating higher adherence to NSCAC and its importance in controlling this diasease.<sup>12</sup> On the other hand, unfortunately, the proportion of skin cancer in the population has increased over the years. In the present study, adherence to NSCAC was higher in individuals who already had skin lesions or risk factors for neoplasms and had a family history of cutaneous neoplasms.

The estimate of new cases of skin cancer is higher among women in Brazil.<sup>1</sup> Studies suggest that women also have more significant participation in skin cancer prevention campaigns. Likewise, in the sample assessed, greater adherence of the female population to NSCAC is suggested. Also, this population is likely to be more attentive to protection strategies and more careful with sun exposure and the use of sunscreen.<sup>12</sup> However, women are also more likely than men to sunbathe and use tanning methods.<sup>13</sup>

Regarding the subtypes of skin cancer, non-melanoma is the most frequent, and basal cell carcinoma is the most frequent in this group. Melanoma skin cancer represents 3% of malignant skin tumors in Brazil. However, it has the worst prognosis, with high invasive and metastatic power.<sup>1,14,15</sup> In the evaluated sam-

From these numbers, it was possible to calculate the accuracy, sensitivity, specificity, and predictive values of dermoscopy				
	Histopathological study positive for neoplasia	Histopathological study negative for neoplasia		
Dermoscopy suggestive of neoplasm	n=37	n=16		
Dermoscopy not suggestive of neoplasia	n=6	n=16		
Total patients	n=43	n=32		

TABLE 2: Correlation between dermoscopy and histopathological study in the identification of malignant skin lesions. From these numbers, it was possible to calculate the accuracy, sensitivity, specificity, and predictive values of dermoscopy

ple, 60.5% of cases were diagnosed with basal cell carcinoma, 30.2% squamous with cell carcinoma, and 9.3% with melanoma, according to table 3. Simultaneously with the demographics of skin cancer,1 our research showed that the older the age, the greater the probability of having a diagnosis in NSCAC. That is, the incidence of cutaneous neoplasms increases with advancing age. According to an American analysis that followed 30 years of skin cancer screening in the United States, the diagnosis of melanoma doubled in individuals with an average age of 60 years and older. <sup>16,17</sup>

The use of sun protection is still lower than necessary, according to a survey in the city of Rio Grande (RS).<sup>18</sup> The study showed that the percentages of individuals in the NSCAC who did not use sunscreen in 2010 and 2011 were 53.01% and 45.58%, respectively. In this context, the present research showed that most patients (62.3%) of NSCAC, when exposed to the sun, did not use sun protection.

Regarding the relationship between skin phototype and suspected skin cancer, literature shows it is more frequent in skin phototypes I and II.<sup>19</sup> Skin phototype II patients were the most adept at NSCAC performed in the southern region of Brazil, with a percentage of 48.1%, followed by patients with skin phototype III, with 31.9%. Therefore, the probability of NSCAC diagnosing a neoplasm in these patients would be increased due to their greater participation.

TABLE 3: Results identified after performing an anatomo-
pathological study in patients who were indicated for
biopsy after performing dermoscopy

Variable	<b>N.</b>
Sample patients biopsied	105
Biopsy reports available	75
Patients diagnosed with malignant lesions	43
Basal cell carcinoma	26
Squamous cell carcinoma	13
Melanoma	4

Based on the data collected in three years of the campaign, the present study compared the ability of dermoscopy to identify malignant lesions to the histopathological study, considered the gold standard. The physician who performed the dermoscopy made his main clinical hypothesis and requested a biopsy for diagnostic confirmation. The comparison was established by relating these two variables to the malignancy or not of the lesion and presented an accuracy of 70%. Similar European studies propose a detection rate for melanoma skin cancer ranging from 0.1% to 2%. Dermoscopy was used in around 78-80% of examinations with clinical suspicion of melanoma, and full-body skin examination was performed in 72-86% of patients.<sup>19, 20</sup> By our results, research suggests that dermoscopy has high discriminatory power, reiterating that this technique also facilitates the detection of skin lesions at an early stage.<sup>9,19,21</sup> Also, an Australian meta-analysis showed that the odds of finding a melanoma were nine times greater with dermoscopy than with naked eye examination alone.8

In our study, the physician who performed the dermoscopy developed his chief clinical hypothesis and requested a biopsy for diagnostic confirmation. The comparison was established by relating these two variables to the malignancy or not of the lesion. It is known that several dermatologists participated in the three-year campaign, that dermoscopy is a component of the physical examination of the dermatologist and that, as it is examiner-dependent, its accuracy tends to improve with clinical practice. Therefore, it is noteworthy that we did not use criteria to determine how much the physician's experience improves the accuracy of the exam, although the authors recognize that this would be relevant in future studies.

#### **Strengths and limitations**

To the authors' knowledge, this is a differentiated study since it assesses the accuracy of dermoscopy for the first time in the southern region of Brazil. Furthermore, the number of participants was high (n=634), which provided statistical significance to the results. On the other hand, our study is also prone to bias. As this was a retrospective analysis, data on neoplasm subtypes and biopsy results could not be accessed. By including campaigns conducted in three consecutive years, we assumed that the evaluators comprised a heterogeneous group, which impacts the results of the accuracy of dermoscopy since the examiner experience has a direct relationship with the dermoscopy performance.

#### CONCLUSION

This study enabled us to conclude that dermoscopy in national skin cancer awareness campaigns has a good level of

sensitivity and specificity when correlated with the final histopathological results. It is one of the pioneering studies on the accuracy of dermoscopy in skin campaigns in Brazil. Thus, it confirms that a skin examination including dermoscopy increases diagnostic accuracy. Also, it was conducted in one of the regions with the highest prevalence of skin cancer in the country. Therefore, its results can guide future research and health promotion measures.

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#### AUTHORS' CONTRIBUTION:

#### Grasiela Cassia Monteiro D ORCID 0000-0001-5110-8626

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Carolina Matté-Dagostini D ORCID 0000-0003-4189-7339

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

### Pedro Henrique Lodi D ORCID 0000-0002-9981-0964

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

### Samantha Lia Ziotti-Bohn-Gonçalves-Soares D ORCID 0000-0003-1061-2580

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript

### Fernando De-Marco-Dos-Santos D ORCID 0000-0002-0366-7068

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.



# Surgical & Cosmetic Dermatology

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# Comparative study to evaluate the wound healing efficacy of topical formulations containing *Triticum aestivum L. (Triticum vulgare)* in a native human skin model

Estudo comparativo para avaliação da eficácia cicatrizante de formulações tópicas contendo Triticum aestivum L. (sinônimo Triticum vulgare) em modelo de pele humana nativa

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#### ABSTRACT

**Introduction:** Plant extracts and actives derived from plants were developed to improve and enhance the skin healing process including *Triticum aestivum L. (Triticum vulgare)*.

**Purpose:** To evaluate the effect of whole grain extract (EGTA-PR) and aqueous extract (EATA-FI) of *Triticum aestivum L.*, on ex vivo skin healing.

**Methods:** Skin fragments obtained from elective plastic surgery were subjected to tissue damage and treated with extracts for eight days for histological evaluation of re-epithelialization and immunofluorescence for epidermal growth factor (EGF).

**Results:** EGTA-PR and EATA-FI accelerated the re-epithelialization process in human skin culture submitted to tissue injury. Additionally, we observed increased EGF protein labeling after treatment with EGTA-PR.

**Conclusion:** EGTA-PR showed a better performance in re-epithelialization when compared to EATA-FI, as it presented a higher protein labeling for EGF in human skin culture. Likewise, the histological results showed that the dermal redensification obtained with EGTA-PR was visually superior to that observed with EATA-FI. The results obtained are promising and corroborate the several biological actions already reported in the literature for *Triticum aestivum L*. extract in tissue healing stages. **Keywords:** Regeneration; Epidermal growth factor; *Triticum; In vitro* techniques; Wound healing

#### RESUMO

**Introdução:** extratos vegetais e ativos derivados de plantas tem sido desenvolvidos com o objetivo de melhorar e potencializar o processo de cicatrização cutânea, dentre eles, o Triticum aestivum L. (sinônimo Triticum vulgare).

**Objetivo:** avaliar o efeito do extrato de grão inteiro (EGTA-PR) e extrato aquoso (EATA-FI) de Triticum aestivum L. na cicatrização cutânea em pele humana ex vivo.

**Métodos:** fragmentos de pele obtidos de cirurgia plástica eletiva foram submetidos a lesões teciduais e tratados com os extratos durante oito dias para avaliação histológica da reepitelização e marcação proteica do fator de crescimento epidérmico (EGF).

**Resultados:** EGTA-PR e EATA-FI aceleraram o processo de reepitelização em cultura de pele humana submetida a lesão tecidual. Adicionalmente, foi observado um aumento da marcação proteica de EGF após o tratamento com EGTA-PR.

**Conclusão:** EGTA-PR apresentou um melhor desempenho na reepitelização quando comparado ao EATA-FI, pois apresentou uma maior marcação proteica para EGF em cultura de pele humana. Da mesma forma, os resultados histológicos mostraram que a redensificação dérmica obtida com o EGTA-PR foi visualmente superior à observada com EATA-FI. Os resultados obtidos são promissores e corroboram as diversas ações biológicas já reportadas na literatura para extrato de Triticum aestivum L. nas etapas da cicatrização tecidual.

Palavras-chave: Regeneração; Fator de Crescimento Epidérmico; Triticum; Técnicas in vitro; Cicatrização

# Original article

Authors:

Brayan Styven Merchan Rojas<sup>1</sup> Jose Luis De-la-hoz<sup>1</sup> Gustavo Facchini<sup>2</sup> Gustavo Henrique da Silva<sup>2</sup> Ana Lúcia Tabarini Alves Pinheiro<sup>3</sup> Samara Eberlin<sup>2</sup>

- <sup>1</sup> Megalabs SAS, Research and Development, Bogotá, Cundinamarca, Colombia.
- <sup>2</sup> Kosmoscience Group, Skin Vitro, Pre-Clinical Safety and Efficacy Laboratory, Valinhos (SP), Brazil.
- <sup>3</sup> Kosmoscience Group, Clinical Research, Valinhos (SP), Brazil.

#### Correspondence:

Samara Eberlin Email: samara@kosmoscience.com Alternative email: samara.eberlin@ gmail.com

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#### INTRODUCTION

Tissue healing is a dynamic and complex process composed of four phases: hemostasis, inflammation, proliferation, and tissue remodeling. After tissue injury, a clot is formed followed by infiltration of neutrophils, macrophages, and endothelial cells, promoting an inflammatory and immune response and providing tissue reconstruction.<sup>1</sup>

This metabolic arsenal produces cytokines, chemokines, and growth factors, stimulating and activating cell proliferation and migration, orchestrating the healing process.<sup>1-2</sup> Among the growth factors, we highlight the epidermal growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF- $\beta$ ), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and insulin-like growth factor (IGF).<sup>3-4</sup>

FGF, TGF- $\beta$ , and PDGF stimulate fibroblast infiltration at the lesion site. TGF- $\beta$  and PDGF also initiate phenotypic changes in these cells, converting fibroblasts into myofibroblasts that line the edges of the extracellular matrix, generating a constrictive force for wound closure.<sup>5-6</sup>

Hours after the damage, the re-epithelialization process begins, releasing EGF,TGF- $\beta$ , FGF, and keratinocyte growth factor (KGF or FGF7), which stimulate the migration and proliferation of epithelial cells. Once the wound is closed, keratinocytes start the process of stratification and differentiation to restore the barrier.<sup>7-8</sup>

Matrix formation requires the removal of granulation tissue. Then the structure is saturated with proteoglycans and glycoproteins. Tissue remodeling involving TGF- $\beta$ -mediated synthesis of new collagen and cleavage of old collagen by PDGF follows this step. The end product of this process is healing tissue.<sup>7-8</sup>

The healing success depends on growth factors, cytokines, and chemokines involved in a harmonic integration of signals that coordinate cellular processes. We assessed the effects of two herbal products for topical use containing standardized extracts of the species *Triticum aestivum L. (synonym: Triticum vulgare)* for skin re-epithelialization and tissue growth factors production using an experimental model of native human skin.

#### **METHODS**

Megalabs SAS, Bogota, Colombia, supplied the topical herbal products containing standardized extracts of *Triticum aestivum L. (Triticum vulgare)*. The chief formulation presents as an active ingredient the whole wheat Triticum aestivum L. grain extract (EG-TA-PR; PROCICAR REGENERIX®). This extract is obtained under standardized time, lighting, and temperature conditions that favor the seeds' activation and germination for subsequent aqueous extraction. These conditions favor the starch enzymatic hydrolysis and oligosaccharides production with certain molecular weights associated with pharmacological activity. To compare the specificities of each extraction method, we evaluated in parallel the biological responses produced by an herbal formulation containing *Triticum aestivum L.* aqueous extract (EATA-FI; FITOSTIMOLINE<sup>®</sup>). The study used human skin from a 36-year-old female donor, skin phototype II, who underwent elective plastic surgery in the abdominal region (abdominoplasty). After the surgical procedure, the skin fragments were collected in plastic bottles with 0.9% saline solution and kept under refrigeration for up to 24 hours. This project does not include the storage and stock of biological material for future use. Therefore, the remaining fragments were properly disposed of as infectious waste. The Research Ethics Committee of Universidade São Francisco – SP, CAAE 82685618.9.0000.5514, approved the use of human skin fragments from elective surgery for this study under the number 2,493,285.

Human skin was fractionated into 12 fragments of approximately 1.5 cm<sup>2</sup>, distributed in triplicate to each of the four experimental groups (Table 1). The basal control group was maintained as the experimental control during the eight days, with only culture medium changes every 48 hours. The positive control included only tissue injury without treatment. The groups treated with EGTA-PR and EATA-FI were submitted to tissue lesions with a scalpel, treated daily with the evaluated products in the proportion of 25–30 mg/cm<sup>2</sup>, and kept in an incubator at 37°C in the presence of 5% of CO<sub>2</sub> for eight consecutive days.

The skin fragments containing tissue lesions were treated during all incubation days. Then, the fragments were submitted to histological analysis to assess the epidermal re-epithelialization by hematoxylin & eosin staining (Sigma, San Luis, MO, USA) and to perform the immunofluorescence assay for EGF. We also collected skin culture supernatants for the quantification of KGF and TGF- $\beta$ .

For histological evaluation, skin fragments were embedded in Tissue-Tek® O.C.T.<sup>TM</sup>, and then serial 12 micron sections were collected directly on cryostat silanized slides (Leica Biosystems, Buffalo Grove, IL, USA). The sections were washed with phosphate buffer and incubated overnight with anti-EGF (Bioss, Woburn, MA, USA). Subsequently, the sections were rinsed again and incubated for one hour with Alexa Flour 488-Secondary Antibody (Life Technologies, Calsbad, CA, USA). We performed a further incubation with DAPI (4'-6-diamidino--2-phenylindole; DNA tag; Sigma) followed by washes with phosphate buffer.

TABLE 1: Experimental study groups				
Experimental group	Tissue injury – scalpel	Product treatment		
Basal control	_	_		
Positive control – tissue injury	Х	-		
EGTA-PR	Х	Х		
EATA-FI	Х	Х		

Slides were prepared using specific mounting media and analyzed under a microscope (Olympus, Tokyo, Japan) using standard CellSens software (© 2010 Olympus Corporation). We evaluated the intensity of the fluorescence parameter emitted by specific antibody labeling. After obtaining the images, the fluorescence intensity was quantified using the ImageJ software (version 1.48; Arbitrary Units – U.A.).

Quantification of KGF and TGF- $\beta$  was conducted in the supernatant by enzyme immunoassay, using a kit purchased commercially (R&D Systems, Minneapolis, MN, USA). The absorbance reading was performed at 450 nm in a Multiskan GO monochromator (Thermo Scientific, Waltham, MA, USA).

The statistical evaluation used the ANOVA test to measure the variation of the results, comparing the data between the groups. Then, the Bonferroni post-test was applied, strengthening and making the ANOVA result more accurate. A significance level of 5% (GraphPad Prism v6) was used.

#### RESULTS

Figure 1 presents the results of the re-epithelialization process in fragments of native human skin submitted to tissue injury and treated with the EGTA-PR and EATA-FI formulations.

We can observe that the skin fragments submitted to the scalpel cut showed a tissue lesion in the epidermis and dermis. After eight days of culture, the group submitted only to the lesion showed a sign of re-epithelialization (represented by the black arrows in figure 1). However, the skin fragments submitted to both treatments with EGTA-PR and EATA-FI showed a higher re-epithelialization compared with the untreated group. Treatment with the formulations also demonstrated an improvement in dermal regeneration, visualized by redensification of the extracellular matrix, with emphasis on treatment with EGTA-PR.



**FIGURE 1:** Histological evaluation (Hematoxylin & eosin staining) of the cutaneous healing process in human skin fragments submitted to tissue injury with a scalpel and treated with the herbal formulations EGTA-PR (Wheat Whole Triticum aestivum L Grain Extract.) and EATA -FI (Triticum aestivum L. aqueous extract) for eight consecutive days. Black arrows represent the extent of re-epithelialization. The reference bar corresponds to 100 µm



**FIGURE 2:** Fluorescent immunostaining of EGF in human skin fragments subjected to tissue injury with a scalpel and treated with herbal formulations EGTA-PR (Wheat whole *Triticum aestivum L*. grain extract) and EATA-FI (*Triticum aestivum L*. aqueous extract) for eight consecutive days. The EGF protein is labeled in green, and the blue label represents the cell nucleus (DNA-DAPI; Thermo). The reference bar corresponds to 50 µm

Figures 2 and 3 show the results of immunostaining and semi-quantitative analysis of EGF, respectively, in *ex vivo* skin fragments submitted to tissue injury with a scalpel and treated with the EGTA-PR and EATA-FI formulations.

Figure 3 represents the quantification of the fluorescence intensity of EGF through analysis of the images obtained in Figure 2. We can observe that the fragments submitted only to tissue injury with a scalpel showed a reduction of 57.18% in the production of EGF regarding the basal control (P<0.001) after eight days of culture. Treatment with the EGTA-PR formulation promoted an increase of 98.68% (P<0.001) in the production of EGF compared to the group submitted only to tissue injury. On the other hand, the EATA-FI formulation did not show significant changes in the production of EGF compared to the group with tissue injury.

#### DISCUSSION

Skin tissue integrity plays a vital role in interfacing with the external environment. Therefore, the occurrence of damage to this organ can result from an unsightly scar to the systemic disruption of the health of the being it involves.

Despite several modern skin care and treatment, healing does not always occur harmoniously. Tissue recovery after the damage is a complex process, dependent on the various cell types and mediators interacting in a highly sophisticated temporal sequence. It is a dynamic process, triggered in response to tissue injury, aiming to repair matrix and cellular damage and restore the integrity of the skin barrier, going through four overlapping phases: hemostasis, inflammation, proliferation, and remodeling.<sup>9</sup>

The healing process begins with the hemostasis phase, which consists of a blood clot formation that fills the lesion to stop bleeding and preserve tissue structures. This step is linked to



FIGURE 3: Semi-quantitative analysis of the fluorescence intensity of EGF synthesis in human skin fragments subjected to tissue injury with a scalpel and treated with the herbal formulations EGTA-PR (Wheat whole Triticum aestivum L. grain extract) and EATA-FI (Triticum aestivum L. aqueous extract) for eight consecutive days. Data represent the mean ± standard deviation of six areas (ANOVA, Bonferroni)

the formation of a temporary matrix, the secretion of cytokines, and other growth factors that, when interacting with the components of the extracellular matrix (ECM), trigger the entire repair process. Subsequently, neutrophils under the influence of macrophages initiate the inflammatory phase, clearing the site of bacteria and debris and releasing pro-inflammatory cytokines and more growth factors responsible for the recruitment and activation of fibroblasts and epithelial cells.<sup>10</sup>

The proliferative phase begins, on average, on the third day of the injury and it is characterized by the reconstruction of the injured tissue and the increase in the number of cells at the wound site due to the migration and proliferation of fibroblasts, endothelial cells, and keratinocytes.<sup>11</sup> During this phase, fibroblasts, in the presence of newly formed blood vessels, proliferate actively and synthesize ECM components that, in addition to their structural role, fulfill a signaling function, regulating the later stages of remodeling. This last phase occurs when the wound surface is contracted, a new epithelium is developed, and the final scar tissue is formed. In this study, we assessed the effects of two topical formulations containing standardized extracts of *Triticum aestivum L. (Triticum vulgare)* on the skin re-epithelialization process, using an experimental model of human skin culture.<sup>12-13</sup> The results showed that the formulation containing the whole wheat *Triticum aestivum L.* grain extract (EGTA-PR) and *Triticum aestivum L.* aqueous extract (EATA-FI) could accelerate the reepithelialization process after eight days of treatment in human skin culture submitted to tissue lesion. Additionally, increased dermal redensification and protein EGF labeling was observed, particularly after treatment with EGTA-PR.

It is essential to highlight that the results obtained with the formulation containing the whole *Triticum aestivum L*. grain extract (EGTA-PR) were more effective than those containing the aqueous extract (EATA-FI) in the parameters evaluated in this study. It is due to the particularities of the different processes for obtaining these extracts, which affect the phytochemical composition and, consequently, the pharmacological specificity. These findings are crucial for the skin healing process, as they indicate the beginning of a proliferative phase that precedes remodeling and the formation of new tissue.<sup>14</sup> The role of epidermal growth factor (EGF) has been extensively investigated in normal wound healing and pathological conditions and is implicated in keratinocyte migration, fibroblast function, and granulation tissue formation.<sup>15</sup>

Skin wound healing has been studied for decades, and several plant extracts and plant-derived actives have been developed to improve and potentiate the repair process. Among them, *Triticum aestivum L. (Triticum vulgare)* has been widely used in traditional medicine thanks to its acceleration of tissue repair properties.<sup>16-20</sup>

Several studies have shown that the *T. aestivum L.* extract could induce the proliferation of fibroblasts and endothelial cells, accelerating wound repair in part due to the presence of malto-oligosaccharides of molecular weight greater than 1000.<sup>21-25</sup> *In vivo* studies in animal models confirmed this action, where the extract regenerated skin lesions.<sup>25</sup> In addition to the extracts regenerating properties, further evidence indicated its ability to reduce the inflammatory response and prevent irreversible tissue damage.<sup>26</sup>

Tito et al. also showed an action of the *T. aestivum L.* (*T. vulgare*) extracts in stimulating the synthesis of fibronectin, a key component in the formation and organization of the extracellular matrix, and also of the enzyme hyaluronan synthase 2, a precursor of the acid hyaluronic acid.<sup>9</sup> These same authors attributed the property of restoring the skin barrier to the extract due to increased ceramides synthesis.<sup>9</sup>

Several extracts and isolated fractions of *T. aestivum L.* were assessed and confirmed the ability of this species in different mechanisms involved in the tissue regeneration process. However, the results reported in the literature and the data presented in this study demonstrate that the applied extraction me-

thod, in addition to the pharmacotechnical basis, is mandatory in the observed biological activity, making comparative performance studies difficult.

The results presented in this research constitute a predictive study using the experimental model of human skin from elective plastic surgery. This system represents, among the alternative methods, the one that is closest to a real condition of use, as it preserves the characteristics of the native skin cell population. Despite the promising results obtained in improving the tissue repair process, additional studies in this model and clinical ones are necessary to prove effectively this *Triticum aestivum L*. extracts action.

#### CONCLUSION

The speed and robustness of the tissue repair process are essential to forming an adequate and esthetically acceptable scar. Despite various modern care and treatments, the use of herbal products plays a vital role in wound healing, especially in complementary medicine. In this study, we assessed the effect of two herbal products for topical use containing standardized extracts of Triticum aestivum L. (Triticum vulgare) on wound healing, using an ex vivo model of skin re-epithelialization. The results allowed us to infer that the whole grain extract (EGTA-PR) presented a better performance in re-epithelialization than the aqueous extract (EATA-FI), as it presented a significantly higher EGF synthesis in human skin culture. Likewise, the histological results show that the dermal redensification obtained with EGTA-PR was visually superior to that observed with the aqueous extract. Although further studies are necessary, the results obtained with the whole wheat Triticum aestivum L. (Triticum vulgare) grain extract (EGTA-PR; PROCICAR REGENERIX®) are promising and corroborate the numerous biological actions already reported in the literature in the stages of tissue healing.

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#### **AUTHOR'S CONTRIBUTION:**

Brayan Styven Merchan Rojas D ORCID 0000-0003-4322-1084

Approval of the final version of the manuscript; study design and planning; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.

Jose Luis De-la-hoz D ORCID 0000-0001-9944-8961

Study design and planning; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.

**Gustavo Facchini O CCID** 0000-0003-0111-7596 Statistical analysis; study design and planning; data collection, analysis, and interpretation.

**Gustavo Henrique da Silva** D ORCID 0000-0003-0215-2246 Statistical analysis; study design and planning; data collection, analysis, and interpretation.

Ana Lúcia Tabarini Alves Pinheiro D ORCID 0000-0002-0226-2544 Study design and planning; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases.

Samara Eberlin D ORCID 0000-0001-7001-801X Preparation and writing of the manuscript; critical literature review.

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# Does SARS-CoV-2 vaccination affect the immediate effect of botulinum toxin? First impressions

A vacinação contra SARS-CoV-2 afeta o efeito imediato da toxina botulínica? Primeiras impressões

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#### ABSTRACT

**Background:** The SARS-CoV-2 infection has spread worldwide rapidly since its identification at the end of 2019. Globally, until April 2021, there have been more than 150 million confirmed cases of Co-vid-19, including over 3 million deaths. Therefore, a race was promptly started to produce an effective vaccine against the new virus. Botulinum toxin injection remains the leading non-surgical cosmetic procedure worldwide, with a high rate of efficacy and patient satisfaction.

Aims: This study aims to analyze the association between the SARS-CoV-2 vaccine and the immediate botulinum toxin response.

**Materials and Methods:** This was an observational, retrospective, and multicenter study. Data were collected between April and June 2021, and a medical record review of 71 patients from 27 to 76 years old treated with botulinum toxin injection.

**Results and Conclusion:** There were no meaningful changes in the immediate outcome of patients vaccinated for Covid-19 and botulinum toxin. However, it is vital to underline that follow-up and further studies are needed to define whether the Covid-19 vaccine can alter the duration of effect and efficiency of the botulinum toxin.

Keywords: Covid-19; Botulinum toxins type A; Vaccination

#### RESUMO

**Introdução:** A infecção por SARS-CoV-2 se espalhou rapidamente pelo mundo desde sua identificação no final de 2019. Globalmente, até abril de 2021, houve mais de 150 milhões de casos confirmados de Covid-19, incluindo mais de 3 milhões de mortes. Portanto, uma corrida foi prontamente iniciada para produzir uma vacina eficaz contra o novo vírus. A injeção de toxina botulínica continua sendo o principal procedimento cosmético não cirúrgico em todo o mundo, com alto índice de eficácia e satisfação do paciente.

**Objetivos:** Este estudo tem como objetivo analisar a associação entre a vacina SARS-CoV-2 e a resposta imediata à toxina botulínica.

**Materiais e Métodos:** Estudo observacional, retrospectivo e multicêntrico. Os dados foram coletados entre abril e junho de 2021, e revisão de prontuários de 71 pacientes de 27 a 76 anos que foram tratados com injeção de toxina botulínica.

**Resultados e Conclusão:** Não houve mudanças significativas no desfecho imediato dos pacientes vacinados para Covid-19 e toxina botulínica, mas é de suma importância ressaltar que são necessários acompanhamento e mais estudos para definir se a vacina Covid-19 é capaz de alterar a duração do efeito e a eficiência da toxina botulínica. **Palavras-chave:** Covid-19; Toxinas botulínicas tipo A; Vacinação em massa

### **Original Article**

#### Authors:

Bruna Souza Felix Bravo<sup>1</sup> Raquel Melo Carvalho<sup>1</sup> Laís Bezerra de Menezes Penedo<sup>1</sup> Fernanda Lourenço Prestes<sup>1</sup> Samantha Talarico<sup>2</sup> Sabrina Talarico<sup>2</sup> Sergio Talarico<sup>2</sup>

- <sup>1</sup> Bravo Clinic, Rio de Janeiro (RJ), Brazil.
- <sup>2</sup> Talarico Dermatology Clinic, São Paulo (SP), Brazil.

#### **Correspondence:**

Raquel Melo Carvalho Email: raqueldemelocarvalho@ gmail.com / Alternative E-mail: raqueldemelocarvalho@gmail. com

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#### INTRODUCTION

The SARS-CoV-2 infection has spread worldwide rapidly since its identification at the end of 2019.<sup>1</sup> Globally, until April 2021, there have been more than 150 million confirmed cases of Covid-19, including over three million deaths.<sup>2</sup>

According to the Plastic Surgery Statistics, over 7.6 million botulinum toxin type A injections were performed in 2019, only in the U.S.A, including onabotulinumtoxinA (Botox Cosmetic, Allergan, Inc., Irvine, CA), abobotulinumtoxinA (Dysport, Valeant Pharmaceuticals International, Montreal, Canada), and incobotulinumtoxinA (Xeomin, Merz Pharmaceuticals, Frankfurt, Germany). This number raised continually year after year: from 2018 to 2019, it increased by 4%, while in the past two decades (2000–2019), when the procedure became popular, it increased by 878%, according to the same statistical source.<sup>3</sup>

Botulinum neurotoxin (BoNT) is a neurotoxic protein produced by the bacterium Clostridium botulinum, used in medical practice.<sup>4</sup> The United States Food and Drug Administration (FDA) approved the OnabotulinumtoxinA (Botox<sup>®</sup>) and botulinum toxin type A (BoNT-A) for temporary improvement of glabellar lines and other noninvasive facial procedures in 2002.<sup>5</sup> The botulinum toxin injection remains the leading non-surgical cosmetic procedure worldwide, with a high rate of efficacy and patient satisfaction.<sup>6</sup>

In this pandemic scenario, a race started promptly to produce an effective vaccine against the new virus. A candidate vaccine against SARS-CoV-2 might act against infection, disease, or transmission. A vaccine capable of reducing these elements could contribute to disease control and prevent further morbidity and mortality.<sup>7</sup> The first vaccine was approved in December 2020, and currently, there are many valid vaccine options in the world. While we were developing this research, ANVISA (National Health Surveillance Agency) approved three vaccines for emergency use in Brazil: CoronaVac (Sinovac), Vaxzevria (AstraZeneca), BNT162b2 (Pfizer-BioNTech). Also, more options like the mRNA-1273 vaccine (Moderna) and JNJ-78436735 (Johnson & Johnson – Janssen) were available abroad.<sup>8</sup>

The Covid-19 pandemic may have changed patients' motivations and priorities for aesthetic procedures. The major ones were to do something positive, refresh their look, and gain confidence. Patients also referred to frustration, anxiety, stress, and disappointment when they couldn't perform aesthetic treatments due to the pandemic.<sup>9</sup>

As aesthetic physician experts, the authors have been asking themselves in their daily practice whether the SARS--Cov-2 vaccine can alter the botulinum toxin response. Considering that botulinum toxin is one of the foremost aesthetic procedures performed worldwide, and the Covid-19 vaccine should be offered to all individuals within the next years, this study aims to analyze the association between the SARS-CoV-2 vaccine and the immediate botulinum toxin response.

#### MATERIALS AND METHODS

We performed an observational, retrospective, and multicenter study for consecutive patients who underwent botulinum toxin (Botox<sup>®</sup>, Allergan; Dysport<sup>®</sup>, Galderma; Xeomin<sup>®</sup>, Merz) injection for aesthetic purposes after having received at least the first dose of SARS-Cov-2 vaccine from April to June 2021 at Bravo Clinic in Rio de Janeiro and Talarico Dermatologic Clinic in São Paulo, Brazil. The study procedure followed the principles of the 1996 Declaration of Helsinki and obtained informed consent from each participant. We performed this research following regional laws and good clinical practice for studies on human subjects. The authors reviewed subjects' basic information, photographs, image analysis results, and subjective assessments. A simple statistical analysis of the data was performed.

#### RESULTS

The sample investigated in this study consisted of n = 71 individuals: 9 men and 62 women. The mean age of the total sample was 48.6 years [range: 26 - 85] (Figure 1).

Fifty-three patients received two doses, while 16 patients received just one dose. Forty-five participants received Corona-Vac (Sinovac), 21 Vaxzevria (AstraZeneca), 4 Comirnaty (Pfizer), and 1 patient received mRNA-1273 (Moderna). Patients received the first dose of vaccines, on average, 1.94 months before the botulinum toxin injection – ranging between 8 months to 24 hours earlier. The mean interval of the second dose was 0.88 months prior, with a maximum limit of 3 months before and 1 month later. Twenty-eight patients (39.43%) were treated with onabotulinumtoxinA (Botox Cosmetic, Allergan, Inc., Irvine, CA), 36 (50.7%) with abobotulinumtoxinA (Dysport, Valeant Pharmaceuticals International, Montreal, Canada), and



Figure 1: Tables and graphics demonstrating the results of this study

7 (9.85%) with incobotulinumtoxinA (Xeomin, Merz Pharmaceuticals, Frankfurt, Germany). The same physician that injected the BoNT-A clinically assessed all the patients enrolled in this study within 14 to 26 days after the procedure. The results were classified as mild, moderate, or satisfactory according to the improvement of dynamic wrinkles in the treatment area. Neither the physicians nor the patients observed significant inferior outcomes in the immediate result of botulinum toxin injection after being vaccinated against SARS-Cov-2 compared to their previous experiences, classifying their results as satisfactory. Only one of our patients had a moderate outcome, thus demanding a higher dose of botulinum toxin to obtain a satisfactory response, which represented 1.4% of studied individuals. Based on the small sample size, the authors reinforce that further studies are necessary to corroborate these findings.

#### DISCUSSION

Botulinum toxin injection is a well-established non-invasive aesthetic procedure with a muscle relaxation function that works by partially blocking nerve impulses for any muscles that have been injected and reducing excessive contractions of these muscles.<sup>10</sup>

The potent zinc proteinase neurotoxin binds to extracellular receptors on cholinergic nerve terminals, cleaving one of the three (SNARE) soluble N-ethylmaleimide-sensitive factor attachment receptor proteins. This action causes reversible inhibition of acetylcholine release by presynaptic vesicles intracellularly, leading to a transient restraint of neurotransmitter release at the neuromuscular junction. SNARE proteins also play an identified role in neurons, recognized to release glutamate, and substance R. Their actions release bradykinin, prostaglandins, histamine, and serotonin, which are proinflammatory mediators.<sup>11</sup>

As proteins synthesized by living organisms (Clostridial bacteria), botulinum toxins are biological products as opposed to conventional synthetic drugs.<sup>12</sup>

The SARS-CoV-2 virus may lead to a severe inflammatory response via elevation of cytokine levels including IL-6, IL-10, and TNF- $\alpha$ .2. In addition to direct viral damage, excessive inflammation and increased pro-inflammatory cytokine levels including IL-6, IL-8, TNF- $\alpha$ , and IL-1 $\beta$  are associated with disease severity and outcome in Covid-19.<sup>13</sup>

The Covid-19 Vaccine AstraZeneca is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2. The SARS-CoV-2 S immunogen in the vaccine is expressed in the trimeric prefusion conformation. The coding sequence has not been modified to stabilize the expressed S-protein in the pre-fusion conformation. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally and stimulates neutralizing antibody and cellular immune responses, which may contribute to protection from Covid-19.<sup>14</sup>

CoronaVac is an inactivated vaccine candidate against Covid-19. SARS-CoV-2 (CN02 strain) was propagated in African green monkey kidney cells (WHO Vero 10-87 cells) to prepare the vaccine. At the end of the incubation period, the virus was harvested, inactivated with  $\beta$ -propiolactone, concentrated, purified, and finally adsorbed onto aluminum hydroxide. The aluminum hydroxide complex was then diluted in sodium chloride, phosphate-buffered saline, and water before being sterilized and filtered for injection.<sup>15</sup>

Pfizer-BioNTech Covid-19 (BNT162b2) vaccine, a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine, encodes the SARS-CoV-2 spike glycoprotein prefusion, the virus that causes coronavirus disease 2019 (Covid-19).Vaccination with the Pfizer-BioNTech Covid-19 vaccine consists of two doses (30  $\mu$ g, 0.3 mL each) administered intramuscularly, three weeks apart.<sup>16</sup>

Moderna Covid-19 (mRNA-1273) vaccine (Moderna-TX, Inc; Cambridge, Massachusetts), a lipid nanoparticle-encapsulated, nucleoside-modified mRNA vaccine, encodes the stabilized SARS-CoV-2 spike glycoprotein prefusion. Vaccination with the Moderna Covid-19 vaccine consists of two doses (100  $\mu$ g, 0.5 mL each) administered intramuscularly, one month (four weeks) apart.<sup>17</sup>

We performed a PubMed search to investigate if there are any reports about changes in the effect of botulinum toxin after vaccination, using the words "botulinum toxin & vaccine", "botulinum toxin & vaccination", and "onabotulinum toxin & vaccine". One relevant article was found, comparing the protein structure of botulinum and tetanus toxins.

The tetanus toxin and BoNTs A and B show 50% amino acid similarity,<sup>18,19</sup> and anti-tetanus toxin antibodies have been shown to bind to BoNTs A and B in vitro.<sup>20,21</sup> It has been theorized that prior Immunogenicity of botulinum toxins immunization against tetanus may prime a patient's immune system to BoNT.<sup>21</sup> A preclinical study conducted in mice showed that prior active immunity against tetanus toxins did not enhance the host antibody response against injected BoNT.<sup>21</sup> However, no clinical studies have been performed to examine whether this holds for humans.<sup>22</sup> As little is known about Covid-19, the relationship between the SARS-Cov-2 vaccine and a possible modification of the immediate response to botulinum toxin has been questioned.

Since the number of patients seeking BTX treatment keeps growing as the vaccination happens throughout the world and the majority of the population gets vaccinated, it is essential to reassure the safety and efficacy of the aesthetic use of botulinum toxin.

Our study observed no meaningful changes in the immediate outcome of the patients who underwent botulinum toxin injection after being vaccinated against SARS-Cov-2 with the CoronaVac and Astrazeneca vaccines. As just one of our patients demanded a higher dose of botulinum toxin to obtain the satisfactory previous result, representing only 1,4% of studied patients, our sample is small and further studies will be necessary to elucidate if it is relevant. The two main limitations of this study are the number of patients and their follow-up; however, this is an initial phase that could set the basis for future complete studies.

To the best of our knowledge, this is the first study analyzing the botulinum toxin immediate response in patients undergoing SArs-Cov-2 vaccination. This study is unprecedented and relevant because it aims to bring information about patients vaccinated for SARS-Cov-2 and treated with botulinum toxin in a moment when little is known about this disease. The injectors, who are experienced dermatologists, clinically evaluated all our patients.

#### CONCLUSION

There was no meaningful change in the immediate outcome of patients vaccinated for Covid-19 and submitted to botulinum toxin procedure. Because the number of patients seeking BTX treatment keeps growing as the vaccination happens throughout the world and the majority of the population gets vaccinated, it is essential to reassure the safety and efficacy of the aesthetic use of botulinum toxin.

It is paramount to underline that follow-up and further studies are necessary to define whether the Covid-19 vaccine can alter the duration of effect and efficiency of the botulinum toxin. There is a need to observe a larger number of cases and a longer follow-up, around six months.

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#### **AUTHORS' CONTRIBUTION:**

#### Bruna Souza Felix Bravo D ORCID 0000-0001-9692-7967

Approval of the final version of the manuscript; study design and planning; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.

#### Raquel Melo Carvalho D ORCID 0000-0002-3991-4569

Preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.

#### Laís Bezerra de Menezes Penedo D ORCID 0000-0002-8629-7196

Statistics analysis; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review.

Fernanda Lourenço Prestes D ORCID 0000-0001-5595-9639

Statistical analysis; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review.

#### Samantha Talarico (D ORCID 0000-0001-9220-6572

Author's Contribution: Approval of the final version of the manuscript; data collection, analysis, and interpretation; critical revision of the manuscript.

#### Sabrina Talarico (D ORCID 0000-0002-7133-4900

Approval of the final version of the manuscript; Data collection, analysis, and interpretation; critical revision of the manuscript.

#### Sergio Talarico (D ORCID 0000-0002-5606-077X)

Approval of the final version of the manuscript; study design and planning; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.

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# Melanoma mortality in the capitals of Northeast Brazil, 2001-2017: analysis by the regression model by inflection points

Mortalidade por melanoma nas capitais do Nordeste do Brasil. 2001-2017: análise pelo modelo de regressão por pontos de inflexão

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#### ABSTRACT

Introduction: Melanoma comprises 3% of all skin tumors and can produce metastasis with high mortality.

**Objective:** To analyze the temporal behavior of mortality from skin melanoma in the capitals of Northeast Brazil from 2001 to 2017.

Methods: We conducted an ecological time series study involving all deaths due to melanoma registered in the capitals of the Northeast region of Brazil from 2001 to 2017. Crude and standardized rates by the world and Brazilian populations were analyzed. We obtained the indicators from the National Cancer Institute (INCA). The regression model by inflection points was used in the statistical analysis, calculating the annual variation and the average annual variation percentages.

Results: There were 954 deaths from melanoma. The three rates analyzed showed a linear growth trend over the time series: proportional mortality increased from 2.1% to 8.28% (AAPC 6.0%; p<0.02), the crude mortality grew from 0.22 to 0.64/100 thousand (AAPC 5.0%; p<0.01) and the mortality adjusted by the world population in the capitals of the Northeast rose from 0.28 to 0.61/100 thousand (AAPC 2.7%; p<0.01).

Conclusion: Mortality from melanoma grew in the Northeastern capitals, with inequality between the sexes and according to the capitals.

Keywords: Epidemiology; Melanoma; Mortality; Skin neoplasms.

#### RESUMO

Introdução: o melanoma compreende 3% dos tumores de pele e apresenta capacidade de produzir metástase e elevada mortalidade.

**Objetivo:** analisar o comportamento temporal da mortalidade por melanoma de pele nas capitais do Nordeste brasileiro, no período de 2001 a 2017.

Métodos: realizou-se um estudo ecológico de séries temporais envolvendo todos os óbitos em decorrência de melanoma registrados nas capitais da região Nordeste no Brasil no período de 2001 a 2017. Analisaram-se as taxas brutas e padronizadas pelas populações mundial e brasileira. Obtiveram-se os indicadores do Instituto Nacional de Câncer (INCA). Na análise estatística, utilizou-se o modelo de regressão por pontos de inflexão, com cálculo do percentual de variação anual e o percentual de variação anual médio.

Resultados: registraram-se 954 óbitos por melanoma. As três taxas analisadas apresentaram tendência de crescimento linear ao longo da série temporal: a mortalidade proporcional passou de 2,1 para 8,28% (AAPC 6,0%; p<0,02); a mortalidade bruta passou de 0,22 para 0,64/100 mil (AAPC 5,0%; p<0,01); e a mortalidade ajustada pela população mundial nas capitais do Nordeste subiu de 0,28 para 0,61/100 mil (AAPC 2,7%; p<0,01).

Conclusão: a mortalidade por melanoma cresceu nas capitais do Nordeste, com desigualdades entre os sexos e de acordo com as capitais.

Palavras-chave: Epidemiologia; Melanoma; Mortalidade; Neoplasias cutâneas.

### **Original Article**

#### Authors:

Amanda Maria Sandes Lemos<sup>1</sup> Beatriz Gomes de Castro André Luis Oliveira do Nascimento<sup>1</sup> Carlos Alberto de Oliveira Rocha<sup>1</sup> João Paulo Oliveira de Almeida Gustavo Nascimento M. Sigueira Myllena Vitória Bispo <del>Sar</del> João Vitor Bispo Santana . lena Vitória Bispo Santana Maria Deysiane Porto Araújo<sup>1</sup> Thaysa Kelly Barbosa Vieira Tomé<sup>1</sup> Rodrigo Feliciano do Carmo<sup>4,5</sup> Carlos Dornels Freire de Souza<sup>1,6</sup>

- Center for the Study of Social and Preventive Medicine, <u>Arapiraca</u> (AL), Brazi
- Federal University of Alagoas, Medical
- School, Maceió (AL), Brazil. Federal University of Vale do São Francisco (UNIVASF), Medical School, Petrolina (PE), Brazil
- Federal University of Vale do São Francisco (UNIVASF), School of Pharmaceutical
- Sciences, Petrolina (PE), Brazil. Federal University of Vale do São Francisco (UNIVASF), Postgraduate Programs in Biosciences and Health and Biological Sciences, Petrolina (PE), Brazil
- Federal University of Alagoas, Postgraduate Program in Family Health, Arapiraca (AL), Brazil.

#### **Correspondence:**

Marielle de Godoi Spader Email: mariellegspader@hotmail.com

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#### 1

#### INTRODUCTION

The progressive increase in chronic degenerative diseases, such as cancer, to the detriment of infectious and parasitic diseases highlights the changes in the Brazilian morbidity and mortality profile.<sup>1</sup> Skin cancer is the most frequent neoplasm in Brazil, with about 190,000 annual records and four thousand deaths.<sup>2</sup>

Skin cancer is classified into melanoma and non-melanoma.<sup>3</sup> Non-melanoma skin cancer is the most frequent, corresponding to 30% of all neoplasms in Brazil,<sup>3</sup> with an estimated 176 thousand cases in 2020.<sup>3,4</sup> Melanoma skin cancer is rarer and comprises 3% of all skin tumors, with an estimated 8,000 cases in 2020.<sup>2</sup>

Melanoma originates from the cells responsible for producing melanin, the melanocytes, found mainly in the skin and also in many other body regions where these cells migrate during embryonic development from the neural crest pluripotent stem cells.<sup>5</sup> Thus, although the largest number of cases of melanoma is cutaneous,<sup>2,6</sup> it may also appear in the different places where melanocytes are present, such as mucosa,<sup>7</sup> meninges,<sup>8,9</sup> and eyes.<sup>10</sup>

Despite the low incidence, cutaneous melanoma has greater malignancy and the ability to produce metastasis, a disordered proliferation of abnormal cells with a tendency to autonomy and durability. These cells can invade other organic structures via hematogenous or lymphatic pathways, producing deleterious effects in other organs.<sup>2,4</sup>

However, the prognosis is good when melanoma skin cancer is detected at an early stage, without metastasis. The five-year survival rate after diagnosis for cutaneous melanoma without metastasis is 99%, while for cutaneous melanoma with metastasis to regional lymph nodes is 65%. For cutaneous melanoma with metastasis, the distance is 25%.<sup>11</sup>

In a country of continental dimensions such as Brazil, where inequalities prevail (economic, environmental, and access to Health Services), it is also noted that epidemiological data differ among regions. In 2020, 8,450 melanoma skin cancer records were estimated. Of these, 1,000 cases (12.8%) are expected for the Northeast,<sup>2</sup> even though this region is responsible for 26.7% of the Brazilian population. Unlike the South and Southeast regions, which concentrate scientific and health centers, in the Northeast, investigations on the prevalence and temporal trends are scarce.<sup>12</sup>

This study aims to analyze the temporal behavior of mortality from melanoma in the capitals of Northeast Brazil from 2001 to 2017.

#### **METHODS**

#### Study design, population, and period

Ecological time series study involving all deaths due to melanoma registered in the capitals of the Northeast region of Brazil from 2001 to 2017.

#### Study scenario

The study was conducted in all nine capitals of the Northeast region of Brazil: São Luís (Maranhão), Teresina (Piauí), Fortaleza (Ceará), Natal (Rio Grande do Norte), João Pessoa (Paraíba), Recife (Pernambuco), Maceió (Alagoas), Aracaju (Sergipe), and Salvador (Bahia).

The Northeast region has a predominantly tropical and semi-arid climate.<sup>13,14</sup> Also, it has the highest solar irradiation rate in Brazil, with an average total daily value of horizontal global irradiation of 5.49 kWh/m<sup>2,15</sup> Highlighting the capitals, the average annual temperature is 27.1°C.<sup>14</sup>

This study included only the capitals, considering the homogeneity of health scenarios; the fact that the capitals concentrate diagnosis and treatment centers for the most complex diseases; and similar environmental and climatic conditions.<sup>14</sup>

#### Study variables and data collection

The following indicators were analyzed:

- Proportional mortality from melanoma;
- Crude melanoma mortality rate; and
- World population-adjusted melanoma mortality rate.

Rates were stratified by sex. Data were obtained from the online Mortality Atlas of the National Cancer Institute José Alencar Gomes da Silva (Instituto Nacional de Câncer José Alencar Gomes da Silva – INCA).<sup>16</sup> The document was accessed on March 30, 2020. It's noteworthy that the rates obtained were already calculated by the INCA platform.

#### Statistical treatment

After data collection, statistical treatment was performed using the joinpoint regression model. The model tests whether a line with multiple segments is statistically more adequate to describe the temporal evolution of a set when compared to a straight line or with fewer segments.<sup>17</sup> Based on the line inclination, trends were classified as increasing, decreasing, or stationary. Also, the annual percent change (APC) and the average annual percent change (AAPC) were obtained considering a 95% confidence interval (95% CI) and 5% significance. The analysis was performed using the joinpoint regression software (version 4.5.0.1, National Center Institute, Bethesda, MD, USA).

#### **Ethical aspects**

The study did not require approval from the ethics committee since it used secondary data in the public domain and there was no individual identification of any patient.

#### RESULTS

#### **Proportional mortality**

From 2001 to 2017, 954 deaths from melanoma were recorded in the capitals of Northeast Brazil. Of these, 57.02% (n=544) were women. Fortaleza (CE) and Salvador (BA) concentrated 23.48% (n=224) and 19.81% (n=189) of the records, respectively. Considering both sexes, the three rates analyzed (proportional mortality, crude rate, and adjusted rate) showed a
linear growth trend over the time series: proportional mortality increased from 4.9% to 7.2% (AAPC 6.0%; p<0.01); crude mortality grew from 3.9% to 6.1% (AAPC 5.0%; p<0.01); and world population-adjusted mortality in capital cities in the Northeast rose from 1.6% to 3.9% (AAPC 2.7%; p<0.01) (Figure 1).

In men, the same temporal growth behavior was observed: proportional mortality increased from 3.8% to 8.2% (AAPC 6.0%; p<0.01); the crude rate rose from 2.8% to 7.2% (AAPC 5.0%; p<0.01); and world population-adjusted mortality rate grew from 1.0% to 5.2% (AAPC 3.1%; p<0.01). In women, proportional mortality showed a linear increase, rising from 4.4% to 7.8% (AAPC 6.1%; p<0.01); the crude rate, also with a linear growth trend, grew from 3.3% to 6.6% (AAPC 5.0; p<0.01); and a stationary pattern was observed in the world population-adjusted rate when considering the total period (2001-2017). In this rate, we observed two inflections and three trends, the last one with significant growth from 2010 (AAPC 4.6%; p<0.01) (Figure 1).

Among the capitals of the Northeast, considering both sexes, five cities showed an increasing temporal trend in the proportional mortality rate: Aracaju (APC 16.7; p<0.01), Fortaleza (APC 7.1; p<0.01), Natal (APC 8.8; p<0.01), São Luís (APC 24.9; p<0.01), and Teresina (APC 25.3; p<0.01). João Pessoa (APC 3.1; p=0.1) and Maceió (APC 11.0; p=0.2) showed stationary trends. Recife and Salvador presented different trends over the years, with a predominant stationary behavior (Table 1).

In men, three capitals showed an increasing temporal trend in the proportional mortality rate for melanoma skin cancer: Fortaleza (APC 7.7; p<0.01), Natal (APC 16.0; p<0.01), and Teresina (APC 39.1; p<0.01). Aracaju (APC 7.4; p=0.4), João Pessoa (APC 24.3; p=0.1), Maceió (APC 24.5; p=0.1), and Salvador showed stationary trends. (APC 4.5; p=0.1). Recife and São Luís presented differences between trends over the years, with a predominance of a stationary trend (Table 1).

In women, five capitals showed an increasing temporal trend in the proportional mortality rate for melanoma: Fortale-



FIGURE 1: Temporal evolution of melanoma skin cancer mortality in the capitals of the Northeast, Brazil, 2001-2017

Lemos AMS, Castro BG, Nascimento ALO, Rocha CAO, Almeida JPO, Siqueira GNM, Santana MVB, Santana JVB, Fernandes TRMO, Araújo MDP, Tomé TKBV, Amorim JR, Carmo RF, Souza CDF

Capital		Proportional mortalit	y rate	Joinpoint regression model	
	2001	2017	Period	(APC or AAPC; IC 95%; p)	Trend
		A	) Both sexes		
Aracaju	5.97	5.97	2001 to 2017	(16.7; 4.4 to 30.5; p<0.01)	Increasing
Fortaleza	2.23	6.25	2001 to 2017	(7.1; 4.3 to 9.9; p<0.01)	Increasing
oão Pessoa	1.64	13.11	2001 to 2017	(3.1; -1.1 to 7.6; p=0.1)	Stationary
Maceió	0.0	9.09	2001 to 2017	(11.0; -5.7 to 30.8; p=0.2)	Stationary
Natal	2.9	11.59	2001 to 2017	(8.8; 4.8 to 13.0; p<0.01)	Increasing
Recife	5.1	8.28	2001 to 2003	18.0 (-41.0 to 136.2; p=0.6)	Stationary
			2003 to 2007	-23.9 (-41.6 to -0.7; p<0.01)	Decreasing
			2007 to 2010	51.3 (-21.4 to 191.2; p=0.2)	Stationary
			2010 to 2017	-4.0 (-9.7 to 2.1; p=0.2)	Stationary
			2001 to 2017	(1.3; -11.4 to 15.7; p=0.9)	Stationary
Salvador	0.53	7.94	2001 to 2003	135.1 (-35.7 to 760.1; p=0.2)	Stationary
			2003 to 2017	1.5 (-2.1 to 5.2; p=0.4)	Stationary
			2001 to 2017	(12.7; -2.8 to 30.8; p=0.1)	Stationary
São Luís	3.7	12.96	2001 to 2017	(24.9; 7.7 to 44.8; p<0.01)	Increasing
Teresina	0.0	6.41	2001 to 2017	(25.3; 6.3 to 47.7; p<0.01)	Increasing
			B) Men		
Aracaju	7.69	7.69	2001 to 2017	(7.4; -10.3 to 28.6; p=0.4)	Stationary
Fortaleza	0.88	5.31	2001 to 2017	(7.7; 3.6 to 11.9; p<0.01)	Increasing
oão Pessoa	0.0	15.62	2001 to 2017	(24.3; -0.1 to 54.7; p=0.1)	Stationary
Maceió	0.0	9.38	2001 to 2017	(24.5; -1.7 to 57.6; p=0.1)	Stationary
Natal	2.22	8.89	2001 to 2017	(16.0; 4.8 to 28.3; p<0.01)	Increasing
Recife	5.26	10.53	2001 to 2007	-22.8 (-37.0 to -5.4; p<0.01)	Increasing
			2007 to 2010	61.7 (-64.9 to 644.8; p=0.5)	Stationary
			2010 to 2017	-5.2 (-19.1 to 11.0; p=0.5)	Stationary
			2001 to 2017	(-3.0; -25.5 to 26.3; p=0.8)	Stationary
Salvador	0.95	8.57	2001 to 2017	(4.5; -1.3 to 10.7; p=0.1)	Stationary
São Luís	6.45	9.68	2001 to 2004	-95.3 (-98.9 to -79.4; p<0.01)	Increasing
			2004 to 2008	687.1 (94.1 to 3091.1; p<0.01)	Increasing
			2008 to 2017	2.3 (-17.1 to 26.1; p=0.8)	Stationary
			2001 to 2017	-4.5 (-36.0 to 42.6; p=0.8)	Stationary
Teresina	0.0	7.69	2001 to 2017	(39.1; 17.6 to 64.5; p<0.01)	Increasing
			C) Women		
Aracaju	3.57	3.57	2001 to 2017	(16.9; -0.2 to 37.0; p=0.1)	Stationary
Fortaleza	3.6	7.21	2001 to 2017	(7.3; 3.0 to 11.8; p<0.01)	Increasing
oão Pessoa	3.45	10.34	2001 to 2017	(-3.2; -21.2 to 18.9; p=0.7)	Stationary
Maceió	0.0	8.7	2001 to 2017	(16.4; -3.3 to 40.2; p=0.1)	Increasing
Natal	4.17	16.67	2001 to 2017	(41.1; 14.1 to 74.3; p<0.01)	Increasing
Recife	4.84	4.84	2001 to 2017	(3.2; -0.0 to 6.6; p=0.1)	Stationary
Salvador	0.0	7.14	2001 to 2003	1013.9 (89.5 to 6447.6; p<0.01)	Increasing
			2003 to 2017	0.9 (-3.9 to 5.9; p=0.7)	Stationary
			2001 to 2017	36.2 (11.2 to 66.8; p<0.01)	Increasing
São Luís	0.0	17.39	2001 to 2017	(30.4; 13.8 to 49.3; p<0.01)	Increasing
Teresina	0.0	3.85	2001 to 2017	(28.3: -1.8  to  67.7:  p=0.1)	Stationary

za (APC 7.3; p<0.01), Maceió (APC 16.4; p=0.1), Natal (APC 41.1; p<0.01), São Luís (APC 30.4; p<0.01), and Salvador (APC 36.2; p<0.01). The latter, however, showed an increasing trend from 2001 to 2003 (APC 1013.9; p<0.01) and stationary from 2003 to 2017 (APC 0.9; p=0.7). Aracaju (APC 16.9; p=0.1), João Pessoa (APC -3.2; p=0.7), Recife (APC 3.2; p=0.1), and Teresina (APC 28.3; p=0.1) showed a stationary trend (Table 1).

### Crude mortality rate

In the analysis of the temporal trend of the crude mortality rate from melanoma skin cancer, considering both sexes, five capitals in the Northeast showed an increasing tendency: Aracaju (APC 10.4; p<0.01), Fortaleza (APC 6.0; p<0.01), Natal (APC 7.7; p<0.01), São Luís (APC 14.9; p<0.01), and Teresina (APC 17.0; p<0.01). João Pessoa (APC 1.4; p=0.5) and Maceió (APC 8.2; p=0.1) presented a stationary trend. Recife and Salvador showed different tendencies during the period, with a prevalence of a stationary pattern (APC 0.7; p=0.9 and APC 11.6; p=0.2, respectively) (Table 2).

When considering men, Fortaleza (APC 6.6; p<0.01), Natal (APC 10.8; p<0.01), and Teresina (APC 26.7; p<0.01) showed an increasing trend. Aracaju (APC 4.8; p=0.5), João Pessoa (APC 14.2; p=0.1), Maceió (APC 14.4; p=0.1), and Salvador (APC 3.9; p=0.2) presented a stationary trend. There were different trends for Recife (APC -3.5; p=0.8) and São Luís (APC -1.7; p=0.9), but both with a predominance of a stationary pattern (Table 2).

In women, there was an increasing trend in Aracaju (APC 10.7; p<0.01), Fortaleza (APC 6.2; p<0.01), Natal (APC 22.1; p<0.01), and São Luís (APC 14.7; p<0.01). João Pessoa (APC -3.4; p=0.6), Maceió (APC 10.0; p=0.1), Recife (APC 2.5; p=0.1), and Teresina (APC 14.5; p=0.1) showed a stationary trend. Salvador presented variation during the period, with a predominance of a stationary pattern (APC 19.5; p=0.1) (Table 2).

### World population-adjusted mortality rate

The temporal trend of world population-adjusted mortality rate in the capitals of the Northeast, considering both sexes, was increasing for five cities: Aracaju (APC 8.6; p<0.01), Fortaleza (APC 3.7; p<0.01), Natal (APC 6.0; p<0.01), São Luís (APC 14.0; p<0.01), and Teresina (APC 16.4; p< 0.01). There was a difference between trends from 2001 to 2017 in Recife (APC -1.3; p=0.9) and Salvador (APC 9.5; p=0.3), both with a stationary predominance. There was also a stationary pattern in the cities of João Pessoa (APC -0.6; p=0.8) and Maceió (APC 5.7; p=0.2) (**Table 3**).

In men, the temporal trend of the adjusted mortality rate increased in three capitals in the Northeast: Fortaleza (APC 4.6; p<0.01), Natal (APC 9.9; p<0.01), and Teresina (APC 27.8; p<0.01). The trend was predominantly stationary in Aracaju (APC 2.7; p=0.7), João Pessoa (APC 14.6; p=0.1), Maceió (APC 13.4; p=0.1), Recife (APC -1.8; p=0.9), Salvador (APC 0.7; p=0.8), and São Luís (APC -2.8; p=0.9) (Table 3).

In women, the temporal trend of the adjusted mortality rate increased in two cities: Natal (APC 19.5; p<0.01) and São Luís (APC 15.0; p<0.01). The trend was stationary in Araca-ju (APC 7.7; p=0.2), Fortaleza (APC 4.2; p=0.1), João Pessoa (APC -5.0; p=0.4), Maceió (APC 7.9; p=0.1), Recife (APC -0.7; p=0.6), Teresina (APC 12.7; p=0.2), and Salvador (APC 18.1; p=0.2) (Table 3).

### DISCUSSION

This study aimed to analyze the trend in mortality from melanoma, allowing us to observe a predominance of an increasing tendency in proportional, crude, and adjusted mortality rates in the capitals of Northeast Brazil between 2001 and 2017, especially in Natal and Fortaleza, with inequalities regarding sex and among the capitals.

International epidemiological data indicate a continuous growth in the incidence of melanoma in Europe, Canada, and the United States in recent decades. The highest incidence rate is in New Zealand, with 50 cases per 100,000 inhabitants.<sup>18</sup> In the United States, United Kingdom, Sweden, and Norway, rates rise by more than 3% per year, and projections estimate that this increase will continue until at least 2022.<sup>19</sup> In the United States, there are almost 7,000 annual deaths due to melanoma.<sup>11</sup> This growth is in line with what we observed in our study regarding the world population-adjusted rate, whose annual growth percentage was 2.7%. On the other hand, the annual increase in proportional mortality reached 6.0%.

Melanoma is a disease with multifactorial etiology. However, it is estimated that at least 80% of cases are due to exposure to the sun, which is the primary risk factor for developing the disease.<sup>20</sup> In this context, the intensity of solar radiation in the Northeast region may represent a risk factor for the disease.

Excessive and cumulative sun exposure in the first 20 years of age and the number of sunburns throughout life increase the chances of developing melanoma skin cancer in adulthood.<sup>20</sup> Childhood, in particular, is a phase more vulnerable to the sun's harmful effects because children spend more time outdoors and exposed to sunlight. Also, approximately 25% to 50% of all sunlight exposure during a lifetime occurs before the age of 21.<sup>20</sup>

Furthermore, individuals who perform work activities subject to this exposure are more likely to develop photobiological skin reactions that lead to the emergence of skin cancer. Although there is incisive legislation on the use of personal protective equipment (PPE), there is none requiring sunscreen, which would be beneficial for specific skin areas where PPE does not provide the desired protection. <sup>21</sup>

International studies indicate that another significant factor for a future increase in skin cancer cases is life expectancy growth. By 2050, it is expected that up to 32% of the world population will be over 60 years, contributing to the progression in numbers, given the increased skin cancer cases due to growing age.18 This increase is because a longer life span means a longer time of photodamage to skin cells and, mainly, more time for the damage to manifest itself in the form of neoplasms.<sup>22</sup> Lemos AMS, Castro BG, Nascimento ALO, Rocha CAO, Almeida JPO, Siqueira GNM, Santana MVB, Santana JVB, Fernandes TRMO, Araújo MDP, Tomé TKBV, Amorim JR, Carmo RF, Souza CDF

Capital		Rate		Joinpoint regression model		
	2001	2017	Period	(APC or AAPC; IC 95%; p)	Trend	
		A) Bo	th sexes			
Aracaju	0.93	0.63	2001 to 2017	(10.4; 2.1 to 19.5; p<0.01)	Increasing	
Fortaleza	0.23	0.54	2001 to 2017	(6.0; 3.2 to 8.7; p<0.01)	Increasing	
João Pessoa	0.16	1.01	2001 to 2017	(1.4; -2.8 to 5.9; p=0.5)	Stationary	
Maceió	0.0	0.49	2001 to 2017	(8.2; -1.6 to 18.9; p=0.1)	Stationary	
Natal	0.27	0.92	2001 to 2017	(7.7; 3.7 to 11.8; p<0.01)	Increasing	
Recife	0.54	0.8	2001 to 2003	17.6 (-41.2 to 135.1; p=0.6)	Stationary	
			2003 to 2007	-24.5 (-42.5 to -0.8; p<0.01)	Decreasing	
			2007 to 2010	50.1 (-22.5 to 190.6; p=0.2)	Stationary	
			2010 to 2017	-4.4 (-10.2 to 1.8; p=0.1)	Stationary	
			2001 to 2017	(0.7; -12.0 to 15.2; p=0.9)	Stationary	
Salvador	0.04	0.51	2001 to 2003	128.6 (-38.1 to 744.6; p=0.2)	Stationary	
			2003 to 2017	0.7 (-2.9 to 4.5; p=0.7)	Stationary	
			2001 to 2017	11.6 (-3.9 to 29.6; p=0.2)	Stationary	
São Luís	0.22	0.65	2001 to 2017	(14.9; 5.7 to 24.9; p<0.01)	Increasing	
Teresina	0.0	0.59	2001 to 2017	(17.0; 4.5 to 31.0; p<0.01)	Increasing	
		B)	Men			
Aracaju	1.31	1.01	2001 to 2017	(4.8; -8.3 to 19.7; p=0.5)	Stationary	
Fortaleza	0.1	0.49	2001 to 2017	(6.6; 2.6 to 10.6; p<0.01)	Increasing	
João Pessoa	0.0	1.35	2001 to 2017	(14.2; -0.8 to 31.3; p=0.1)	Stationary	
Maceió	0.0	0.63	2001 to 2017	(14.4; -0.8 to 32.0; p=0.1)	Stationary	
Natal	0.28	0.97	2001 to 2017	(10.8; 3.6 to 18.5; p<0.01)	Increasing	
Recife	0.72	1.33	2001 to 2007	-23.1 (-37.3 to -5.7; p<0.01)	Decreasing	
			2007 to 2010	60.7 (-64.9 to 636.7; p=0.5)	Stationary	
			2010 to 2017	-5.7 (-19.5 to 10.6; p=0.4)	Stationary	
			2001 to 2017	-3.5 (-25.8 to 25.6; p=0.8)	Stationary	
Salvador	0.08	0.65	2001 to 2017	(3.9; -1.9 to 9.9; p=0.2)	Stationary	
São Luís	0.47	0.6	2001 to 2004	-82.6 (-94.1 to -48.2; p<0.01)	Decreasing	
			2004 to 2008	229.1 (16.3 to 830.9; p<0.01)	Increasing	
			2008 to 2017	2.2 (-12.7 to 19.6; p=0.8)	Stationary	
			2001 to 2017	-1.7 (-26.9 to 32.2; p=0.9)	Stationary	
Teresina	0.0	1.01	2001 to 2017	(26.7; 12.8 to 42.3; p<0.01)	Increasing	
		C) W	7omen			
Aracaju	0.39	0.3	2001 to 2017	(10.7; 0.1 to 22.5; p<0.01)	Increasing	
Fortaleza	0.34	0.58	2001 to 2017	(6.2; 1.9 to 10.7; p<0.01)	Increasing	
João Pessoa	0.31	0.71	2001 to 2017	(-3.4; -15.1 to 9.9; p=0.6)	Stationary	
Maceió	0.0	0.37	2001 to 2017	(10.0; -0.1 to 21.1; p=0.1)	Stationary	
Natal	0.26	0.88	2001 to 2017	(22.1; 7.8 to 38.3; p<0.01)	Increasing	
Recife	0.39	0.35	2001 to 2017	(2.5; -0.7 to 5.8; p=0.1)	Stationary	
Salvador	0.0	0.39	2001 to 2003	287.3 (-34.3 to 2181.2; p=0.1)	Stationary	
			2003 to 2017	1.1 (-3.8 to 6.2; p=0.6)	Stationary	
			2001 to 2017	(19.5; -2.4 to 46.5; p=0.1)	Stationary	
São Luís	0.0	0.7	2001 to 2017	(14.7; 6.1 to 24.0; p<0.01)	Increasing	
Teresina	0.0	0.22	2001 to 2017	(14.5; -2.9  to  35.0; n=0.1)	Stationary	

TABLE 3: Temporal tre	end in melanoma ski	n cancer mortal	ity rate adjusted by wo	rld population in Northeast capitals, B	razil, 2001-2017
Capital		Rate		Joinpoint regression model	
	2001	2017	Period	(APC or AAPC; IC 95%; p)	Trend
			A) Both sexes		
Aracaju	1.16	0.66	2001 to 2017	(8.6; 0.0 to 17.9; p<0.01)	Increasing
Fortaleza	0.28	0.53	2001 to 2017	(3.7; 0.9 to 6.6; p<0.01)	Increasing
João Pessoa	0.26	0.92	2001 to 2017	(-0.6; -4.8 to 3.7; p=0.8)	Stationary
Maceió	0.0	0.46	2001 to 2017	(5.7; -4.2 to 16.6; p=0.2)	Stationary
Natal	0.33	0.88	2001 to 2017	(6.0; 1.9 to 10.2; p<0.01)	Increasing
Recife	0.58	0.64	2001 to 2003	20.5 (-49.5 to 187.9; p=0.6)	Stationary
			2003 to 2007	-25.5 (-44.1 to -0.6; p<0.01)	Decreasing
			2007 to 2010	44.4 (-32.6 to 209.4; p=0.3)	Stationary
			2010 to 2017	-7.1 (-12.9 to -0.9; p<0.01)	Decreasing
			2001 to 2017	-1.3 (-15.6 to 15.4; p=0.9)	Stationary
Salvador	0.05	0.5	2001 to 2003	145.8 (-42.7 to 954.9; p=0.2)	Stationary
			2003 to 2017	-2.4 (-6.6 to 1.9; p=0.2)	Stationary
			2001 to 2017	9.5 (-7.3 to 29.5; p=0.3)	Stationary
São Luís	0.35	0.66	2001 to 2017	(14.0; 4.1 to 24.8; p<0.01)	Increasing
Teresina	0.00	0.71	2001 to 2017	(16.4; 3.0 to 31.6; p<0.01)	Increasing
			B) Men		
Aracaju	2.25	1.38	2001 to 2017	(2.7; -10.5 to 17.8; p=0.7)	Stationary
Fortaleza	0.15	0.6	2001 to 2017	(4.6; 0.7 to 8.6; p<0.01)	Increasing
João Pessoa	0.0	1.53	2001 to 2017	(14.6; -1.4 to 33.0; p=0.1)	Stationary
Maceió	0.0	0.74	2001 to 2017	(13.4; -3.0 to 32.7; p=0.1)	Stationary
Natal	0.38	1.06	2001 to 2017	(9.9; 2.2 to 18.2; p<0.01)	Increasing
Recife	1	1.33	2001 to 2008	-19.7 (-28.4 to -10.0; p<0.01)	Decreasing
			2008 to 2011	86.6 (-39.5 to 475.5; p=0.2)	Stationary
			2011 to 2014	-36.6 (-79.4 to 95.7; p=0.4)	Stationary
			2014 to 2017	28.2 (-21.7 to 109.9; p=0.3)	Stationary
			2001 to 2017	-1.8 (-23.8 to 26.6; p=0.9)	Stationary
Salvador	0.17	0.71	2001 to 2017	(0.7; -5.4 to 7.2; p=0.8)	Stationary
São Luís	0.96	0.64	2001 to 2004	-85.0 (-95.7 to -47.7; p<0.01)	Decreasing
			2004 to 2008	269.6 (9.6 to 1146.5; p<0.01)	Increasing
			2008 to 2017	0.1 (-17.1 to 20.8; p=1.0)	Stationary
			2001 to 2017	-2.8 (-31.2 to 37.2; p=0.9)	Stationary
Teresina	0.0	1.63	2001 to 2017	27.8 (12.0 to 45.8; p<0.01)	Increasing
			C) Women		
Aracaju	0.4	0.19	2001 to 2017	(7.7; -3.4 to 20.0; p=0.2)	Stationary
Fortaleza	0.36	0.54	2001 to 2017	(4.2; -0.3 to 8.9; p=0.1)	Stationary
João Pessoa	0.44	0.54	2001 to 2017	(-5.0; -16.4 to 8.0; p=0.4)	Stationary
Maceió	0.0	0.26	2001 to 2017	(7.9; -1.4 to 18.0; p=0.1)	Stationary
Natal	0.3	0.77	2001 to 2017	(19.5; 5.7 to 35.1; p<0.01)	Increasing
Recife	0.34	0.2	2001 to 2017	(-0.7; -3.9 to 2.6; p=0.6)	Stationary
Salvador	0.0	0.37	2001 to 2003	339.7 (-55.2 to 4218.1; p=0.2)	Stationary
			2003 to 2017	-2.1 (-8.1 to 4.2; p=0.5)	Stationary
			2001 to 2017	(18.1; -9.1 to 53.4; p=0.2)	Stationary
São Luís	0.0	0.71	2001 to 2017	(15.0; 5.8 to 25.0; p<0.01)	Increasing
Teresina	0.0	0.17	2001 to 2017	(12.7; -5.5  to  34.4; p=0.2)	Stationary

A study conducted in Teresina, the capital of the state of Piauí, showed that most of the cutaneous melanoma diagnoses performed at the referral service were in patients over 50 years. The lesion was found predominantly in chronically photoexposed areas, such as the head and neck, trunk – especially in men – and limbs.<sup>12</sup>

Melanoma also shows high variation in its incidence in different ethnic groups, mainly due to the photoprotective property of melanin, which is reduced in certain ethnicities.<sup>23</sup> North American studies indicate that the risk for developing melanoma during life is 2.6% for whites, 0.6% for Hispanics, and 0.1% for blacks.<sup>24</sup> The states of the capitals with a significant increasing trend in the rates analyzed, Natal and Fortaleza, had, according to the last IBGE Demographic Census, 41.2% and 32% self-declared white, respectively.<sup>25</sup>

The adjusted mortality rates analysis demonstrated stationary predominance for both sexes. However, proportional and crude mortality rates showed a predominance of increasing trends for women and stationary for men. In the adjusted mortality rate the opposite was observed – more increasing trends for men (three capitals – Fortaleza, Natal, and Teresina) than for women (two capitals – Natal and Teresina). In general, men use Health Services less than women. The reasons revolve around the difference in the health needs profile, the search for these services between genders, and the existence of more public health policies aimed at the female population.<sup>26,27</sup>

Early diagnosis is still the most effective way to reduce mortality from melanoma.12 The early discovery of skin lesions by neoplastic melanocytes still restricted to the epidermis or superficial dermis provides a greater possibility of cure through adequate treatment.<sup>27</sup> In recent decades, an improvement in five-year survival was observed with a decrease in the overall mortality rate between 70% and 80% due to early diagnosis and treatment.<sup>28</sup> The Brazilian Society of Dermatology (Sociedade Brasileira de Dermatologia - SBD) started, in 2014, the national skin cancer prevention campaign called "Orange December". Among other educational actions, the campaign warns about the dangers of unprotected sun exposure. Also, SBD conducted 26,161 consultations in 2018, identifying 3,852 cases of skin cancer, including 363 melanomas, in an early detection campaign implemented since 1999.<sup>29</sup>

The present study, although considering all the necessary methodological precautions, has limitations. The first concerns the use of secondary data, which is influenced by the operational context of surveillance services in the states of the region, with consequent underdiagnosis of the disease and underreporting of deaths (there were capitals with zero cases in certain years, such as Maceió and Teresina in 2001). The second refers to the lack of standardization in data centralization and collection, making it difficult to conduct investigations and comparisons between regions. The third comprises the scarcity of epidemiological studies on the subject.

### CONCLUSION

The analysis of the time series of mortality from melanoma in the capitals of the Northeast region of Brazil between 2001 and 2017 showed an increasing trend for crude mortality, proportional mortality, and adjusted mortality rates considering both sexes in five capitals: Aracaju, Fortaleza, Natal, São Luís, and Teresina. In men, Fortaleza, Natal, and Teresina showed a growing trend in the three rates. In women, we observed a variation according to the rate: five capitals in proportional mortality, four in the crude rate, and two in the adjusted rate.

The results found can have significant value in understanding the health scenario of the region, and they can support the development of prevention and early diagnosis strategies aimed at the regional reality of the Brazilian Northeast and, in particular, its capitals.

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### AUTHORS' CONTRIBUTION:

Amanda Maria Sandes Lemos ORCID\_0000-0002-0655-4093 Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review; critical revision of the manuscript.

# Beatriz Gomes de Castro DORCID 0000-0002-7547-1240

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review; critical revision of the manuscript.

# André Luis Oliveira do Nascimento D ORCID 0000-0001-5274-3277

Approval of the final version of the manuscript; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.

# Carlos Alberto de Oliveira Rocha D ORCID 0000-0003-2927-5043

Approval of the final version of the manuscript; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.

# João Paulo Oliveira de Almeida 🔟 ORCID 0000-0002-0414-4744

Approval of the final version of the manuscript; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.

# Gustavo Nascimento Monteiro Siqueira D ORCID 0000-0002-3966-2488

Approval of the final version of the manuscript; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.

# Myllena Vitória Bispo Santana 🕒 ORCID 0000-0001-8090-0911

Approval of the final version of the manuscript; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.

# João Vitor Bispo Santana D ORCID 0000-0002-5642-1643

Approval of the final version of the manuscript; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.

# Tânia Rita Moreno de Oliveira Fernandes DORCID 0000-0002-7061-2825

Approval of the final version of the manuscript; active participation in research orientation; critical literature review; critical revision of the manuscript.

# Maria Deysiane Porto Araújo 🝺 ORCID 0000-0002-1258-0845

Approval of the final version of the manuscript; active participation in research orientation; critical literature review; critical revision of the manuscript.

# Thaysa Kelly Barbosa Vieira Tomé DORCID 0000-0001-5538-3772

Approval of the final version of the manuscript; active participation in research orientation; critical literature review; critical revision of the manuscript.

### José Roberto Amorim D ORCID 0000-0001-5884-639X

Approval of the final version of the manuscript; active participation in research orientation; critical literature review; critical revision of the manuscript.

# Rodrigo Feliciano do Carmo D ORCID 0000-0001-9601-6995

Approval of the final version of the manuscript; preparation and writing of the manuscript; active participation in research orientation; critical literature review; critical revision of the manuscript.

### Carlos Dornels Freire de Souza DORCID 0000-0001-7995-1893

Statistical analysis; approval of the final version of the manuscript; study design and planning; active participation in research orientation; critical literature review; critical revision of the manuscript.

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# Scientometrics: a tool for the insertion of Brazilian Dermatology in the world scientific production

Cienciometria: uma ferramenta para inserção da Dermatologia brasileira na produção científica mundial

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### ABSTRACT

**Introduction:** The Brazilian scientific production in Dermatology in the international scenario was verified by scientometrics (Sociology segment on quantitative aspects of science).

**Objective:** The insertion of Brazil in the international scientific production scenario can and should be conducted from a more strategic perspective, and it is necessary to observe the production of documents indexed in Scopus in the Dermatology area and related topics in a more detailed way.

**Methods:** Through exploratory, inductive, quantitative, and qualitative research on the Scopus platform – a digital platform comprising more than 25 thousand scientific articles and analytical tools to extract results and trends in the field of research, it was possible to obtain quantitative data on Brazilian scientific production in General Dermatology and six prominent dermatoses.

**Results:** It was possible to analyze and point out the most prominent dermatoses currently in the literature and the related authors, compare Brazilian data with those from other countries that stand out in the scientific literature in Dermatology, and elaborate and justify effective strategies for the international insertion of Brazilian Dermatology scientific production.

Keywords: Impact production; Dermatology; Database; Science

### RESUMO

**Introdução:** foi verificada a produção científica brasileira em Dermatologia no cenário internacional pela Cienciometria (segmento da Sociologia sobre aspectos quantitativos da ciência).

**Objetivo:** é plausível afirmar que a inserção do Brasil na produção científica internacional pode e deve ser realizada a partir de uma perspectiva mais estratégica, sendo necessário observar a produção de documentos indexados em Scopus na área de Dermatologia e temas relacionados de forma mais minuciosa.

**Métodos:** por meio de pesquisa exploratória, quanti-quali indutiva na plataforma Scopus - plataforma digital que reúne mais de 25 mil artigos científicos e disponibiliza ferramentas analíticas para extrair resultados e tendências no campo da pesquisa -, foi possível obter dados quantitativos sobre a produção científica brasileira em Dermatologia geral e em seis dermatoses proeminentes.

**Resultados:** foi possível extrair análise a fim de apontar as dermatoses mais importantes atualmente na literatura e os autores relacionados, comparar os dados brasileiros com os de outros países que se destacam na literatura científica em Dermatologia e elaborar e justificar as estratégias efetivas de inserção internacional da produção científica da Dermatologia brasileira.

Palavras-chave: Produção do impacto; Dermatologia; Base de dados; Ciência

# **Original Article**

**Authors:** 

- Henrique Seiji Furukawa<sup>1</sup> Ana Clara Ladeira Cruz<sup>2</sup> Edileia Bagatin<sup>2</sup> Guilherme Sydow Nunes Bueno Brandão<sup>3</sup>
- <sup>1</sup> Federal University of São Paulo, Paulista School of Medicine, São Paulo (SP), Brazil.
- <sup>2</sup> Federal University of São Paulo, Paulista School of Medicine, Dermatology, São Paulo (SP), Brazil.
- <sup>3</sup> Federal University of São Paulo, Technological and Social Innovation Agency of Unifesp (Agits/Unifesp), São Paulo (SP), Brazil.

### **Correspondence:**

Henrique Seiji Furukawa<sup>1</sup> Email: henrique.seiji@unifesp.br

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### INTRODUCTION Research guestion

A search using the keyword "Dermatology" in the Scopus database,<sup>1</sup> between 2014 and 2017, shows Brazil as the 15th producer, with 426 publications. This production represents 10% of the total of the United States, which ranks first with 4,191 published documents. The most cited article by Brazilian authors, entitled "Computational methods for the image segmentation of pigmented skin lesions: a review", has 95 citations but does not include any dermatologists, although the topic involves the Dermatology field. In the most cited article in the sample, only one Brazilian author collaborated with 25 foreigners.<sup>2</sup>

Even though Brazilian production can be categorized as small (approximately 10% of the publications of the largest producer), it is possible to observe that there is room for a more effective collaboration of Brazilian authors in Dermatology and related topics. In the two cases mentioned, Brazil participates in the most cited documents and collaborates with notable countries. Furthermore, in 2018, Brazil had 831 residency vacancies in Dermatology and 8,317 specialist physicians associated with the Brazilian Society of Dermatology,<sup>3</sup> increasing the demand for this project results.

Therefore, the insertion of Brazil into the international scientific production can and should be conducted from a more strategic perspective and it is necessary to observe the production of documents indexed in Scopus in the Dermatology area and related topics in a more comprehensive way. Also, we need to observe in detail which countries produce more documents, their citations, the Field-Weighted Citation Impact (FWCI), and the prominence of the most important themes. From these quantitative data, it will be possible to design an insertion plan better contextualized for this area. The final objective is a more significant internationalization of Brazil in the Dermatology field, with more mobility and exchange of experiences, in the widest possible way, with other countries that have outstanding production, quantitatively and qualitatively, aiming at generating effective impacts.

It is essential to emphasize that this survey must be conducted critically, that is, its effectiveness, including social, economic, and scientific impact, must be solid. According to the 2012 document "Indicators – basic guidelines applied to public management", from the Ministry of Planning, Budget and Management,<sup>4</sup> effectiveness is one of the performance evaluation indicators in public management and is defined as:

Effectiveness: measures the positive or negative effects on the reality that underwent the intervention, that is, it indicates whether there were socioeconomic, environmental, or institutional changes resulting from the outcomes obtained by the policy, plan, or program. It is what matters for social transformation.

Thus, the themes must be contextualized to the Brazilian reality and also among the most prominent countries in the international literature due to their significance in Dermatology clinical practice. It is plausible to foresee the publication of documents stating that it is not coherent for Brazil to produce science on certain global topics, as these topics do not concern the Brazilian reality. A scientometric diagnosis is a set of indications that require a detailed qualitative analysis and this exercise expands the frontiers of scientific research. So whatever the outcome, the effort is worth it.

### Question

What is the impact of Brazilian Dermatology scientific production on the international scene regarding the most prominent dermatoses? Which dermatoses, types of collaboration, and collaborators could help increase this production and generate more social, economic, and scientific impact?

### **Primary objective**

To build more effective strategies for the insertion and scientific interaction of Brazil into prominent countries and the scientific production of relevant topics in the Dermatology field.

### Secondary objectives

- Search for quantitative data on Brazilian scientific production, in General Dermatology, and six prominent dermatoses.

- Search Scopus and Web of Science databases and collect data about the outstanding production in the Dermatology field.

- Point out the most prominent dermatoses in the literature nowadays and related authors.

- Compare Brazilian data with those from other countries that stand out in the scientific literature in Dermatology.

- Develop and justify effective strategies for the international insertion of scientific production in Brazilian Dermatology.

### METHODS

The research conducted is quantitative, qualitative, and exploratory.

Quantitative research focuses on objectivity, using mathematical language to describe the causes of a phenomenon, the relationships between variables, etc.<sup>5</sup>

This approach is necessary to know in detail, from Scientometrics, the countries that produce more documents, their citations, the FWCI, and the prominence of the most important themes.

Qualitative research, on the other hand, is not concerned with numerical representation but with the deepening of the understanding of a social group, an organization, etc.<sup>6</sup>

Thus, the qualitative approach is necessary to justify a deeper insertion route in a criticism, considering the Brazilian reality.

Qualitative and quantitative methods are different and potentially complementary ways to collect data, whose usefulness depends on the suitability for a particular research task.<sup>6</sup> Therefore, the use of both methods is significant since this research proposes to conduct a data collection of a more numerical bias and critically analyze them to identify more effective international insertion alternatives for the Brazilian Dermatology scientific production. Thus, it is coherent to affirm that this project is quantitative-qualitative, based on the words of Minayo and Sanches:<sup>6</sup>

The relationship between quantitative and qualitative, between objectivity and subjectivity, cannot be reduced to a continuum, it cannot be thought of as a contradictory opposition. On the contrary, it is desirable that social relations can be analyzed in their most "ecological" and "concrete" aspects and deepened in their most essential meanings. Thus, the quantitative study can generate questions to be qualitatively deepened and vice versa.

Using Flick's words freely,<sup>7</sup> this approach aims to provide more credibility and legitimacy to the results to be made available at the end of the project.

The research project still presents an inductive perspective since, from the data observation, hypotheses are formulated to expand knowledge about routes for the effective internationalization of Dermatology scientific production.<sup>7</sup>

According to Gil,<sup>7</sup> exploratory research aims to provide greater familiarity with the problem, intending to make it more explicit or build hypotheses. One of the ways to conduct this study is through bibliographic surveys, such as in our research. It assesses the impact of the Brazilian Dermatology scientific production on the international scene concerning the most prominent dermatoses through data collection in the Scopus and Web of Science databases and, based on this information, seeks themes and partners to make a more effective international insertion for Brazilian Dermatology. The choice of Scopus is justified because it is the largest database in the world, used as a parameter to develop articles in the Scientometrics area.

We searched the databases based on the selected dermatoses, using the "article title, abstract, and keywords" tab, limited to the period 2012-2018.<sup>1</sup> We observed the most cited articles and extracted the analysis of the results to obtain the main authors, universities, and countries. Once we collected the data of interest (prominent dermatoses and others relevant to the objectives) from this procedure, we performed the sample analysis, and constructed the hypotheses of effective international insertion for the Brazilian Dermatology scientific production.

### Context

We found 81,300 publications in the search conducted on 04/17/2021 in the Scopus database with the keyword "Dermatology", from 1897 to 12/31/2020, using the article title, abstract, and keywords tabs.1 The most cited article in the sample had 3,030 citations. The United States was the country that published the most, with 23,642 documents. Brazil was the 11th country, with 1,642 publications. The most cited Brazilian article was produced in international collaboration and had 757 citations. The largest international partner was the USA, with 174 articles.

A new search, in the same database, with the same keywords between quotation marks and the title tab, between 1898 and 12/31/2020, retrieved 18,772 publications. The most cited article remained the same, with 3,030 citations. The United States remained the country that published the most, with 4,289 publications. Brazil occupied the 11th position, with 290 publications. The most cited article had 164 citations. The largest international partner, the USA, cooperated on 35 articles.

The leading Brazilian journal in Dermatology – "Anais Brasileiros de Dermatologia" – is in quartile 3 of the Scimago Journal and Country Rank, and, in 2019, only 7.69% of its publications had international collaboration. The total number of citations of documents published by the journal between 2016 and 2019 was 900, while the total number of the British Journal of Dermatology, a quartile 1 journal, was 5,937.1

Therefore, it is inferred that the Brazilian scientific production in Dermatology can be categorized as small, little internationalized, and cited compared to notable countries. By applying Scientometrics, it is possible to map and analyze the current state of Brazilian scientific production in Dermatology, and to build effective strategies for the insertion and scientific interaction of Brazil with distinguished countries in relevant themes of Dermatology.

### Scientometric data

We selected eight dermatoses from the article "Nosological profile of dermatological consultations in Brazil" to compare the scientific production of prominent dermatoses in Brazil, which has the production of the United States, Germany, China, and India, using institutional authorship, that is, from the Brazilian Society of Dermatology.<sup>8</sup> The document aimed to verify the frequency of the principal diagnoses in the practice of dermatologists. A sample of dermatologists surveyed for a week the diagnoses referring to dermatological outpatient care were, and 49 services offering medical residency. The results presented were based on more than 57 thousand dermatological consultations. Table 1 shows the main causes of registered consultations.

Based on the 13 chief causes of medical consultations in the article, searches were performed with the keywords in Scopus: "acne", "superficial mycoses", "pigmentation disorder", "skin aging", "contact dermatitis", "seborrheic dermatitis", "verruca", "melanocytic nevus", "eczema", "psoriasis", "atopic dermatitis", "seborrheic keratosis", and "nonmelanoma skin cancer", spelled like this and with quotation marks, using the "title, abstract, and keywords" tab and a time limit between 2012–2018.

To expand the topic to be explored, the dermatosis "actinic keratosis" was replaced by "skin aging" and "photoaging" ("photo-aging") while "basal cell carcinoma" was replaced by "nonmelanoma skin cancer" ("non-melanoma skin cancer").

Among these dermatoses, we chose the seven that resulted in more documents to compare the productions of the

TABLE 1	Nosological profile	e of dermatological consultations in Brazil - with the main causes of	consultations	registered	in Dermatology
Posto	CID-10	(Letter + 2 digits)	N.	%	% accumulated
1	L70	Acne	8.049	14	14
2	B35	B37 - Superficial mycoses	5.003	8.7	22.8
3	L81	Pigmentation disorders	4.822	8.4	31.2
4	L57	Actinic keratosis	2.953	5.1	36.3
5	L23 and L25	Contact dermatitis	2.241	3.9	40.2
6	L21	Seborrheic dermatitis	2.005	3.5	43.7
7	B07	Viral warts	1.958	3.4	47.1
8	D22	Melanocytic nevi	1.881	3.3	50.4
9	L30	Dermatitis: eczema / dyshidrosis / pityriasis alba	1.520	2.7	53.1
10	L40	Psoriasis	1.422	2.5	55.5
11	L20	Atopic dermatitis	1.391	2.4	58
12	L28	Seborrheic keratosis	1.305	2.3	60.3
13	C80	Unespecified malignant neoplasm – basal cell carcinoma	1.248	2.2	62.4
14	L65	Non-scarring alopecias/ telogen effluvium	1.221	2.1	64.6
15	L85	Epidermal thickening/Xerosis cutis	974	1.7	66.3
16	L72	Follicular cysts of the skin and subcutaneous tissue	891	1.6	67.8
17	L64	Androgenetic alopecia	863	1.5	69.3
18	B86	Scabies	799	1.4	70.7
19	L80	Vitiligo	780	1.4	72.1
20	A30	Leprosy	708	1.2	73.3
21	L28	Lichen simplex chronicus and prurigo nodularis	678	1.2	74.5
22	Q82	Congenital skin malformation / acrochordon	636	1.1	75.6
23	L50	Urticaria	633	1.1	76.6
24	L73	Other follicular disorders/ folliculitis	624	1.1	77.8
25	L90	Atrophic striae/scars and skin fibrosis	564	1	78.8
All diagnos	es		57343	100	100

United States, Germany, China, India, and Brazil. When the "title, abstract, and keywords" tab was activated, with a time limit between 2012-2018, the number of documents per search was as follows:

"acne"	11.647
"superficial mycoses"	137
"pigmentation disorder"	999
"skin aging"	3.984
"contact dermatitis"	5.909
"seborrheic dermatitis"	1.180
"verruca"	1.872
"melanocytic nevus"	1.451
"eczema"	9.853
"psoriasis"	21.155
"atopic dermatitis"	12.825

"seborrheic keratosis"	1.019
"non melanoma skin cancer"	2.902
"photoaging"	1.709

Due to the greater number of documents in Scopus, the eight dermatoses chosen for a pre-study were: acne, contact dermatitis, eczema, psoriasis, atopic dermatitis, basal cell carcinoma, photoaging, and skin aging. The pre-study included the following data: number of documents published between 2012 and 2018, primary sources of documents, main authors, number of documents by affiliation, most important funders, number of documents by country, area of study, and document types.

The graphics below show the total number of documents between 2012 and 2018 and the number of documents per country for the eight dermatoses.

Acne - Graphics 1.1 and 1.2 Skin aging - Graphics 2.1 and 2.2 Contact dermatitis - Graphics 3.1 and 3.2 Eczema - Graphics 4.1 and 4.2 Non melanoma skin cancer - Graphics 5.1 and 5.1 Psoriasis - Graphics 6.1 and 6.2 Atopic dermatitis - Graphics 7.1 and 7.2 Photoaging - Graphics 8.1 and 8.2

### Analysis

Once the pre-analysis data of these dermatoses are exposed, the dermatoses chosen for a deeper analysis will be presented and justified.

It is necessary to define effectiveness and efficiency within the context of this research to achieve the objective of elaborating and justifying effective strategies for the international insertion of the scientific production of Brazilian Dermatology.

Effectiveness refers to the greater internationalization of Brazil in the Dermatology field, with more mobility and exchange of experiences, in the widest possible way, with foreign countries that have outstanding production quantitatively and qualitatively. This strategy aims to generate effective impacts, that is, solutions to the problems found in the most cited Brazilian articles. Efficiency is defined by the speed in generating effective impacts and reducing costs.<sup>5</sup>

Given the concepts described above and the objective of the research, we chose the dermatoses "photoaging" and "skin aging" for analysis. Skin aging is the set of skin changes caused by intrinsic and extrinsic factors. Photoaging is the set of early skin changes caused by environmental factors, particularly chronic and uncontrolled exposure to the sun. We chose these dermatoses because they are prevalent and present the possibility



**GRAPHIC 1.1:** Total number of documents between 2012 and 2018 – Acne



**GRAPHIC 1.2:** Total number of documents between 2012 and 2018 – Acne



**GRAPHIC 2.1:** Total number of documents between 2012 and 2018 – Skin aging



**GRAPHIC 2.2:** Total number of documents between 2012 and 2018 – Skin aging

of reducing public health costs through prevention and early treatment. Also, they may reduce the incidence of nonmelanoma skin cancers (basal and squamous cell carcinomas), highly prevalent in sunny countries and with a culture of intense exposure to the sun. Solar radiation, particularly ultraviolet, is the primary environmental factor in premature skin aging, with epidermal and dermal damage and cellular mutations.

Nonmelanoma skin cancer is the type of malignant neoplasm most frequently diagnosed in both sexes.<sup>9</sup> According to the National Cancer Institute (INCA), in Brazil, the number of new cases of nonmelanoma skin cancer expected for each year of the 2020-2022 triennium will be 83,770 in men and 93,160 in women, corresponding to an estimated risk of 80.12 new cases per 100,000 men and 86.65 new cases per 100,000 women. Also, in Brazil, there were 1,301 deaths from nonmelanoma skin cancer in men in 2017, corresponding to a risk of 0.92/100 thousand; and 949 deaths in women, with a risk of 0.92/100 thousand.<sup>9</sup>

Skin cancer, including the most serious one (melanoma), is directly related to chronic, uncontrolled, and unprotected exposure to solar radiation.<sup>10</sup> Of course, there are other risk factors, such as skin and eye color, and genetic predisposition, among others. Solar radiation also causes premature skin aging. It represents a complex biological process influenced by a combination of endogenous or intrinsic factors, such as genetics, and exogenous or extrinsic factors, such as exposure to solar radiation, pollution, diet, stress, smoking, drugs, systemic diseases, hormones, etc. These factors lead to progressive changes in skin structure and physiology, especially in areas exposed to the sun, where extrinsic factors account for 85% of the "aged skin" phenotype. Over time, solar lentigines, leukoderma punctata, thickening in some areas, atrophy in others, wrinkles, and pre-malignant lesions







**GRAPHIC 3.2:** Total number of documents between 2012 and 2018 – Contact dermatitis

called actinic or solar keratoses (AKs) appear. These, isolated or multiple, represent one of the signs of advanced photodamage and are considered risk markers for developing malignant lesions, especially basal and squamous cell carcinomas.10 Thus, prevention and early treatment of skin aging might reduce the incidence of AKs and nonmelanoma skin cancer.

According to the article "Estimated cost of treating nonmelanoma skin cancer in the State of São Paulo – Brazil", the average annual cost of treating nonmelanoma skin cancer in the State of São Paulo between 2000 and 2007, per patient, was R\$ 1,172  $\pm$  R\$ 424 in SUS, and total treatment expenses were R\$ 37,773,449.92.<sup>11</sup>

Therefore, nonmelanoma skin cancer is a condition that represents a high cost for public health in Brazil. The prevention and treatment of skin aging and the early diagnosis and treatment of nonmelanoma skin cancer can result in reduced health costs, also avoiding invasive surgeries and procedures for patients.

Between 2012 and 2018, the term "photoaging", in the search for "article title, abstract, keywords", resulted in 1,709 documents in Scopus, with the United States being the largest producer (464) and Brazil the fifth (101).<sup>1</sup>

Between 2012 and 2018, the term "skin aging", in the search for "article title, abstract, keywords", resulted in 3,984 documents in Scopus, with the United States being the largest producer (1,327) and Brazil the seventh (212).<sup>1</sup>

Assessing the main problems found in the semantics of the Brazilian articles most cited in Scopus about skin aging and photoaging, it will be possible to find potential international collaborators that help generate effective impacts.

The search in Scopus1 with the term "skin aging", limited to Brazil, analyzed the 10 most cited documents between 2012 and 2020.



**GRAPHIC 4.1:** Total number of documents between 2012 and 2018 – Eczema



**GRAPHIC 4.2:** Total number of documents between 2012 and 2018 – Eczema



**GRAPHIC 5.1:** Total number of documents between 2012 and 2018 – Nonmelanoma skin cancer



**GRAPHIC 5.2:** Total number of documents between 2012 and 2018 – Nonmelanoma skin cancer







**GRAPHIC 6.2:** Total number of documents between 2012 and 2018 – Psoriasis







**GRAPHIC 7.2:** Total number of documents between 2012 and 2018 – Atopic dermatitis







**GRAPHIC 8.2:** Total number of documents between 2012 and 2018 – Photoaging

Results of the survey carried out on 04/03/2021:

TITLE-ABS-KEY ("Skin aging") AND (LIMIT-TO (AFFILCOUNTRY, "Brazil") AND (LIMIT-TO (PUBYE AR, 2020) OR LIMIT-TO (PUBYEAR, 2019) OR LIMIT-TO (PUBYEAR, 2018) OR LIMIT-TO (PUBYEAR, 2017) OR LIMIT-TO (PUBYEAR, 2016) OR LIMIT-TO (PUBYEAR, 2015) OR LIMIT-TO (PUBYEAR, 2014) OR LIMIT-TO (PUBYEA R, 2013) OR LIMIT-TO (PUBYEAR, 2012)

Of the 10 most cited articles, three had as their central theme the relationship between skin aging and oral or dietary supplementation ("Carotenoids and polyphenols in nutricosmetics, nutraceuticals, and cosmeceuticals";<sup>12</sup> "Oral supplementation of specific collagen peptides has beneficial effects on human skin physiology: A double-blind, placebo-controlled study";<sup>13</sup> and "Oral intake of specific bioactive collagen peptides reduces skin wrinkles and increases dermal matrix synthesis"<sup>14</sup>).

Also, four articles addressed the study of substances in cosmetics that can alter skin aging ("Cosmetic attributes of algae – A review";<sup>15</sup> "Plant extracts and natural compounds used against UVB-induced photoaging";<sup>16</sup> "Oral intake of specific bioactive collagen peptides reduces skin wrinkles and increases dermal matrix synthesis";<sup>14</sup> and "Anti-aging cosmetics: Facts and controversies"<sup>17</sup>).

Thus, studies on the relationship between skin aging and oral supplementation and the study of cosmetic substances are relevant topics in Brazil.

From the search in Scopus1 using the term "photoaging", the search was limited to Brazil and analyzed the 20 most cited documents between 2012 and 2020. Results of the survey conducted on 07/31/2021: TITLE-ABS-KEY (photoaging) AND (LIMIT-TO) (AFFILCOUNTRY , "Brazil") AND (LIMIT-TO) (PUBYEAR, 2020) OR LIMIT-TO (PUBYEAR, 2019) OR LIMIT-TO (PUBYEAR, 2018) OR LIMIT-TO (PUBYEAR, 2017) OR LIMIT-TO (PUBYEAR, 2016) OR LIMIT-TO (PUBYEAR, 2015) OR LIMIT-TO (PUBYEAR, 2014) O R LIMIT-TO (PUBYEAR, 2013) OR LIMIT-TO (PUBYEAR, 2012)

Of the 20 most cited documents, seven had as their central theme the study of the photoprotective properties of some compounds ("Plant extracts and natural compounds used against UVB-induced photoaging";<sup>16</sup> "Low-dose oral isotretinoin versus topical retinoic acid for photoaging: A randomized, comparative study";<sup>18</sup> "Rutin increases the critical wavelength of systems containing a single UV filter and with good skin compatibility";<sup>19</sup> "Dihydrocaffeic acid prevents UVB-induced oxidative stress leading to the inhibition of apoptosis and MMP-1 expression via p38 signaling pathway";<sup>20</sup> "Mechanism of Aloe Vera extract protection against UVA: Shelter of lysosomal membrane avoids photodamage";<sup>21</sup> "Comparison of the effects of carboxytherapy and radiofrequency on skin rejuvenation";22 and "Use of Flavonoids and Cinnamates, the Main Photoprotectors with Natural Origin"<sup>23</sup>).

Therefore, according to the semantic analysis of the most cited Brazilian articles, the study of compounds with photoprotective properties is relevant research in Brazil on photoaging.

Once the most relevant topics to be studied are exposed, it is also necessary to study the possible forms of international collaboration.

### Forms of collaboration

The classification used to define the types of collaboration will be that of FAPESP. According to this Foundation, here are the possible collaborations.<sup>24,25</sup> (Table 2 and 3).

### **Discussion of analysis**

In the search on Scopus,<sup>1</sup> between 2012 and 2020, using the term "photoaging", Brazil appears as the fifth largest producer of publications on the subject. It is important to note that the United States ranks first, but South Korea and China are, respectively, the second and third largest producers.

TABLE 2: FAPESP scholarships in the country and scholarships abroad					
Scholarships in the country and abroad					
Scholarships in the country	Young Investigator				
Scientific initiation	Improvement in Public Education				
Master's degree	Scientific Journalism				
Doctoral degree	Participation in courses				
Doctoral (Direct)	Scholarships abroad				
Post-doctoral	Research Internship Abroad (BEPE)				
Technical Training	Research Abroad (BPE)				

### TABLE 3: FAPESP research grants

**Research** grants Regular Thematic project Young investigator Engineering Research Centers (CPE) Research, Innovation And Dissemination Centers (CEPID) Multi-User Equipment Program (EMU) Organization of scientific meeting São Paulo School Of Advanced Science (ESPCA) Participation in Scientific Meeting Visiting researcher Sectorial Consortia for Research and Innovation (CONSITEC) Research Partnership for Technological Innovation Program (PITE) Support of Intellectual Property Rights Program (PAPI) Public Policy Program Improvement in Public Education FAP-Books Program Innovative Research in Small Business (PIPE) Publications Equipment repair Technical Reserve for Support of Connectivity to the ANSP network Technical Reserve For Program Coordination Technical Reserve For Research Institutional Infrastructure

In the search for the term "skin aging", in the same period, the first three producers are the United States, South Korea, and China, respectively, while Brazil is the ninth. Thus, more in-depth studies on photoaging, with better methodological quality, can be a source of collaboration with Asian countries, especially South Korea.

The South Korean journal "Annals of Dermatology", which is in Q2 of Scimago with an index of 0.496, has shown high growth in the last ten years in the SJR indicator, documents citations, and international collaborations.<sup>1</sup> (Graphics 9.1 and 9.2).

According to the UOL news story "K-Beauty: all about the Korean cosmetics boom + list of brands",<sup>26</sup> the beauty industry in South Korea was valued at US\$ 11 billion in 2016, and the country exported more than US\$ 2.64 billion in cosmetics. In 2015, the country overtook Japan and the US to become the second largest cosmetics exporter to China, behind only France. Korea is the fifth country with higher investment in Research & Development (R&D) in the beauty industry. Furthermore, the news also states that the Ministry of Health and Welfare will support the expansion of investment in R&D for anti-aging products and other cosmetics. Also, in 2016, LVMH purchased a stake in Clio Cosmetics, a Korean company, for US\$ 50 million, and Goldman Sachs, along with Bain Capital Private Equity, acquired a majority stake in the Carver Korea brand for US\$ 307 million, according to Reuters.

The expansion of investments in anti-aging products in South Korea is in line with the main topics researched in Brazil about skin aging and photoaging. Thus, South Korea is an essential potential international collaborator in Brazilian Dermatology.

Therefore, according to the analysis of the data collected, an effective form of international collaboration would be the researchers' exchange between Brazil and South Korea, elaborating studies on the relationship between skin aging and oral supplementation and studying new substances for cosmetic use that act in the prevention and control of skin aging, in addition to new compounds with photoprotective properties. Thus, it is coherent to highlight that the appropriate forms of international collaboration are:

The Visiting Researcher Grant, according to FAPESP, "intends to cover, in whole or in part, the expenses related to the visit of an experienced researcher, linked to the research institution abroad or in other States of Brazil, to a research institution in the State of São Paulo, for a continuous period not exceeding one year. The main objective is to facilitate collaboration between researchers in de research projects in progress, or about to be started, at the host institution". This aid would enable to invite Chinese and Korean professors to teach at universities in the State of São Paulo and encourage them to seek graduation or master's students to conduct research in South Korea through the Research Internship Abroad Scholarship (Bolsa Estágio de Pesquisa no Exterior – BEPE). The scholarship intends to support short and medium-term research internships by FAPESP









Scientific Initiation, Master's, Direct Doctorate, Doctoral, and Post-Doctoral fellows, and it must be enjoyed during the scholarship in the country.

Brazilian doctors must also conduct research in South Korea through the Research Scholarship Abroad (Bolsa de Pesquisa no Exterior – BPE), considering the possibility of a lasting partnership and knowledge exchange. According to FAPESP, this scholarship "is intended for the researcher with the title of doctor or equivalent qualification, proven by its summary, linked to a research institution in the State of São Paulo, to conduct research activities in an institution abroad".

Given the forms of collaboration mentioned above, it is necessary to identify possible authors, universities, and funders most suitable for researchers' exchange.

### Conclusion

This research aimed to build effective strategies for the insertion and scientific interaction of Brazil with notable countries in Dermatology relevant themes. In this context, we must consider: 1) The Brazilian scientific production in Dermatology can be categorized as small, little internationalized and cited, compared to prominent countries.

2) "Photoaging" and "skin aging" are prevalent dermatoses, with the possibility of reducing public health expenses through prevention and early treatment that may reduce the incidence of non-melanoma skin cancers (basal and squamous cell carcinomas).

3) South Korea proved to be an essential potential research collaborator due to the number of publications on "photoaging" and "skin aging", the growth in the number of international collaborations in the last ten years, and the high investments in anti-aging products and other cosmetics in the world.

4) To specify the possibilities for funding scholarships, we used the FAPESP classification.

5) According to the analysis of the data collected, an effective form of international collaboration would be the exchange of researchers between Brazil and South Korea through FAPESP modalities of Visiting Researcher Grant, Research Internship Abroad Scholarship (BEPE), and Research Abroad Scholarship. Abroad (BPE). Through these funds, it will be possible to exchange professors, undergraduate, and master's students between these two countries.

### **Final considerations**

The results presented are the viable conclusion of the study conducted. Collaboration with other countries, other types of partnership, study topics, and forms of funding should be considered to construct more effective strategies for the insertion and scientific interaction of Brazil with notable countries in the Dermatology field. The results of this research cannot be generalized, and all Brazilian Dermatology funding efforts should not be aimed exclusively at South Korea since there are several significant markets for different reasons. The choice of South Korea in this study is mainly due to a large number of Korean publications on "photoaging" and "skin aging", increased international collaborations in the last ten years, and high investments in research and development in anti-aging products and other cosmetics in the country. As a result of the country's intense investment in anti-aging products and other cosmetics, the Korean beauty industry was valued at US\$ 11 billion, and the country exported more than US\$ 2.64 billion in cosmetics, in addition to having conducted multi-million dollar transactions with Western companies. Therefore, we expect that research on photoaging and skin aging can value the Brazilian cosmetics industry and increase international investments in the country.

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### **AUTHORS' CONTRIBUTION:**

**Henrique Seiji Furukawa** D ORCID 0000-0002-0720-1468 Preparation and writing of the manuscript; data collection, analysis, and interpretation.

**Ana Clara Ladeira Cruz** D ORCID 0000-0003-4389-7789 Critical revision of the manuscript.

### Guilherme Sydow Nunes Bueno Brandão D ORCID 0000-0001-7777-7844

Approval of the final version of the manuscript; study design and planning; active participation in research orientation; critical revision of the manuscript.

### Edileia Bagatin D ORCID 0000-0001-7190-8241

Approval of the final version of the manuscript; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.

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# Microneedling and epidermal growth factor (EGF) as strategies for the acne scars treatment

Microagulhamento e fator de crescimento epidérmico (EGF) como estratégias para o tratamento de cicatrizes de acne

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### ABSTRACT

**Background:** The microneedling technique and the transdermal drug delivery are indicated to treat acne scars.

**Objective:** Evaluation of the microneedling technique associated with the drug delivery of the epidermal growth factor (EGF).

**Methods:** Randomized double-blind clinical trial of 30 patients divided into two groups: (1) - two microneedling sessions with a 30-day interval, (2) - two microneedling sessions with the same interval but associated with EGF drug delivery. The patients were evaluated clinically (global acne scarring grading system - Goodman and Baron) global acne scarring grading system via multispectral image and through self-perception questionnaires. The statistical analysis (Student T-test, SNK test, analysis of variance) was performed with the SisVar software (UFLA, 1996).

**Results:** The groups were homogeneous regarding age, gender, and phototype. Clinical assessments showed a reduction in severity scores for both groups. The multispectral analysis revealed a decrease in porphyrins (p = 0.0296) and an improvement in skin texture in group two subjects.

**Conclusion:** Microneedling therapy was effective and safe for the acne scars treatment, and EGF demonstrated to be a promising strategy as well.

Keywords: Acne vulgaris; Cicatrix; Skin

### RESUMO

**Introdução:** a técnica de microagulhamento e aplicação de drug delivery transdérmico é indicada para o tratamento das cicatrizes de acne.

**Objetivos:** avaliar a técnica de microagulhamento associada a aplicação de fator de crescimento epidérmico (EGF) em drug delivery.

**Métodos:** ensaio clínico duplo-cego randomizado, com seleção de 30 pacientes, divididos em dois grupos: (1) duas sessões de microagulhamento com intervalo de 30 dias e (2) duas sessões de microagulhamento com mesmo intervalo e associação de drug delivery de EGF. Os pacientes foram submetidos à avaliação clínica (escala global de cicatriz de acne - Goodman e Baron, 2006), a avaliação por imagem multiespectral e por questionários de autopercepção. A avaliação estatística (Teste T Student, Teste SNK, análise de variância) foi realizada com o software estatístico SisVar (UFLA, 1996).

**Resultados:** os grupos foram homogêneos quanto à idade, sexo e fototipo. Na avaliação clínica, houve redução dos escores de gravidade para ambos os grupos. A análise multiespectral revelou redução das porfirinas (p=0,0296) e melhora da textura da pele, ambas para o grupo 2.

**Conclusão:** a terapia com microagulhamento foi eficaz e segura para o tratamento de cicatrizes de acne, e o EGF demonstrou ser um ativo promissor.

Palavras-chave: Acne vulgar; Cicatriz; Pele

# **Original article**

#### **Authors:**

- Mônica Albuquerque Costa<sup>1</sup> Érika Santos Freire<sup>1</sup> Maria Cristina Vieira Andrade<sup>1</sup> Marcio Roberto Silva<sup>2</sup> Maria Christina Marques Nogueira Castañon<sup>3</sup> Nádia Rezende Barbosa Raposo<sup>1</sup>
- <sup>1</sup> Universidade Federal de Juiz de Fora, Center for Health Science Research and Innovation, Juiz de Fora (MG), Brazil.
- <sup>2</sup> Embrapa, Research and Development, Juiz de Fora (MG), Brazil.
- <sup>3</sup> Universidade Federal de Juiz de Fora, Microbiology Sector and Department of Morphology, Juiz de Fora (MG), Brazil.

### Correspondence:

Mônica Albuquerque Costa Email: monica\_dealbuquerque@ hotmail.com / Alternative email: monica\_dealbuquerque@hotmail. com

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### INTRODUCTION

Acne is an inflammatory disorder, and its primary complication is the development of scars.<sup>1</sup> These can occur at any stage of the disease, but early intervention in the treatment of acne is believed to be the most effective way to prevent them.<sup>2</sup> They cause a negative aesthetic impact and generate psychosocial damage, reducing the quality of life of affected patients.<sup>3</sup> The treatment of acne scars still represents a challenge and instigates the search for other therapies and/or safer and more effective procedures.

The microneedling technique, also known as percutaneous collagen induction,<sup>4</sup> is considered a minimally invasive procedure, where a device pierces the skin, physically breaking up compact bands of collagen in the superficial layer of the dermis, leading to the formation of microchannels, thus allowing the transdermal administration of substances (drug delivery).<sup>5</sup> This technique can induce an inflammatory response and stimulate neovascularization and formation of type III collagen, later replaced by type I collagen.<sup>6</sup> Also, it promotes the release of transforming growth factors (TGF) alpha and beta, connective tissue growth factors (CTGF), platelet-derived growth factors (PDGF), and fibroblast-derived growth factors (bFGF), as well as epidermal growth factor (EGF).<sup>7</sup>

EGF decreases sebum production by suppressing lipogenesis. It also demonstrates an anti-inflammatory effect, modulating the expression of cytokines in keratinocytes, inducing changes in the differentiation and maturation of suprabasal keratinocytes, and promoting downregulation of pro-fibrotic factors such as TGF beta-<sup>1.8</sup> These effects suggest that its use is effective and that it is a promising therapeutic option for acne scars.

It is the first clinical trial that assessed the influence of EGF in drug delivery associated with microneedling technique, simultaneously comparing these strategies through multispectral analysis of skin conditions and acne scar assessment tools: global acne scarring grading system (Goodman, Baron, 2006), quality of life assessment questionnaires – Dermatology Quality of Life Index (DLQI), and adapted Cardiff Acne Disability Index (CADI).

### **METHODS**

It was a randomized, double-blind, experimental clinical study with a quantitative research model, conducted in a group of patients with acne scars who underwent two microneedling sessions associated or not with EGF drug delivery, performed by a dermatologist. The Ethics Committee in Research with Human Beings of the Federal University of Juiz de Fora approved this study under protocol number 2,702,622. Informed consent was obtained from all participants included in the study.

We performed randomization using Excel software, allocating patients randomly and equally (n=15) into group one (intervention = two microneedling sessions) or group two (intervention = two microneedling sessions associated with drug

delivery of EGF), with subsequent loss to follow-up of two patients, one from each group.

The study design was entirely randomized, with responses repeated over time. The criteria analyzed to obtain the results were: analysis of the parameters obtained in the technological device (VISIA<sup>®</sup>) that performs multispectral analysis of skin conditions; responses obtained through the adapted CADI and DLQI questionnaires; and the values obtained in the Goodman and Baron's (2006) global acne scarring grading system. The groups analyzed over time were formed by a combination of treatments (one and two) and sex (woman and man), constituting four groups.

We included patients with a clinical diagnosis of acne scars, of both sexes, aged between 18-45 years, Fitzpatrick's skin phototype IV, and who did not use any type of systemic and/ or topical dermatological or aesthetic treatment in the last six months in the face. We excluded individuals who were pregnant/lactating, who presented photosensitivity, immunosuppression, active infection (such as herpes simplex, impetigo, among others), severe types of acne (acne conglobata and fulminant), predisposition to keloid formation, presence of cutaneous malignancies, self-declared allergy to EGF and/or anesthetic, and those who did not complete all stages of the study.

In group one, two microneedling sessions were performed as a single strategy and with an interval of 30 days between sessions, and in group two, in addition to the two microneedling sessions of the same interval, application of 1 ml of epidermal growth factor (EPIfactor<sup>®</sup> in 30g of vehicle – 4000 ng/g) after the procedure. Only the use of sunscreen was indicated for home care.

The disposable manual device used was a dermaroller (DrRoller MTS Roller, MiRoll, Korea), containing a mobile cylinder with eight rows of 2 mm stainless steel needles, totaling 192 needles.

The facial skin surface was sanitized with 70% ethanol, and then an anesthetic block was performed using 2% lidocaine and 4% lidocaine cream (topical) to minimize discomfort.

Each facial region was pierced eight times in different directions (vertical, up and down, horizontal, right and left, and both diagonal directions) to achieve the endpoint of uniform petechiae and purpura across the entire face. We did not conduct skin preparation with retinoid derivatives or depigmenting agents to avoid confounding bias in the study.

At time zero (T0), we perform the clinical assessment and classification of acne scars using the Goodman and Baron scale (2006), multispectral skin analysis, and quality of life assessment using the adapted DLQI and CADI questionnaires. At time one (T1), corresponding to three to seven days after T0, we performed the first session of microneedling alone or associated with EGF. We conducted the second microneedling session, multispectral imaging assessment, clinical assessment, and quality of life assessment at time two (T2 – 30 days after T1). At time three

(T3 - 60 days after T1) and time four (T4 - 90 days after T1), we performed multispectral analysis and clinical evaluation. The last quality of life assessment was performed applying the described questionnaires at time five (T5 - 180 days after T1). The same investigator conducted all these instruments for each volunteer.

For the statistical analysis, the transformation of the mean values and the tests were conducted: T-Test (to compare the groups between the proposed treatments) and SNK Test (to compare the treatments over the study period).

The simple stratified sampling method with stratification defined for four groups, aiming to meet the analysis domains established for the study (treatment strategies: one [microneedling] and two [microneedling associated with EGF drug delivery], in addition to gender [man and woman]), was used as a strategy to reduce the coefficient of variation and, thus, allow intragroup and intergroup comparisons over time. Therefore, each individual became his or her control over time.

### RESULTS

Demographic characteristics

There were no statistically significant differences regarding the demographic characteristics (age, sex, and skin type) of the patients between the two treatment groups (Table 1). Regarding the clinical pattern of acne scar classification, all patients had a combination of atrophic scar subtypes in the studied period: icepick, boxcar, and rolling.

### **Clinical assessment**

The classification of acne scars severity by Goodman and Baron (2006) global acne scarring grading system scores four grades that classify them into grade one (macular scar); grade two (mild), grade three (moderate), and grade four (severe). Before performing any treatment strategy (time zero or baseline), two (7.1%) patients were classified as grade two (mild) and 26 (92.8%) as grade three (moderate), considering the studied population (n=28). At the end of treatment (90 days - T4), 10 (35.71%) patients were classified as mild and 18 (64.28%) as moderate, considering the population studied. Table 2 summarizes the results regarding the stratification by groups, and no statistically significant differences were found between the initial and final scores for both strategies employed (p=0.25 for group one and p=0.12 for group two).

### **Multispectral analysis**

There was a reduction in porphyrin means, which may reflect a reduction in bacterial colonization by Cutibacterium acnes (C. acnes) (p=0.0296). Porphyrins means in group one in both sexes did not change significantly over time, but for treatment group two, they tended to decrease at time 60 (men) and time 30 (women). At time 60, the porphyrin means in both groups was significantly different for men, with a higher mean for group one than for group two, indicating that the use of EGF in group two was important to control the proliferation of C. acnes and thus reduce the total amount of porphyrins on the face (Table 3 and Figures 1A and 1B).

For the variables pores, wrinkles, red area, and spots on the entire face, the comparison of means between the times and treatments performed did not show a statistically significant difference (p>0.05). However, regarding texture in the frontal region, the overall analysis without stratification by sex and skin phototype showed a trend towards improved skin quality (p=0.059) for the treatment effect. Regarding the texture in the lateral area, when performing stratification by sex and skin phototype, a slight increase in the mean values of this parameter was observed, which clinically translates into a skin improvement (Chart 1) without, however, being statistically significant (p=0.18). In figure 2, it is possible to notice the improvement in the skin texture of patients belonging to the proposed treatments.

TABLE 1: Demographic characteristics of the population studied as a function of the treatment strategies
used for acne scars.

	Trea		
	Microneedling (%)	Microneedling + EGF (%)	Total (%)
Age (mean) ±SD	28.3±5.2	$27.4 \pm 4.8$	$27.9 \pm 4.9$
Gender			
Women	57.14	61.2	60.7
Men	42.8	35.7	39.2
Fitzpatrick Skin Phototype			
II	14.2	7.14	10.7
III	64.2	57.1	60.7
IV	21.4	35.7	28.5
Total of participants	14	14	28

Caption: EGF = epidermal growth factor; SD = standard deviation

TABLE 2: Grading o	of severity of acne scars by Goodm	an and Baron (2006) betwe	een treatment groups.
		<b>Clinical Evaluation</b>	
	Microneedling		Microneedling + EGF
Paceline (T0)	Grade 2: 14.2% (2/14)	Baseline (T0)	Grade 2:0
Dasenne (10)	Grade 3:85.7% (12/14)		Grade 3: 100% (14/14)
$T_{4}(00, 1,)$	Grade 2: 42.8% (6/14)	$T_{4}(00, 1,)$	Grade 2: 28.5% (4/14)
14 (90 days)	Grade 3: 57.1% (8/14)	14 (90 days)	Grade 3:71.4% (10/14)

*Caption:* EGF = epidermal growth factor

# TABLE 3: Mean score for the presence of porphyrins obtained by multispectral analysis of facial skin (laterals: right and left) over time for participants submitted to the proposed treatments and stratified by sex.

Time (days) / Porphyrin (mean score)	0	30	60	90
Treatment 1	2537.6	2133.8	2706.6	2567
Men	Aa	Aa	B*a	Aa
Treatment 1	1637.75	1265.5	1575	1975.5
Women	Aa	Aa	AB <b>★</b> a★	Aab*
Treatment 2	1656	1590	718.6	1291
Men	Ab	Ab	Aa*	Ab
Treatment 2	1777.6	1072.8	1455.8	1436.2
Women	Ab	Aa	AB*ab*	Aab

**Caption:** Capital letters (A, B) compare treatments (1 and 2) within the same time, and lowercase letters (a, b) compare the times within the same treatment (1 or 2). Analysis with root transformation. Tests performed to compare the means: T and SNK test. Markings with the symbol (\*) refer to different means (p<0.05)



**FIGURE 1:** Image showing the reduction in the presence of porphyrins in the treatment group: microneedling with drug delivery of EGF. **A** = microneedling.

- **B** = microneedling + EGF
- **1** = start of treatment Time o/baseline
- **2** = end of treatment Time 4/90 days



**CHART 1:** Texture score assessed on patients' faces over time



**FIGURE 2:** Comparative image of skin conditions of patients in treatment groups 1 and 2 at baseline and end of follow-up.

A = microneedling.
B = microneedling + EGF
1 = start of treatment - Time o/baseline
2 = end of treatment - Time 4/90 days

### Self-perception assessment

DLQI is a questionnaire that assesses skin diseases in general and grades them according to the following score: 1 (0-1 point) the skin disease does not interfere with the patient's quality of life; 2 (2-5 points), the skin disease interferes little with the quality of life; 3 (6-10 points), the interference is moderate; 4 (11-20 points), there is a lot of interference in the quality of life; and 5 (21-30 points), there is huge interference in the quality of life of those affected. The results showed no significant differences in the total variation of scores (final score - initial score) for both treatments used (p=0.25 for treatment one and p=0.12 for treatment two). Before the intervention (time zero or baseline), of the 28 patients who participated of the study, 7 (25%) were classified as score 1; 12 (42.85%) as score 2; 4 (14, 28%) patients as score 3; 5 (17.85%) as score 4; and no patient was classified as score 5 (n=28). Based on the stratification of the groups by treatment, in treatment one (microneedling), 3 (21.42%) patients were classified as grade 1; 8 (57.14%) as grade 2; 1 (7.14%) as grade 3; and 2 (14.28%) as grade 4 (n=14). For treatment two (microneedling associated with drug delivery of EGF), 4 patients (25.57%) were classified as grade 1; 4 (25.57%) as grade 2; 3 (21.42%) as grade 3; and 3 (21, 42%) as grade 4 (n=14). At the end of the treatment, 7 (25%) patients scored 1; 19 (67.85%) scored 2; 3 (10.71%) scored 3; and no patients scored 4 and 5, considering the population studied (n=28). Based on the stratification of the groups by treatments, in treatment one (microneedling), 5 (35.71%) patients were classified as grade 1; 7 (50%) as grade 2; and 2 (14.28%) as grade 3 (n =14). For treatment two (microneedling associated with drug delivery of EGF), 2 (14.28%) patients were classified as grade 1 and 12 (85.71%) as grade 2 (n=14) (Chart 2).

The score obtained in the CADI questionnaire grades acne as mild (1) when the sum of the points obtained in the questionnaire varies from 0-5; moderate (2), when the sum varies from 6-10; and severe (3), when this sum varies from 11-15 points. Before conducting the intervention (time 0 or baseline), 15 (53.57%) patients were ranked as mild; 12 (42.85%) as moderate; and 1 (3.57%) as severe. In the last period of evaluation (time 5/180 days), 26 (92.85%) patients were graded as mild,



Chart 2: EGF - Caption: DLQI: Dermatology Quality of Life Index; 1= microneedling; 2= microneedling + EGF

and 2 (7.14%) as moderate (n=28). In treatment group one (time 0 or baseline), 8 (57.14%) patients were classified as mild, 5 (35.71%) as moderate, and 1 patient (7.14%) as severe. At the end of the study (time 5/180 days), 13 (92.85%) patients were graded as mild and only 1 (7.14%) as moderate (p=0.062). For treatment group two, 7 (50%) patients were ranked as mild and 7 as moderate, at time 0-baseline. At the end of treatment (time 5/180 days), 13 (92.85%) patients were classified as mild and only 1 (7.14%) as moderate (p = 0.12) (Chart 3).

### DISCUSSION

Acne scar management has been a challenging task and a focus of interest for dermatologists. Skin microneedling is a modality for remodeling acne scars, with minimal damage to the epidermis, few adverse events, and shorter recovery time after the procedure, compared to other methods with the same purpose.<sup>10,5,11</sup> Regarding patient selection, the literature presents several clinical trials with microneedling treatment for acne scars in young patients of both sexes. As verified by Harris et al. (2015), the average number of microneedling sessions needed to achieve satisfactory results was three sessions with mean intervals of four weeks (two to eight weeks), chiefly using 1.5 mm needles (1 mm to 3 mm) in length.<sup>12</sup> In agreement with most of the studies analyzed, we selected 30 patients with acne scars, with a mean age of 27.9  $\pm$  4.9 years, skin phototypes IV, of both sexes. After the loss to follow-up (n=2), 17 women and 11 men completed the study (n=28). Two microneedling sessions were performed using a 2 mm needle at an interval of four weeks between them.

Kalil, Frainer *et al.* (2015) selected 10 patients aged 20-40 years, of both sexes, with atrophic acne scars, who underwent three sessions of microneedling using a 2mm needle. The study used anatomopathological analysis and digital photographs.<sup>13</sup> There was application drug delivery of growth factors (EGF, IGF, TGF-beta3) using masks. The authors did not find improvement in icepick scars, but they did notice an overall improvement in skin texture and a slight improvement in acne scars. In our study,

we also observed an overall improvement in skin texture, especially in those patients who had EGF drug delivery after two microneedling sessions. Additionally, icepick scars slightly improved with shallowing of their depths.

The literature describes that EGF decreases sebum production and has an anti-inflammatory effect, reducing follicular hyperkeratosis. In addition to acting on active acne, it also stimulates the production of dermal matrix constituents, stimulating the production of organized collagen, downregulating TGF-beta1, which has a pro-fibrotic action. With its application in drug delivery, it is expected not only improvement of acne scars but also an enhancement in those patients who have associated active acne (Kim, Yeo, Li *et al.*, 2014; Draelos, 2016; Lian and Li, 2016).<sup>8,14,15</sup>

Based on these data, applying EGF in drug delivery after microneedling is justified due to its direct effect on the pathogenesis of acne and acne scars and its anti-inflammatory action, which can be beneficial for a more efficient repair of the lesion caused by the procedure.

Al Qarqaz et al. (2018) evaluated 48 patients with skin phototypes III-VI treated with microneedling (Dermastamp® electronic device) and noticed a statistically significant improvement when comparing the treatment scores (before and after) obtained by the Goodman and Baron scales and the post-acne hyperpigmentation index (PAHPI).<sup>16</sup> Our study also used different methods to assess the effectiveness of the procedure: Goodman and Baron's global acne scarring grading system, digital photographs, and adapted generic (DLQI) and specific (CADI) self-perception questionnaires. The generic questionnaires assess the quality of life outside the clinical context (Halioua, Beumont, and Lunel, 2000).<sup>17</sup> The specific ones, in turn, are used for a particular disease and, considering that they are manifestations of a determined clinical condition, they are more sensitive when compared to generics. Also, our study demonstrated a reduction in the global acne scarring grading system when comparing the scores before and after treatment, but without statistically significant



Chart 3: Distribution of the study sample (n=14/treatment), according to the classification obtained by the assessment of self-perception using the CADI questionnaire, over time for the proposed treatments

differences between the grades obtained at the beginning and the end of the treatment.

A literature review performed in consultation with PubMed from 1946-2015 and Embase from 1947-2015, by Harris *et al.* (2015)<sup>12</sup>, for microneedling research to treat acne scars, assessed the effectiveness of the procedure alone, combined with other therapies, histological changes, and adverse events. When assessing the technique in isolation, all studies showed improvement with treatment with a reduction in scar severity, based on the Goodman and Baron scale, one of which decreased from 11.7 points to 6.5. Our study showed a reduction in the means with this same assessment instrument in both treatment groups and for both sexes. However, this difference between the beginning (baseline, time zero) in which 7.1% of the patients were classified as grade 2 (mild), and 92.8% as grade 3 (moderate), and the end of the follow-up (90 days, time four) where 35.7% of

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patients were classified as grade 2 (mild) and 64.2% as grade 3 (moderate), was not statistically significant. However, it is worth noting that the 28.6% reduction in cases classified as grade 3 in both groups may translate into clinical improvement.

### CONCLUSION

Microneedling therapy was effective and safe for treating acne scars, with minimal adverse events and short recovery time. The clinical response, expressed through the variation of the global acne scarring grading system, showed that all patients improved to varying degrees. EGF, used in drug delivery, proved to be a promising active pharmaceutical ingredient as an adjuvant in the acne scars treatment and most patients presented an improvement in quality of life, expressed by the reduction of the values obtained in the adapted DLQI and CADI questionnaires when compared to the initial values. •

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### AUTHORS' CONTRIBUTION:

### Mônica Albuquerque Costa D ORCID 0000-0002-7254-4379

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

### Érika Santos Freire D ORCID 0000-0002-2106-2310

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

### Maria Cristina Vieira Andrade D ORCID 0000-0002-4205-0618

Author's contribution: Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

### Marcio Roberto Silva D ORCID 0000-0002-0755-4415

Statistical analysis; approval of the final version of the manuscript; study design and planning; active participation in research orientation.

### Maria Christina Marques Nogueira Castañon 🝺 ORCID 0000-0002-2995-1761

Approval of the final version of the manuscript; preparation and writing of the manuscript; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

### Nádia Rezende Barbosa Raposo iD ORCID 0000-0001-5271-1048

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

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# A systematic review and meta-analysis on the association between androgenic alopecia and the risk of metabolic syndrome

Uma revisão sistemática e metanálise sobre a associação entre alopecia androgenética e o risco de síndrome metabólica

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### ABSTRACT

This study conducted a systematic review of studies on the relationship between androgenic alopecia and metabolic syndrome. We performed a comprehensive review of databases including PubMed, Web of Knowledge, Google Scholar, Scopus, and Embase, and extracted relevant articles published from 2010 to 2018. The case reports, review articles, or studies lacking full-text articles were excluded. We examined nine studies for the meta-analysis step. The results showed a significant relationship between alopecia and metabolic syndrome (OR = 2.81; CI 95% = 2.16-3.66; I2 = 73%; P = 0.0003). There is a significant correlation between androgenic alopecia and metabolic syndrome.

Keywords: Alopecia; Systematic review; Metabolic syndrome; Hair diseases; Insulin resistance; Review hair

#### RESUMO

Este estudo conduziu uma revisão sistemática de estudos sobre a relação entre alopecia androgênica e síndrome metabólica. Realizamos uma revisão abrangente de bancos de dados, incluindo PubMed, Web of Knowledge, Google Scholar, Scopus e Embase, e extraímos artigos relevantes publicados de 2010 a 2018. Os relatos de caso, artigos de revisão ou artigos sem textos completos foram excluídos. Nove estudos foram examinados para a etapa de metanálise. Os resultados mostraram uma relação significativa entre alopecia e síndrome metabólica (OR = 2,81; IC 95% = 2,16-3,66; I2 = 73%; P = 0,0003). Existe uma correlação significativa entre a alopecia androgênica e a síndrome metabólica. **Palavras-chave:** Alopecia; Revisão sistemática; Síndrome metabólica

# **Review Article**

#### Authors:

- Afsaneh Sadeghzadeh-Bazargan<sup>1</sup> Masoumeh Roohaninasab<sup>1</sup> Farnoosh Seirafianpour<sup>2</sup> Mahsa Shemshadi<sup>1</sup> Arezoo Mohammadi<sup>2</sup> Samaneh Mozafarpoor<sup>3</sup> Azadeh Goodarzi<sup>1</sup>
- <sup>1</sup> Department of Dermatology, Rasool Akram Medical Complex Clinical Research Development Center (RCRDC), School of Medicine, Iran University of Medical Sciences, Tehran, Iran
- <sup>2</sup> Student Research Committee, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
- <sup>3</sup> Department of Dermatology, Skin Diseases and Leishmaniasis Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

#### **Correspondence:**

Azadeh Goodarzi (author) azadeh\_goodarzi1984@yahoo. com Masoumeh Roohaninasab (co-author) rohaninasab.m@iums.ac.ir

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### INTRODUCTION

Androgenetic Alopecia (AGA) is a type of alopecia that shows hair thinning and loss in the frontal and central regions of the head or the vertex.<sup>1</sup>

According to evidence, 50% of men and women suffer from androgenic alopecia.<sup>2</sup> AGA mainly affects people in the third and fourth decades of life but can occur any time after puberty and is more common in men than women. Also, the pattern of hair loss is different between the sexes.<sup>3</sup>

The etiology of AGA is multifactorial. Two fundamental changes occur in the hair cycle causing the condition: first, the hair anagen phase decreases, producing vellus and miniaturized hairs; second, the distance between the telogen and anagen phases increases, resulting in an increased number of empty hair follicles.<sup>4</sup> Dihydrotestosterone (DHT) is a major factor in AGA pathogenesis. Five-alpha reductase enzyme converts testosterone to DHT. There are two types of 5-alpha reductase enzymes: type 1 and type 2. Type-2 5-alpha reductase plays an essential role in AGA. DHT binds to androgen receptors in the dermal papilla of the hair follicle, inhibits adenyl cyclase, and activates the genes responsible for transforming terminal hair to vellus hair in the anagen phase, resulting in empty follicles.<sup>5,6</sup> Excess insulin and insulin resistance decrease the sex hormone-binding globulin levels and lead high free testosterone levels.7-9An increased serum androgen level also causes hypertension through the androgen receptors in the arterial endothelium, causing the proliferation and hyperplasia of smooth muscle cells in the arteries and contracting the lumen leading to high blood pressure.<sup>10,11</sup> Also, microvascular disorders and follicular hypoxia decrease the number of hair follicles.12

Studies on the effects of androgens on the serum lipid index show that anabolic steroids such as testosterone cause decreased HDL, increased LDL, hyperlipidemia, and coronary artery disease.<sup>13</sup> Research show that androgenic alopecia is a risk factor for insulin resistance and type-2 *diabetes mellitus* in men.<sup>13,14</sup> Insulin resistance and high blood insulin levels are also risk factors for cardiovascular disease.<sup>15</sup> Metabolic syndrome consists of insulin resistance, obesity, dyslipidemia, and hypertension, increasing the risk of cardiovascular diseases, stroke, and diabetes.<sup>16-18</sup> Studies show that some dermatologic conditions and metabolic syndrome are correlated,<sup>19</sup> but there is still controversy about the association between AGA and metabolic syndrome.<sup>7,8</sup>

The classic pattern of hair loss in men involves the frontal, temporal, and vertex regions of the scalp, while the hair on the parietal and occipital areas remains.<sup>1</sup> Female Pattern Hair Loss (FPHL) appears first as thinning and then as hair loss around the ear. However, some women experience other configurations, such as centralized, Christmas tree, or male patterns. The scattered pattern is graded using the Ludwig scale, the centralized pattern using the Olsen scale, and the male pattern using the Hamilton-Norwood scale to assess AGA.<sup>3</sup>

The present study systematically reviewed studies on the relationship between AGA and metabolic syndrome.

### **Protocol and Registration**

All the design steps were based on the PRISMA guidelines and the study sought to answer the question of whether the prevalence of the metabolic syndrome is higher in androgenic alopecia patients than in healthy controls.

### **Information Sources**

We conducted a comprehensive review of databases including PubMed, Web of Knowledge, Google Scholar, Scopus, and Embase, and extracted pertinent articles.

The keywords used to find the articles included: Metabolic syndrome, central obesity, high blood pressure, high blood sugar, high serum triglycerides, low serum high-density lipoprotein, and androgenic alopecia.

### Search Strategy

The search strategy for PubMed was: (Metabolic syndrome) OR (central obesity) OR (high blood sugar) OR (high serum triglycerides) OR (low serum high density lipoprotein) AND (androgenic alopecia) AND ("2010/01/01" [PDat]: "2018/12/31" [PDat])

After extracting pertinent articles from the databases, we entered all of them into Endnote and removed the duplicates. Subsequently, two researchers selected the articles independently, and whenever there was disagreement about the selections for the final review, a third researcher was recruited to make the final decision.

### **Eligibility Criteria**

This study included all articles published in English from 2010 to 1018 on patients with androgenic alopecia examined in terms of metabolic syndrome. Case reports, review articles, or studies lacking full-text articles were excluded.

### **Evidence Synthesis and Results**

STATA version 13.2 and Metan software were used to determine the prevalence of the condition. The pooled odds ratio was finally calculated, and the result was determined based on a 95% confidence interval (CI). The heterogeneity of the results of the studies was determined based on  $I^2$  statistics and P-value. Publication bias was also determined based on a funnel plot graph and Egger test.

### RESULT

There was a significant relationship between metabolic syndrome and alopecia. This result is contrary to the findings of some studies, perhaps because these other studies had not appropriately examined the confounding factors. The odds ratio (OR) of 2.81 shows that androgenic alopecia is a risk factor for metabolic syndrome. The incidence of metabolic syndrome was 43% to 51% in the groups with androgenic alopecia and 20% to 28% in the healthy controls.

Figure 1 shows the selection process for the databases.

### **METHODS**

The meta-analysis included a total of nine studies. The total sample size of the studies was 1,452, and 880 cases had AGA. Table 1 presents the list of studies included in the meta-analysis. Table 2 shows the risk of bias in the studies. We used a forest plot chart to calculate the numerical results of the studies (Fig. 2). Based on this chart, the results showed a significant relationship between alopecia and metabolic syndrome (OR = 2.81; 95% CI = 2.16-3.66; I<sup>2</sup> = 73%; P = 0.0003).

Figure 2: The forest plot chart for examining the OR and significance of the relationship between alopecia and metabolic syndrome.

The funnel plot chart was used to investigate publication

bias. As shown in figure 3, the studies are reasonably accurate, and there is no significant publication bias.

Figure 3: The funnel plot investigating the symmetry between the studies

### DISCUSSION

Just two review studies have been conducted on metabolic syndrome and endogenous alopecia, and both confirm the results of our analysis. According to these analyses, there is a significant correlation between androgenic alopecia and metabolic syndrome.

In 1972, Cotton et al.<sup>20</sup> showed a significant relationship



FIGURE 1: PRISMA diagrams examining the process of include and exclude studies to meta-analysis

Table 1: Details of the reviewed studies							
Reference	Title	Year of Publica- tion	Country	Patient Size	Alopecia Grading Scale	Result	
Acibucu <i>et al.</i> <sup>21</sup>	The association of insulin resistance and metabolic syndrome in early androgenetic alopecia	2010	Turkey	128	Hamilton- Norwood Scale	Significant in the alopecia group	
Mumcuoglu et al. <sup>22</sup>	The investigation of insulin resistance and metabolic syndrome in male patients with early-onset androgenet- ic alopecia	2011	Turkey	90	Hamilton- Norwood Scale	Significant in the alopecia group	
Chakrabarty <i>et al.</i> <sup>23</sup>	Association of premature androgenet- ic alopecia and metabolic syndrome in a young Indian population	2014	India	170	Norwood- Hamilton Scale	Significant in the alopecia group	
Bakry <i>et</i> al. <sup>38</sup>	Androgenetic alopecia, metabolic syndrome, and insulin resistance: Is there any association? A case-control study.	2014	India	200	Hamilton- Norwood Scale	Significant in the alopecia group	
Ozbas Gok et al. <sup>24</sup>	Is there really relationship between androgenetic alopecia and metabolic syndrome?	2015	Turky	116	Hamilton- Norwood Scale	Not significant between the two groups	
Ertas <sup>39</sup>	Androgenetic alopecia as an indicator of metabolic syndrome and cardio- vascular risk.	2016	Turky	68	Hamilton- Norwood scale and the presence of vertex hair loss	Significant in the alopecia group	
Agamia et al. <sup>25</sup>	Benign prostatic hyperplasia, meta- bolic syndrome and androgenic alo- pecia: Is there a possible relationship?	2016	Egypt	68	Hamilton- Norwood Scale	Significant in the alopecia group	
Pengsalae <i>et al.</i> <sup>26</sup>	Association of early-onset androge- netic alopecia and metabolic syn- drome in Thai men: a case-control study	2013	Thailand	400	Hamilton- Norwood Scale	Significant in the alopecia group	
Banger et al. <sup>18</sup>	Is early onset androgenic alopecia a marker of metabolic syndrome and carotid artery atherosclerosis in young Indian male patients?	2015	India	200	Hamilton- Norwood Scale	Significant in the alopecia group	

between hair loss and cardiovascular diseases for the first time. In 2010, Acibucu *et al.*<sup>21</sup> revealed, assessing 168 patients, that the probability of metabolic syndrome was 2.7 times higher in the AGA group than in the control group. The main problem of their study was the small sample size in the control group, al-though they showed significant intergroup correlations.<sup>21</sup> In 2011, in Turkey, Mumcuoglu *et al.*<sup>22</sup> examined insulin resistance and metabolic syndrome in men with early androgenic alopecia and showed that insulin resistance-related diseases and coronary artery diseases are more common in men with androgenic alopecia. This study included 50 men (18–30 years) with AGA  $\geq$ 3

on the Hamilton-Norwood scale and BMI <27 and 40 men matched in weight and age. According to the results, high Homeostatic Model Assessment for Insulin Resistance (HOMA--IR) and Fasting Insulin Resistance Index (FIRI) scores indicate that men with AGA have insulin resistance.<sup>22</sup> In a 2014 case--control study, Chakrabarty *et al.*<sup>23</sup> examined the frequency of metabolic syndrome in people with primary AGA at a cognitive therapy clinic in Bangalore, India. They assessed 85 cases of AGA and 85 matched controls using the Norwood-Hamilton scale to evaluate the degree of AGA. The study used the Chi-square test to compare the ratios between the groups and compared the

	Random Sequence Allocation	Selection Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Biases
Acibucu et al. <sup>21</sup>	+	?	_	_	?	+
Mumcuoglu et al. <sup>22</sup>	?	?	?	_	+	?
Chakrabarty et al. <sup>23</sup>	?	?	?	_	?	+
Bakry et al. 38	?	?	?	+	_	+
Banger et al. 18	+	+	+	+	+	_
Ozbas Gok <i>et al.</i> <sup>24</sup>	?	?	_	_	?	+
Ertas et al. <sup>39</sup>	+	?	?	+	?	+
Agamia et al. <sup>25</sup>	?	?	?	_	?	?
Pengsalae <i>et al.</i> <sup>26</sup>	?	_	+	_	_	?

### TABLE 2: The risk of bias in the reviewed studies

	Experimental		Control		Odds ratio		Odds ratio		ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixe	ed, 95% Cl
10.1111/j.1365-2133.2010.09816x	25			80	7.3%	3.18 [1.20, 846]	2010		
10.1684/ejd.2010.1193	4	50	2	50	2.6%	2.09 [0.36, 11.95]	2011		
PMD- 23001602	21	40	10	40	6 7%	2 22 [1 20 8 55]	2012		<b>_</b>
10.4103/0974 - 7753 138586	21	10	n 0	100	0.770	3.32[1.23, 0.33]	2013		<b>_</b>
	22	10	0 8	100	<b>0.0</b> %	3.24[1.37,7.09]	2014		-
10.4103/2229 - 51/8.13///6.	39	10	0 19	100	0 16.4%	2.73 [1.44, 5.18]	2014		<b>_</b>
10.4103/0974 - 7753.171566.	37	85	3	85	2.4%	21.07 [6.16, 72.03]	2015		
10.1155/2015/980310	35	74	26	42	24.7%	0.55 [0.26, 1.20]	2016	-	
10.1016/j.aju.2016.01.003	153	30	0 28	100	29.0%	2.68 [1.64, 4.38]	2016		
10.3109/08037051.2015.1111021	25	51	2	17	2.2%	7.21 [1.49, 34.81]	2016		
Total (95% CI) Total events	361	88	0	582	2 100%	2.81 [2.16, 3.66]			•
Hererogeneity: Chi <sup>2</sup> = 29.20, df = $\beta$ (p = 0.0003); l <sup>2</sup> = 73% Test for overall effect: Z = 7.73 (p <0.00001)							0.01 Favou	0.1 1 rs [experimenta	10 100 nl] Favours [control]

FIGURE 2: Forest Plot Chart, checking OR and Significant Relationship Between Alopecia and Metabolic Syndrome

means between the subjects with metabolic syndrome and the controls using the independent t-test.

AGA was associated with metabolic syndrome in Indian men younger than 30 years old (P<0.001), but the severity of AGA was not correlated with metabolic syndrome. A 2015 case-control study by Banger *et al.*<sup>18</sup> in India examined the clinical characteristics of AGA and the presence of metabolic syndrome and carotid artery atherosclerosis in men with early AGA and compared the results against a control group. The samples consisted of 100 men aged 18-35 years with AGA and several healthy controls; 22% of the patients with early androgenic alopecia met the criteria for metabolic syndrome compared to 8% in the control group. Nonetheless, there was no significant difference in the mean cholesterol levels. The research found an atherosclerotic plaque in two patients in the case group and no plaque in the control group.

Another case-control study by Ozbas Gok S. *et al.*<sup>24</sup> in 2015 in Turkey assessed 74 men with AGA and 42 male controls. Of the 74 male AGA patients (age range of 20–50 years, mean age of 32.14 years), 24 were in stage 2, 26 in stage 3, 17 in stage 4, 1 in stage 5, and 5 were in stage 7. In the case group, 35 out of 74 individuals had metabolic syndrome. However, 26 out of the


**FIGURE 3:** Funnel plot, investigating the symmetry of Existing Studies

42 subjects in the control group were affected. There was no significant difference in metabolic syndrome prevalence between the AGA patients and the control group (P=0.135). Among the studied parameters, only systolic blood pressure was significantly higher in the AGA group than in the control group. <sup>24</sup>A study by Agamia et al.25 in Egypt in 2016 found a significant association between benign prostatic hyperplasia (BPH) and metabolic syndrome with AGA: the risk of metabolic syndrome was 2.68 times higher in the patients with androgenic alopecia. Androgenic changes in men's bodies also increase the chance of developing prostate cancer.<sup>25</sup> A study by Pengsalae et al.<sup>26</sup> in Thailand in 2013 evaluated the association between androgenic alopecia and metabolic syndrome in Thai men. The research selected 80 male subjects, including 40 with early diagnosis of AGA (before 35 years of age) and 40 controls without alopecia. The patients with early androgenic alopecia were 3.48 times more likely to have metabolic syndrome than the control group (P =0.015, OR = 3.48, 95% CI = 1.25–9.75). Pengsalae et al.<sup>26</sup> found a significant association between androgenic alopecia and metabolic syndrome. Also, they observed a correlation between the severity of AGA and metabolic syndrome (P= 0.629). They concluded that the early detection of metabolic syndrome in this population might be helpful in preventing cardiovascular diseases.<sup>26</sup>A study in South Korea by Yi et al.27 in 2012 using the Norwood scale for men and the Ludwig scale for women examined a total of

3,408 individuals (1,707 men and 1,701 women) from January 2008 to February 2010. The relationship between AGA and all five metabolic syndrome components (waist circumference, triglycerides, high-density lipoprotein, blood glucose, and blood pressure) was statistically non-significant.

When multiple regressions were used to adjust for age, family history, and smoking status, there was no significant relationship between the prevalence of metabolic syndrome and AGA in the male group. In contrast, there was a statistically significant relationship between the prevalence of metabolic syndrome and AGA in the female group. A 2010 study by Acibucu et al.<sup>21</sup> in Singapore assessed the frequency of insulin resistance, hyperinsulinemia, and metabolic syndrome in patients with androgenic alopecia. The study analyzed 80 patients with primary AGA and 48 healthy controls. The results showed that the difference in insulin resistance between the groups was statistically significant, as this index was higher in patients with preterm AGA compared to the healthy controls. Also, the incidence of metabolic syndrome was significantly higher in the AGA group than in the control group. The study showed that the prevalence of insulin resistance and metabolic syndrome increases in patients with AGA.<sup>21</sup> A 2010 study by Su L. H. et al. in Taiwan evaluated the relationship between metabolic syndrome and androgenic alopecia in 740 individuals aged 40 to 91 years.<sup>6</sup> It used the Norwood scale to evaluate the rate of hair loss. The research

collected data on the components of metabolic syndrome and other possible risk factors, and the results showed a significant relationship between AGA and metabolic syndrome (OR= 1.67, 95% CI= 1.01-2.74) as well as a significant relationship between AGA and the number of components of the metabolic syndrome (OR= 1.21, 95% CI= 1.03-1.42). Among the components of the metabolic syndrome, high-density lipoprotein cholesterol (HDL-C) was identified as the most important factor associated with AGA (OR= 2.36, 95% CI= 1.41-3.95; P= 0.001). This finding may have significant implications for the detection of metabolic syndrome in patients with moderate or severe AGA.<sup>6</sup> A 2016 cross-sectional study by Gopinath H. et al.<sup>17</sup> in India, examined the association between metabolic syndrome and early androgenic alopecia in men aged 18-55 years. The research included 85 cases with clinically diagnosed early-onset (less than 35 years) androgenic alopecia (Norwood III) plus 85 controls without androgenic alopecia. Metabolic syndrome was observed in 19 (22.4%) patients with androgenic alopecia and eight (4.9%) controls (P = 0.021). Abdominal obesity, hypertension, and low-density lipoprotein levels were higher in patients with androgenic alopecia compared to the controls.<sup>17</sup> A 2014 study by Eckel et al.28 in India evaluated the link between metabolic syndrome and insulin resistance in patients with AGA. It recruited 100 men with stages III-VII AGA based on the Hamilton--Norwood scale and 100 controls of the same sex and age. They observed a significant correlation between AGA and metabolic syndrome (P = 0.002) and between AGA and IR (P < 0.001).

There are many articles on the rise regarding the significant association between dermatologic disorders, metabolic syndrome, and its correlated laboratory markers and also possible logical adjunctive therapeutic options, especially psoriasis, acne, androgenic alopecia, acanthosis nigricans, hidradenitis suppurativa, and lichen planus.<sup>19,29-42</sup> This systematic review and meta-analysis focused on the association between androgenic alopecia and metabolic syndrome. •

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#### Abbreviations:

AGA: Androgenic Alopecia DHT: Dihydrotestosterone FPHL: Female Pattern Hair Loss HOMA-IR: Homeostatic Model Assessment for Insulin Resistance FIRI: Fasting Insulin Resistance Index; BPH: Benign Prostatic Hyperplasia HDL-C: High-Density Lipoprotein Cholesterol

#### **Review criteria:**

- This systematic review was conducted using five databases to assess the relationship between androgenic alopecia (AGA) and metabolic syndrome.
- This systematic review adheres to the PRISMA guidelines. Two independent reviewers extracted data, and an expert epidemiologist performed the meta-analysis.

#### Implications for clinical practice:

- According to the results of this study, there was a significant relationship between metabolic syndrome and androgenic alopecia;
- Androgenic alopecia could be a risk factor for metabolic syndrome;
- The incidence of metabolic syndrome was 43% to 51% in the groups with androgenic alopecia and 20% to 28% in the healthy groups.

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#### **AUTHOR'S CONTRIBUTION:**

#### Afsaneh Sadeghzadeh-Bazargan D ORCID 0000-0003-1102-6241

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review.

#### Masoumeh Roohaninasab (D ORCID 0000-0002-2862-6422

Approval of the final version of the manuscript; preparation and writing of the manuscript; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Farnoosh Seirafianpour D ORCID 0000-0003-3794-6206

Approval of the final version of the manuscript; data collection, analysis, and interpretation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Mahsa Shemshadi D ORCID 0000-0002-6912-0532

Author's Contribution: Statistical analysis; approval of the final version of the manuscript; data collection, analysis, and interpretation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review.

#### Arezoo Mohammadi D ORCID 0000-0002-8881-6340

Approval of the final version of the manuscript; data collection, analysis, and interpretation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review.

#### Samaneh Mozafarpoor D ORCID 0000-0001-9417-4295

Statistical analysis; approval of the final version of the manuscript; data collection, analysis and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Azadeh Goodarzi D ORCID 0000-0002-1249-4429

Statistical analysis; approval of the final version of the manuscript; preparation and writing of the manuscript; data collection, analysis, and interpretation active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

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# Collagen and skin: from the structure to scientific evidence of oral supplementation

Colágeno e pele: da estrutura às evidências de sua suplementação oral

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#### ABSTRACT

In the aging process, the intracellular routes that regulate collagen homeostasis are influenced by the exposome, resulting in its degradation and decreased synthesis, leading to sagging skin. Current evidence indicates that oral collagen supplementation may promote wrinkles reduction in the eye area, wound healing, skin elasticity and hydration improvement, enhancement of cellulite, some dermatitis, and nails fragility. Large-scale and methodologically more robust studies are still needed to consider the use of oral collagen as an effective adjuvant treatment to different dermatological conditions. **Keywords:** Collagen; Skin; Dietary supplements

#### RESUMO

Durante o processo de envelhecimento, as rotas intracelulares que regulam a homeostase do colágeno são influenciadas pelo expossoma, resultando na sua degradação e diminuição de síntese, levando à flacidez da pele. As evidências atuais disponíveis apontam que a suplementação oral de colágeno poderia promover redução de rugas na região dos olhos, cicatrização de feridas, melhora da elasticidade e hidratação da pele, melhora da celulite, de algumas dermatites e da fragilidade das unhas. Ainda são necessários mais estudos em larga escala e metodologicamente mais robustos para afirmar que o uso do colágeno oral para tratamento adjuvante de diferentes condições dermatológicas seja realmente eficaz. **Palavras-chave:** Colágeno; Pele; Suplementos nutricionais

### **Review Article**

#### **Authors:**

Francine Papaiordanou<sup>1</sup> Gabriela Pacheco de-Oliveira<sup>2</sup> Doris Hexsel<sup>3</sup> Antonio Carlos Amedeo Vattimo<sup>4</sup>

- <sup>1</sup> Francine Papaiordanou Dermatologia, Dermatology, São Paulo (SP), Brazil
- <sup>2</sup> Aché Laboratórios Farmacêuticos, Scientific Department, São Paulo (SP), Brazil.
- <sup>3</sup> Clínica Hexsel de Dermatologia, Center for Studies in Dermatology, Porto Alegre (RS), Brazil.
- <sup>4</sup> Aché Laboratórios Farmacêuticos, Medical Department, São Paulo (SP), Brazil

#### **Correspondence:**

Francine Papaiordanou francinepapaiordanou@gmail.com

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#### INTRODUCTION

Collagen represents a family of 28 different proteins, which make up about 30% of the total mass of all proteins in the human body. It plays an essential role in the structure of various tissues such as skin and bones, providing rigidity, flexibility, traction, and integrity<sup>1,2</sup> (Table 1).

The dermis is composed of a large extracellular matrix rich in collagen. Dermal collagen represents the most abundant protein in the extracellular matrix and constitutes most of the skin, corresponding to 90% of its dry mass.<sup>3</sup>

The collagen of the dermal connective tissue is essentially responsible for the skin's strength and the mechanical and structural integrity.<sup>3</sup> The complex fibers, fibrils, microfibrils, and collagen molecules form the collagen fibers. Collagen fibers provide elasticity to the skin and elastic fibers for delivering the tone.<sup>4</sup>

Over the years, profound changes occur in the dermis and epidermis structure through intrinsic and extrinsic aging processes. Collagen density in the dermis significantly decreases with age, associated with a reduction in dermal thickness. The dermal collagen network becomes increasingly fragmented, presenting shorter and less organized fibers, accumulating degraded collagen fragments, largely caused by an increased expression of matrix metalloproteinases. In parallel, the synthesis of extracellular matrix new components by fibroblasts is slower, preventing an adequate replacement of the degraded matrix. The elastic fibers of the papillary dermis lose their integrity and do not reach the dermal-epidermal junction. This global loss of elasticity and strength leads to sagging and wrinkling of the skin.<sup>5</sup>

In addition to its structural role in the skin, collagen and its fragments control different cellular functions, including cell differentiation, migration, and synthesis of several proteins.<sup>6</sup> There is evidence that collagen plays a role in regulating genes such as Gprc, Krt, and Krtap, which encode structural components of the epidermis and skin appendages, such as hair, hair follicles, and nails.<sup>7</sup>

Collagen also participates in all stages of the healing process. In the hemostasis stage, platelets aggregate around the collagen exposed by the lesion and then secrete factors that stimulate the coagulation cascade. During the inflammation phase, inflammatory cells that have migrated to the lesion site secrete proteolytic enzymes. The action of proteolytic enzymes on the extracellular matrix constituents (mainly collagen) originates several peptides, which have a chemotactic effect for the recruitment of other defense cells, such as neutrophils and macrophages.<sup>8</sup> When activated, these cells secrete TNF-alfa and IL-1beta, which directly influence collagen deposition in the wound, stimulating its synthesis via fibroblasts and tissue inhibitors of metalloproteinases. The collagen synthesis products also act by stimulating fibroblasts and keratinocytes proliferation, thus promoting re-epithelialization and angiogenesis.<sup>6</sup>

# Molecular structure and skin collagen degradation process

A triple helix of parallel polypeptides forms the primary collagen molecular structure (protein), where each third amino acid residue is a glycine (GLY). It results in X-Y-GLY, where X and Y are often proline (PRO) and 4-hydroxyproline (HYP – a subunit unique to collagen), respectively, forming PRO-HYP--GLY, the most common triple chain found in collagen. The triple helix structure is characteristic of collagens.<sup>7</sup>

The collagen turnover rate in adult humans is vastly low. Intracellular degradation is more linked to physiological processes, while extracellular degradation is more connected to pathological processes.<sup>9</sup>

Collagen molecules have a certain resistance to proteolytic actions due to their helical structure; however, there are proteolytic enzymes with high collagen specificity. This group of proteolytic enzymes is the metalloproteinases (MMPs), with 23 known types. Most of them are produced and secreted as inactive proenzymes.<sup>9</sup>

The MMPs responsible for fibrillar collagen degradation are MMP-1 (collagenase 1); MMP-2 (gelatinase A); MMP-8 (collagenase 2); MMP-12 (collagenase 3); MT1-MMP; and MT3M. MMP-3, MMP-10, and MP (membrane-associated matrix metalloproteinases) are responsible for degrading type 3 collagen.<sup>9</sup>

#### Collagen and the aging process

Aging is a biological process that leads to gradual changes in tissue function and structure. Intrinsic and extrinsic factors directly influence this process, which we currently call exposome. The exposome is based on internal factors (physiology, age, body morphology, genome), general external factors (socioeconomic and sociodemographic condition), and specific external factors (diet, environmental and occupational exposures, and lifestyle, among others)<sup>10</sup> (Table 2).

These factors influence the intracellular pathways that regulate collagen homeostasis. Time and ultraviolet radiation in dermal fibroblasts lead to increased MMP activity, resulting in collagen degradation and decreased synthesis. In addition to collagen production, biological processes such as cell migration and proliferation, and neoangiogenesis decrease over the years. With time, the action of oxidative stress, and the formation of free radicals, there is intensification in the activity of MMPs and cytokines, resulting in an increase in collagen breakdown and a decrease in its synthesis. Clinically, this process can be seen as skin flaccidity.<sup>10</sup>

The main histological changes in sagging skin are the reduction in the number of collagen fibers and their fragmentation and disorganization. Elastic fibers also undergo degradation, with loss of the regular morphological pattern (fibrillary).<sup>11,12,13</sup>

	Table 1. Main types of collagen found in skin and appendages 3.9							
Collagen types in skin structure and appendages								
Type I	More abundant in skin, tendons, bones. Composed of flexible fibers with high tensile strength (these are the major components of the MEC).							
Type III	Associated with type I. It has finer nets. Present in the basement membrane and papillary layer.							
Type IV	Present in the lamina densa of the basal layer.							
Type VI	Formed by a microfibrillary network. Mediator of the architecture and composition of the extracellular matrix. Participates in the skin healing process.							
Type VII	It forms the anchoring fibrils. It is the key structure for dermoepidermal adhesion.							

# TABLE 2: Aggravating or triggering factors forsagging skin 11,12,13

Aggravating or triggering factors for sagging skin

Aging Frequent weight variations Rapid and excessive weight loss Excessive liposuction Presence of multiple and atrophic striae

#### Skin collagen assessment methods

There are some methods available for skin collagen assessment, often used in studies and clinical research. These are direct assessment methods (such as Cutometer, Ballistometer, SkinFibrometer) and indirect assessment (Dermascan and Ultrascan).

Direct methods assess firmness, skin relaxation after traction (return to the original state), and skin elastic properties after suction. Indirect methods consist of high-frequency ultrasound with the ability to measure the thickness of the dermis and objectively assess changes in the dermis using ultrasound markers.<sup>14-18</sup>

#### Oral Collagen Supplementation And Pro-Collagen Supplementation

Oral collagen supplementation in Dermatology remains a controversial topic due to the lack of regulatory control of the quality and quantity of ingredients in the supplement market, as well as the scarcity of scientific articles on the topic. However, the interest of researchers in this subject has been growing over the years.<sup>19</sup>

Gelatin, hydrolyzed collagen, and bioactive collagen peptides are used for oral supplementation. Collagen can be extracted from connective tissue in different ways: when denatured by heat, collagen forms gelatin. After new enzymatic hydrolysis, hydrolyzed collagen (HC) is produced, composed of peptides of different lengths. HC has a lower molecular weight than gelatin, is more water-soluble, and does not harden in room air: thus, it can be formulated into liquids for oral consumption. This low molecular weight protein has been widely used because of its good biocompatibility, excellent degradability, and poor antigenicity.<sup>20</sup> HC can be re-hydrolyzed to bioactive collagen peptides, including dipeptides and tripeptides, which are resistant to hydrolysis by peptidases and systemic hydrolytic enzymes.<sup>19</sup>

Hydrolyzed collagen can cross the intestinal barrier and reach blood circulation. These peptides are digested, absorbed, and transported to the systemic circulation as peptides in the small intestine.<sup>20</sup> Bioavailability studies in humans demonstrate that dipeptides and tripeptides can be detected in the systemic circulation after oral ingestion. Also, in vitro studies have shown that oral ingestion of HC induces collagenase at the level of mRNA transcription and protein translation, promoting antioxidant activity and producing firmer collagen fibrils. Animal model studies conducted with rats demonstrate that tri (Gly--Pro-Hyp) and dipeptides (Pro-Hyp) reach the skin rapidly after oral ingestion, occurring after 10 minutes, and they are retained in the tissue for up to two weeks.<sup>19,20</sup>

A placebo-controlled animal model study by Zague et al. demonstrated a significant increase in collagen types I and IV in the skin's extracellular matrix and a decrease in metalloproteinase 2.<sup>21</sup> The antioxidant properties of HC are mainly due to the presence of hydrophobic amino acids in the peptide; however, its mechanism of action is not yet fully elucidated.<sup>20</sup>

To date, the literature has identified more than 30 peptides in the blood after ingestion of hydrolyzed collagen, mainly Pro--Hyp.These peptides can exert several functions in the body, such as fibroblasts proliferation.<sup>20</sup> However, specific peptide sequences have demonstrated more particular beneficial effects.<sup>1,2</sup> When the collagen protein is hydrolyzed through a specific process with known enzymes, cleavages occur at certain points leading to the formation of bioactive peptides with functionality in the skin tissue.<sup>22</sup>

The literature suggests three different possible mecha-

outcomes									
Article	N.	Intervention	Time	Results					
Asserin, 2015 <sup>5</sup>	106 healthy women	<ul><li>HC peptide 10g/daily (fish)</li><li>Placebo</li></ul>	180 days	Improved collagen density and fragmentation compared to placebo					
Genovese, 2017 <sup>23</sup>	120 healthy volunteers	<ul> <li>HC peptide 5g/daily (fish)</li> <li>Blend with hyaluronic acid, borage oil, n-acetylglucosamine, and antioxidant</li> <li>Placebo</li> </ul>	90 days	Improved skin elasticity compared to placebo					
Choi, 2014 <sup>24</sup>	40 healthy volunteers	<ul> <li>HC (tripeptides) 3g/daily</li> <li>HC (tripeptides) 3g/daily + vitamin C 500 mg</li> <li>Control</li> </ul>	84 days + 28 days	Improved hydration and post-laser erythema					
Inoue, 2016 <sup>25</sup>	85 healthy women	<ul> <li>HC 10g/daily with dipeptides 10 mg</li> <li>HC 10g/daily with dipeptides 0,5 mg</li> <li>Placebo</li> </ul>	56 days	Hydrolyzed fish collagen with dipeptides 10 mg, significantly superior to placebo in improving hydration, elasticity, and wrinkles					

TABLE 4: Randomized controlled trials assessing supplementation with hydrolyzed collagen composed of bioactive collagen peptides in skin and appendage-related outcomes									
Article	N.	Intervention	Time	Results					
Proksch, 2014 <sup>30</sup>	69 healthy women	<ul> <li>HC 2,5g (bioactive collagen peptides)</li> <li>HC 5g (bioactive collagen peptides)</li> <li>Placebo</li> </ul>	56 days	Improved skin elasticity compared to placebo					
Proksch, 2013 <sup>29</sup>	114 healthy women	<ul><li>HC 2,5g (bioactive collagen peptides)</li><li>Placebo</li></ul>	56 days	Improved wrinkle volume and pro- collagen type I and elastin content compared to placebo					
Schunck, 2015 <sup>26</sup>	105 healthy women	<ul><li>HC 2,5g (bioactive collagen peptides)</li><li>Placebo</li></ul>	180 days	Improved cellulite grade and skin dim- pling and improved dermal density in regular weight and overweight women compared to placebo					
Hexsel, 2017 <sup>31</sup>	25 healthy volunteers	<ul><li>HC 2,5g (bioactive collagen peptides)</li><li>Control</li></ul>	28 days	Increased nail growth and decreased breakage					

nisms by which oral collagen ingestion may benefit the skin: (a) collagen fragments may be precursors for collagen synthesis in the skin; (b) collagen fragments can stimulate the production of collagen and proteoglycans in the skin; and (c) collagen and its fragments can increase skin turnover by inducing regulatory T cells (Tregs) and M2 macrophages.<sup>22</sup>

Scientific evidence of the effectiveness of oral supplementation of hydrolyzed collagen and bioactive collagen

#### peptides

In a recently published systematic review, were analyzed randomized controlled trials using oral collagen and its effectiveness in improving skin quality, anti-aging benefits, and potential use in dermatological pathologies. The review included 11 studies were, totaling 805 patients, 699 women, 17 men, and 89 unspecified participants. The mean duration of the studies was 69.2 weeks (approximately 17 months). There were reports of eight studies conducted with hydrolyzed collagen, two studies conducted with tripeptides, and one study conducted with collagen dipeptides.<sup>23</sup> The results demonstrate that the use of collagen supplementation is promising for the short and long term in wound healing and skin aging. Collagen supplements improved collagen elasticity, hydration, and density (in the methods assessed)<sup>19</sup> (Table 3 and 4).

HC has been used to treat several dermatological conditions, including pressure ulcers, xerosis, and skin aging. A marked improvement in skin elasticity was observed with the use of HC. A study of 106 Caucasian women aged 40-65 years (for 12 weeks) showed that oral intake of 10g/day of hydrolyzed fish collagen led to an 8.83% increase in collagen density (versus 0% with placebo, p<0.01), and 31.2% reduction in collagen fragmentation (versus increased fragmentation with placebo, p<0.05).<sup>5</sup> The same authors evaluated 33 women with low skin hydration who received fish collagen peptides 10g/day, porcine collagen peptides 10g/day, and placebo for 56 days. They found that fish and porcine collagen led to a 12% and 28% increase, respectively, in skin hydration compared to the placebo.<sup>5</sup>

Another study assessed, for 90 days, 120 patients, aged between 40-60 years, who consumed a nutricosmetic containing HC 5g, hyaluronic acid, borage oil, n-acetylglucosamine, and antioxidants. The participants showed a significant increase in skin elasticity (7.5% compared to baseline versus placebo, p < 0.01).<sup>24,25</sup>

Two studies analyzed 40 patients (32 women and eight men) using collagen tripeptides 3g/day for four or 12 weeks. Eight patients (33-44 years old) underwent an 1150 nm fractional non-ablative laser procedure. Participants who received supplementation with bioactive peptides had a significant improvement in skin hydration on the third day (p<0.05%) and in skin elasticity on the 14th day (p<0.05%) compared to the group that received placebo. The use of collagen post-procedure also showed an improvement in post-laser erythema.<sup>26</sup>

There was a report of only one study with collagen dipeptides. This study assessed, for eight weeks, 85 Chinese women aged 25-57. Consumption of collagen dipeptide supplements improved skin hydration and elasticity, as well as decreased the number, depth, and roughness of wrinkles, as measured by VisioFace (Courage-Khazaka, Germany), compared to participants who received placebo (p<0.05%).<sup>27</sup>

Preliminary results regarding the use of HC in the treatment of xerosis, aging, cellulitis, and pressure ulcers are promising. Effects include improved hydration, skin elasticity, dermal collagen density, procollagen type 1 and elastin levels, and also decreased collagen fragmentation, transepidermal water loss (TEWL), and expression of MMPs 1 and 12.<sup>19</sup>

The use of collagen can benefit other issues not related to aesthetics. A good indication for its use is allergic contact dermatitis and atopic dermatitis (AD).

Atopic dermatitis is a disease that presents an alteration in the skin barrier function. Although no placebo was used, a 12week study of AD patients (13 participants in total: six receiving tripeptides 3.9 g and seven receiving common collagen 3.9g) demonstrated a deficit in the production of chemokines expressed by macrophages and stromal thymic lymphopoietin. After 12 weeks, lesions, severity index (SCORAD), qualitative hydration, PTA, and pruritus improved significantly in the group that received tripeptides. The different responses to different types of collagen in AD may occur analogously in other diseases with an altered barrier function.<sup>19</sup>

#### **Bioactive collagen peptides**

Although it is generally believed that collagen peptides are hydrolyzed to amino acids in the gastrointestinal tract before being absorbed into the bloodstream, considerable evidence exists to show that peptides can be absorbed partially intact. Several studies on bioavailability in animals and humans with collagen peptides administered orally demonstrate that they are absorbed as free amino acids and also as peptides.<sup>26</sup> The bioavailability of collagen peptides is 99%, that is, in the ingestion of 2.5 grams of bioactive peptides, 2.25 grams are absorbed.<sup>29</sup>

Ingested collagen peptides can cross the intestinal barrier and, through the integrin membrane receptor, fibroblasts signal stimulating the biosynthesis of type I collagen, proteoglycans, and elastin in the dermal extracellular matrix.<sup>28</sup> Within the target connective tissue, the peptides can exert their action on the skin's metabolic processes.<sup>28</sup>

#### Elasticity, hydration, and transepidermal water loss

A randomized, double-blind, placebo-controlled study assessed the effectiveness of hydrolyzed collagen composed of bioactive collagen peptides on skin biophysical parameters related to skin aging. The research randomized 69 women aged 35-55 years to receive 2.5 g or 5 g of hydrolyzed collagen composed of specific peptides or a placebo once daily for eight weeks. The authors objectively measured skin elasticity, hydration, roughness, and transepidermal water loss before the first administration of the product (t0) and after four (t1) and eight (t2) weeks of regular ingestion. The study also assessed skin elasticity four weeks after the last product intake. The results showed that both doses of hydrolyzed collagen improved the parameters evaluated compared to placebo. In the assessment of skin elasticity through cutometry, there was a statistically significant improvement in both doses compared to placebo. After four weeks of the last ingestion of the peptides, significantly superior skin elasticity was demonstrated in the subgroup of elderly patients, with about 98% of positive effect after the ingestion of hydrolyzed collagen. The assessment of skin hydration by corneometry showed an increase of 11-14% in hydration in women over 50 years of age. Regarding transepidermal water loss, there was a 6-7% reduction in water evaporation in women over 50 years old. No differences were demonstrated regarding skin roughness. The results show that oral ingestion of bioactive collagen peptides promotes a significant difference in skin elasticity. Also, the effects are long-lasting, especially in women over 50.30,31

A randomized, double-blind, placebo-controlled study evaluated the efficacy of taking 5 g of hydrolyzed collagen orally in 36 postmenopausal women. The research assessed participants for skin elasticity of the cheeks using cutometry at baseline, two and four weeks after randomization, and four weeks after treatment discontinuation. The skin elasticity of participants who received HC increased compared to placebo (p=0.006 and 0.03, respectively). After four weeks of treatment discontinuation (week eight), the skin elasticity of the cheeks remained superior in the HC group compared to the placebo group (p=0.01 and 0.004, respectively).<sup>32</sup> More recently, Miyanaga et al. (2021) conducted a double-blind, randomized, controlled trial to evaluate supplementation of 1 g to 5 g collagen peptides versus placebo regarding skin quality. The study assessed skin water content, transepidermal water loss (TEWL), skin elasticity, and thickness before treatment and after four, eight, and 12 weeks in 99 healthy patients. The research also quantified the level of natural hydration factor before treatment and after 12 weeks. The results demonstrated that oral ingestion of collagen peptides increased water content in the stratum corneum and epidermis and decreased transepidermal water loss. The study also showed an increased level of natural hydration factor in the stratum corneum. Skin elasticity and skin thickness remained unchanged.33

#### Wrinkles

Regarding wrinkles, a double-blind, randomized, placebo-controlled study evaluated 114 women aged 35-55 years who were randomized to receive 2.5 g of bioactive collagen peptides or placebo once daily for eight weeks. The study objectively assessed the wrinkles in all participants before the start of treatment, after four and eight weeks of treatment, and four weeks after the last ingestion. The authors established a subgroup to perform suction blister biopsies, analyzing pro-collagen I, elastin, and fibrillin at the beginning of treatment and after eight weeks. The ingestion of the bioactive collagen peptides promoted a statistically significant reduction (7.2%) in the volume of wrinkles in the eye region compared to placebo after four weeks of treatment. The effect was even more pronounced after eight weeks of treatment, with an average reduction of 20.1% compared to placebo (p<0.01). Four weeks after the last ingestion of the product, the group that received the bioactive collagen peptides continued to demonstrate a significant 11.5% reduction in the volume of wrinkles in the eye region. After eight weeks of administration, a significantly higher amount of procollagen type I (65%) and elastin (18%) content was detected in the group treated with bioactive peptides compared to the group receiving placebo. For fibrillin, an increase of 6% was detected.32

#### Cellulitis

Bioactive collagen peptides also demonstrated a relationship with clinical improvement in the treatment of moderate cellulite, in a study conducted with 105 healthy women aged 24-50 years, skin phototypes 1–3. Supplementation was performed with 2.5g/day for 180 days, resulting in a statistically significant decrease in the degree of cellulite and skin dimpling (p<0.05) in normal-weight women. The data revealed a 5.3% reduction in cellulite score after three months and a 9% reduction after six months compared to placebo. Concerning skin dimpling, there was a significant 11% reduction in normal-weight women. Also, dermal density improved significantly (p<0.05) compared to placebo. The study also observed the effectiveness of the peptides in overweight women, although the impact was less pronounced compared to normal-weight women.<sup>28</sup>

#### **Fragile nails**

An open-label study assessed the effectiveness of collagen peptides in 25 patients with brittle nail syndrome. Patients received bioactive collagen peptides 2.5 g once daily for 24 weeks, followed by a four-week treatment-free period. Bioactive collagen peptides promoted a 12% increase in the nail growth rate and a 42% reduction in the broken nails frequency. Additionally, 64% of participants achieved clinical improvement in brittle nails, and 88% showed improvement within four weeks of treatment. The study demonstrates that daily intake of bioactive collagen peptides increases nail growth and improves brittle nail syndrome, with a notable reduction in the frequency of broken nails.<sup>33</sup>

#### Wound healing and re-epithelialization

Animal studies indicate a positive effect of the oral collagen peptides on epithelialization and reduced healing time, improving angiogenesis. In this sense, an observational study assessed the impact of bioactive collagen peptides on wound healing. The study followed up 22 patients with postsurgical wounds (Group A - 12 receiving the peptides and 10 receiving the placebo) and 20 patients with unhealed wounds (Group B - 10 receiving the peptides and 10 receiving the placebo). In both groups, patients who received bioactive collagen peptides presented significantly better healing than patients treated with placebo, who had poor or suboptimal outcomes in most cases. The results of this investigation demonstrate a positive impact of the use of collagen on wound healing, even in cases where normal healing is expected to obtain aesthetic results. The positive effect on the skin is mainly due to the direct impact on the dermal extracellular matrix turnover, with a significant increase in collagen and elastin synthesis.<sup>34</sup>

#### DISCUSSION

There is growing evidence showing different benefits of oral collagen peptide supplementation for the skin. To date, the available studies are heterogeneous and present methodological limitations, which makes the results often not comparable with each other, so the evidence on collagen supplementation remains controversial.

The response to oral collagen depends on several factors. The age of the patient can have a direct influence on the results. Patients over 50 years old show a better improvement in elasticity than young patients since younger patients have a higher basal elasticity and are expected to obtain a milder response.<sup>19</sup>

Other factors such as gender, ethnicity, skin type, lifestyle, comorbidities, and the patient's skin condition may also play a role. Thus, further studies are needed to assess the efficacy in different patient niches and determine the most adequate response time. The appropriate dose remains undefined. High doses of oral collagen (15 g 3x/day) have shown improvement in healing processes, but doses of 2.5 g of bioactive peptides have already been shown to be effective in improving periorbital wrinkles.<sup>19</sup> Most studies were conducted with healthy women, which leads to a concern regarding the effectiveness of collagen use in patients with comorbidities.

It is noteworthy that patients who seek the use of oral collagen-based supplements, in general, have high expectations regarding their results, most of the time due to a lack of adequate information.

The results reported in the studies presented are highly dependent on measurement tools (transepidermal loss, skin hydration, elasticity, collagen density, etc.). However, patient satisfaction is also an important indicator of improved quality of life, and participants included in the studies mentioned reported positive feedback after using oral collagen.

#### CONCLUSION

The evidence available to date indicates that oral collagen supplementation may have an adjunctive role in the treatment of the following conditions:

- Improved skin elasticity;
- Wrinkle reduction in the eye area;
- Wound healing (including pressure ulcers);
- Cellulite improvement;Improved skin hydration;
- Improved atopic dermatitis and allergic contact dermatitis;
- Improved brittleness and increased nail growth.

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Studies have also shown that, in healthy patients, the use of oral collagen is safe even at higher doses, with no reports of adverse events related to its use. Patient satisfaction with treatment has also shown good results in available studies.

However, the effectiveness of oral collagen remains controversial due to the lack of large-scale controlled studies with recognized methodology. Studies that robustly prove the superiority of collagen ingestion versus the ingestion of other sources of proteins and amino acids are recommended, as well as research proving that collagen ingested orally can be used preferentially to improve the dermis.

There is also a need for additional studies that elucidate the role of collagen in barrier function and diseases such as atopic dermatitis, thus determining the most appropriate dose for each condition, and defining the ideal patient based on age, gender, skin type, ethnicity, and presence of comorbidities.

Comparing the results of current literature with those available a few years ago, it is possible to conclude that oral collagen has shown increasing evidence of its effectiveness in the adjuvant treatment of different conditions for patients in the dermatological office. Given the high demand and good acceptance, prescribers need to be aware of the available evidence to advise patients on the expected benefits.

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#### AUTHORS' CONTRIBUTION:

**Francine Papaiordanou** ORCID 0000-0003-0138-8361 Study design and planning; preparation and writing of the manuscript critical literature review.

**Gabriela Pacheco de-Oliveira** ORCID 0000-0001-5464-3501 Preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review

### Doris Hexsel D ORCID 0000-0002-0615-9026

Approval of the final version of the manuscript; study design and planning; active participation in research orientation; critical revision of the manuscript.

### Antonio Carlos Amedeo Vattimo D ORCID 0000-0002-1976-7434

Approval of the final version of the manuscript; critical revision of the manuscript.

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# Radiofrequency in facial wrinkles: a scientometric analysis

Radiofrequência em rugas faciais: uma análise cienciométrica

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#### ABSTRACT

The present study is a scientometric analysis aiming to verify the scientific production about radiofrequency in facial wrinkles. The databases used were the Web of Science and Pubmed. We searched the literature for all articles with the terms "Radiofrequency", "Facial", and "Wrinkle" in the title, abstract, or keywords. For each study, we analyzed the following scientometric indicators: publication number per year, name of the journal, authors, impact factor, country of publication, and type of study. **Keywords:** Aging; Aesthetic equipment; Plasma

#### RESUMO

O presente trabalho faz uma análise a partir de um estudo bibliográfico com técnicas cienciométricas, objetivando verificar a produção científica sobre o tema "radiofrequência em rugas faciais". As bases de dados utilizadas foram o Web of Science e o Pubmed. Foi realizada uma busca de todos os trabalhos que apresentavam no título, resumo ou palavras-chave os termos "Radiofrequency", "Facial", "Wrinkle". Para cada estudo, foram analisados os seguintes indicadores cienciométricos: número de publicação por ano, nome do periódico em que o trabalho foi publicado, autores das publicações, fator de impacto dos periódicos, país de publicação e tipo de trabalho. Palavras-chave: Envelhecimento; Equipamentos para estética; Plasma

### **Review Article**

#### Authors:

Adamiane Silva Moraes Schwaickardt<sup>1</sup> Ederson Schwaickardt<sup>1</sup> Lucas Henrique Sampaio<sup>1</sup>

<sup>1</sup> Universidade Estadual de Goiás, Goiânia (GO), Brazil.

#### Correspondence:

Lucas Henrique Sampaio Email: lucas.sampaio@ueg.br / Alternative email: lucashfs@gmail. com

Financial support: None. Conflict of interest: None.

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#### INTRODUCTION

Radiofrequency is a daily treatment modality for a range of medical and aesthetic indications due to its versatility, efficacy, and safety.<sup>1,2,3</sup> The technology is used to treat cellulite, acne scars, sagging skin, and facial rejuvenation. Also, it is suitable for various skin types.<sup>4,5,6</sup> Its effects are based on heating the skin layers inducing thermal damage to stimulate neocollagenesis or adipolysis, subsequently remodeling the cutaneous and subcutaneous tissues.<sup>1,2,7</sup> Previous studies show beneficial effects of radiofrequency in treating sagging skin and wrinkless.<sup>3,8</sup>

As a result of aging, facial wrinkles are a frequent concern. There is an alteration of enzymes and proteins, reduced cell proliferation, and loss of tissue elasticity, affecting the appearance negatively. Radiofrequency helps to decrease the effects of skin aging.<sup>2</sup> There is a vast literature on radiofrequency devices with an effective, safe, and less invasive therapeutic proposal, with a low risk of complications in facial rejuvenation.<sup>9</sup> However, because it is an evolving field, clinical evidence lacks robustness. Many of these devices have not been tested, and their parameters and results have little scientific evidence. Little is known about the methodological quality level of equipment with national or imported manufacturers.<sup>10</sup>

Scientometrics enables to survey quantitative aspects of scientific production, making it possible to identify patterns or trends in specific themes, authors, and institutions, contributing to periodically ordering a set of information and results already produced. Scientometrics also aims to explain and increase the visibility of scientific and technological development.<sup>11</sup> This study aims to analyze, through scientometrics, the scientific production on the topic "radiofrequency in facial wrinkles".

#### **METHODS**

It is a scientometric study on facial radiofrequency in wrinkles. The analysis aimed to measure the scientific production published in journals indexed in Pubmed and Web of Science. We searched the literature in May 2021 using the following descriptors: "Radiofrequency" and "Facial" and "Wrinkle". Then, we selected the scientific articles through the evaluation of titles and abstracts. The selected studies followed these inclusion criteria: literature review, experimental research, cohort study, case study, and publications related to facial radiofrequency in wrinkles. Opinion articles were excluded due to the unavailability of the text or abstract. We also excluded studies whose descriptors did not correspond to the proposed theme, for example, the use of the word "wrinkles" in an article on botulinum toxin or the word "radiofrequency" used as a treatment of a body region. This method used is characterized as bibliographic and exploratory.

The data analysis of these studies allowed the identification of the following information: number of publications per year, authors of the articles, year of publication, names of the journals, countries of the journals, areas of concentration, and classification of the journals according to the WebQualis criterion. We analyzed the articles from 2000, the first year of registration for the topic, to October 2019. Data were exported from Pubmed in XML via NCBI (National Center for Biotechnology Information), and from Web of Science, in tabulated text format. All data were imported, processed, and analyzed in Graphpad Prism, version 9.0. The data were presented descriptively through the construction of tables and graphs.

#### **RESULTS AND DISCUSSION**

We identified 352 studies in the literature search, 269 in the PubMed database and 93 in the Web of Science database. After excluding duplicate articles (found in both databases) and applying the inclusion and exclusion criteria, 212 articles were selected (Figure 1). These were published in 51 different journals.

Most of the articles were published in the following journals: Dermatology Surgery (n=28), Journal of Cosmetic and Laser Therapy (n=27), Journal of Drugs in Dermatology (n=25), and Journal of Cosmetic Dermatology (n=16) (Table 1). We found only one publication in a Brazilian journal, the Anais Brasileiros de Dermatologia. Table 1 shows the journals with two or more publications. The journals with the highest impact factor (IF) that published articles on the topic "radiofrequency in the treatment of wrinkles" were the Archives of Dermatology (FI=10,282 in 2020) and the Journal of the American Academy of Dermatology (JAAD) (FI =8,277 in the year 2020). The journal with the lowest impact factor with published studies on radiofrequency to treat wrinkles was the French Revue de Laryngologie D'otologie et de Rhinologie (FI=0.056). For comparison, the mean impact factors of the journals published in the area in question was also calculated (mean FI = 2,830).

Figure 2 displays the data referring to the temporal analysis of the publications. We observed that the studies directed at facial radiofrequency in wrinkles started in 2000 (n=2), persisting without great numerical expression until 2003. From 2004, there was an upward trend in publications. In 2020, we noted a drop in scientific production on the subject. However, we believe this phenomenon has been observed in health topics not related to the COVID-19 pandemic. The years in which most articles on the theme were published were 2016 (n=19), 2017 (n=20), 2018 (n=20) and 2019 (n=26) (Figure 2).

We believe this increasing trend in the number of publications regarding radiofrequency is linked to the fact that, in 2002, the Food and Drug Administration (FDA) approved the first radiofrequency device aiming at a non-invasive treatment to attenuate wrinkles and improve the temporary appearance of cellulite.<sup>13,14</sup> The increased publications in the last decade regarding "radiofrequency in facial wrinkles" indicates a raised interest in this field, as well as its scientific and technological progress, considering that the number of publications is one of the most used measures to quantify the progress and evolution of a given topic in science.<sup>15</sup>



Regarding the authors who wrote the most on the theme "facial radiofrequency in wrinkles", Neil S. Sadick (n=11) and Michael H. Gold (n=10) stand out. Table 2 shows the authors with a minimum of three publications on the subject. According to Sadick, as aging affects the population in our society, new technologies and promising procedures for rejuvenation emerge. Stimulated by this technological advance, Sadick considers radiofrequency a new method to treat many aesthetic and medical indications and seeks to elucidate the safety and efficacy of these innovative devices.<sup>16</sup> He also recommends acquiring more than one device to meet the needs of patients' different aesthetic complaints since these instruments differ in terms of energy delivery, number of electrodes, and ability to be associated with other treatments. The author considers radiofrequency, at temperatures between 55oC and 68oC, safe and capable of generating satisfactory results for rejuvenation, although there is a lack of research evaluating the ideal temperature.<sup>17</sup>

The studies published by Michael Gold comprised in this

study are related to fractional and bipolar radiofrequency devices.<sup>18,19</sup> The author also seeks to elucidate the safety and efficacy of different application techniques and draws our attention to the versatility of this treatment modality due to the possibility of domestic use. His study used a radiofrequency device associated with LED to treat periorbital wrinkles and improve the appearance of the skin, presenting safety and efficacy.<sup>20</sup>

Regarding the affiliation of authors with more publications, we observed that 75.1% of the articles on radiofrequency in facial wrinkles were developed in educational institutions. The institutions with the most papers on the topic were Cornell Medical College, with 15.1% of the papers, followed by the Tennessee Clinical Research Center and Seoul National University, with 14.1% and 13.2% of the publications, respectively.

Among the countries with the most publications on the topic "facial radiofrequency in wrinkles", the United States (n=159), England (n=46), and South Korea (n=23) stood out. In this scenario, Brazil presented only one published work.

TABLE 1: List of journals, impact factor, and number of publications									
Journal	IF	Publications							
Dermatologic Surgery	3,398	28							
Journal of Cosmetic and Laser Therapy	1,266	27							
Journal of Drugs in Dermatology	1,464	25							
Journal of Cosmetic Dermatology	1,611	16							
Lasers in Surgery and Medicine	3,020	12							
Facial Plastic Surgery Clinics of North America	1,918	6							
Clinics in Plastic Surgery	1,959	5							
Aesthetic Surgery Journal	4,283	5							
Seminars in Cutaneous Medicine and Surgery	1,425	3							
Facial Plastic Surgery	1,446	3							
Lasers in Medical Science	2,342	3							
Archives of Facial Plastic Surgery	4,611	3							
Journal of the American Academy of Dermatology	8,277	3							
Archives of Dermatology	10,282	3							
Revue de Laryngologie D'otologie et de Rhinologie	0,56	2							
Ophthalmic Plastic and Reconstructive Surgery	1,331	2							
Annals of Dermatology	1,412	2							
The Journal of Clinical and Aesthetic Dermatology	1,531	2							
Journal of Dermatological Treatment	1,669	2							
Dermatologic Therapy	2,327	2							
Journal of the German Society of Dermatology	5,584	2							

*IF* = Impact factor of journals that published on the researched topic. Publications = Quantitative number of articles published on the topic by each journal over the period surveyed. Only journals that published two or more articles on the search topic "Radiofrequency" and "Facial" and "Wrinkle" are present in the table.



Despite being the second country in the world in aesthetic surgical procedures and the third largest global market for beauty and aesthetics, Brazil has not yet given due importance to the research for developing the area.<sup>21</sup> It forces the Brazilian market to import radiofrequency technology from other countries or, worse, to use national equipment without satisfactory safety and effectiveness studies, adequate scientific parameters, or even not yet tested as safe.<sup>10,22</sup>

Among the studies analyzed, 69.6% were in humans. Of these, only 7.0% (15 articles) were randomized clinical trials; 28.4%, bibliographic reviews; 7.6%, case studies; and 6.0%, cohort studies. Although the number of publications of clinical trials was high, most of the studies were uncontrolled studies, presenting some biases such as selection with convenience sampling, small groups, unblinded study, or incomplete blinding.<sup>23</sup> Only 4,2 % (9 articles) generated a patent. It means that most of the studies were conducted using already patented equipment.

Another criterion that assesses scientific studies is the

TABLE 2: Authors who published the most on the topic "radiofrequency and wrinkles"										
Author	Publications	Institutions								
Neil S. Sadick	11	Cornell Medical College								
Michael H. Gold	10	Tennessee Clinical Research Center								
Beom Joon Kim	9	Seoul National University								
Mitchel P. Goldman	8	University of California in San Diego								
David J. Goldberg	6	Skin Laser & Surgery Center of New York								
Robert Weiss	6	Maryland Dermatology Laser Skin & Vein								
Gyeong-hun Park	5	Seoul National University								
Macrene A. Alexiades	5	Dermatology and Laser Center of New York								
Yohei Tanaka	4	Reconstructive Surgery and Aging Center of Japan								
Bradley Renton	3	Main Line Center for Laser Surgery of Pennsylvania								
Hyuk Kim	3	Incheon Medical Center								
James Newman	3	Stanford University								
Jeffrey S. Dover	3	Yale School of Medicine								
Kei Negishi	3	Seoul National University								
Kenneth O. Rothaus	3	Cornell Medical College, New York								
Kui Young Park	3	Chung-Ang University Hospital of Korea								
Tina S. Alster	3	Georgetown University Medical in Washington								
Whitney Sensing	3	Tennessee Clinical Research Center								
Won-Seok Park	3	Chonbuk National College of Medicine of Korea								

Publications = Quantitative number of publications by the author on the topic "radiofrequency and wrinkles". Institutions = Institution to which the author is affiliated

frequency an article is cited by other publications. The number of citations is used to analyze the impact of the research on the scientific community and is directly linked to the field of the study. Thus, it is expected that several other authors will cite a comprehensive study with interesting and innovative results. However, most published articles, in general, are not cited or have a low citation frequency.<sup>24</sup> The present study maintained this pattern. About 63.2% (133) of the studies were not cited, and more than 5% (11 articles) were cited only once. Three articles stood out due to the high number of citations (over 50 citations): Hruza *et al.*, 2009, with 76 citations; Sadick & Trelles, 2005, 56 citations; and Gold *et al.*, 2007, 53 citations.<sup>25,26,27</sup>

We observed a trend in academic-scientific research: the collaboration between researchers and institutions to develop a study. When studies are conducted in partnership, there is a reduction in the distances to enter the international spheres of publication, improving the research qualitatively and quantitatively.<sup>28</sup> Our study confirmed this pattern of collaborative research. One hundred and fifty-eight (74.5%) articles analyzed presented two or more authors. Also, 132 (62.2%) studies were conducted in collaboration by more than one institution. Thus, this scientometric analysis confirms an international trend that science today must be carried out collectively and collaboratively.

#### CONCLUSION

The present study demonstrated, through scientometric techniques, that the scientific production on the theme "facial radiofrequency" has increased significantly in the last decade. The country that stood out with the highest number of publications on the subject was the United States, and the year with the highest number of publications was 2019. Among the experimental studies in humans, the predominant type of experiment was the uncontrolled clinical trial. Most of the articles were published in the Dermatologic Surgery and the Journal of Cosmetic and Laser Therapy. Despite the growing demand for radiofrequency devices in Brazil, national studies conducted on this topic have not followed this increase. The effectiveness and safety of Brazilian equipment also need to be elucidated. Despite the positive role in clinical practice, the lack of techniques parameterization makes radiofrequency technology to treat facial wrinkles remain an insufficiently researched field, as the findings are usually based on uncontrolled case series, with limited validity. We consider it crucial to investigate the safety and effectiveness of new techniques that employ radiofrequency technology. It would also be essential to conduct a study demonstrating whether radiofrequency has superior benefits than other methods, with controlled, randomized, double-blind studies to increase the level of evidence.

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#### **AUTHORS' CONTRIBUTION:**

Adamiane Silva Moraes Schwaickardt DCCD 0000-0003-3423-9936 Study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation.

**Ederson Schwaickardt** D ORCID 0000-0002-2566-9451 Data collection, analysis, and interpretation.

#### Lucas Henrique Sampaio 🝺 ORCID 0000-0002-2256-1883

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; critical literature review; critical revision of the manuscript.

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### Previous fat grafting and hair transplantation using the FUE technique on scalp scars: Update

Enxerto de gordura prévio e transplante pela técnica FUE em cicatrizes do couro cabeludo: Atualização

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#### ABSTRACT

We developed a narrative literature review on the association of fat grafting and hair transplantation using the Follicular Unit Extraction (FUE) technique in scalp scars. Data were collected from studies found in Medline, Lilacs, and IBECS databases. Bibliographical records of several authors who researched mesenchymal cells in adipose tissue were cited, describing the techniques used. The conclusion was that the two-stage hair transplantation technique, with previous fat transplantation, is effective, according to the reviewed articles.

Keywords: Stem Cells; Mesenchymal Stromal Cells; Adipose Tissue; Hair transplantation

#### RESUMO

Foi realizada uma revisão de literatura narrativa, sobre a associação de enxerto de gordura e transplante de cabelos com a técnica FUE (Follicular Unit Extraction) em cicatrizes do couro cabeludo. Os dados foram coletados a partir de estudos encontrados nas bases Medline, Lilacs e IBECS. Foram citados registros bibliográficos de vários autores que pesquisaram as células me¬senquimais do tecido gorduroso, com descrição das técnicas utilizadas. A conclusão foi de que a técnica de transplante capilar em duas etapas, com transplante prévio de gordura é eficaz, segundo os artigos revisados.

Palavras-chave: Células-tronco; Células-tronco mesenquimais; Tecido adiposo; Transplante de cabelos

### Review

#### Authors:

- Estele Yumi Odo Toledo de Barros<sup>1</sup> Letícia Megumi Odo<sup>1, 2</sup> Marina Emiko Yagima Odo<sup>1</sup>
- <sup>1</sup> Odo Clinic, São Paulo (SP), Brazil
   <sup>2</sup> Hospital Israelita Albert Einstein, São Paulo (SP), Brazil

#### Correspondence:

. Marina Emiko Yagima Odo Email: marinaodo@gmail.com

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#### INTRODUCTION

"The Fascinating History of Fat Grafting", by Mazzola and Mazzola,<sup>1</sup> reports the origin of fat grafting, in 1893, when the physician Neuber transplanted adipose tissue from an arm to the orbit to correct a depressed and adherent scar, a sequela of osteomyelitis. Soon after, another surgeon removed a lipoma and filled in the space after removing fibrocystic mastitis nodules. Still in the 19th century, filling with paraffin - discovered by a German chemist - began to be performed. The filler was mixed with Vaseline or olive oil. The disastrous consequences soon appeared: there was the formation of large edemas, difficult to remove, and the paraffinoma infiltrated until resulting in pulmonary embolism and other infections. In 1926, another surgeon, Hollander, observed that grafted fat resulted in a high reabsorption rate. Thus, he mixed the patient's fat with mutton fat: he heated it until a fluid point and then injected it with a syringe. At first, the patient felt severe pain for two or three days. In Chicago (USA), Miller used gutta-percha and crumb rubber, recommending fat for saddle lips and nose.

The history of hair transplantation began in 1822 when Dieffenbach<sup>2</sup> described transplantation in birds. Only in 1959 Norman Orentreich,<sup>3</sup> considered the "father of hair transplantation", applied the technique in humans, using 4 mm punches. In 1998, Barrera<sup>4</sup> described the attempt to graft fat in scars after burns. Scleroderma, post-traumatic and post-surgical scars treatment followed. Barrera interprets that micro and mini-hair grafts present lower metabolic needs and that mesenchymal stem cells derived from adipose tissue are comparable to bone marrow cells.

This review aims to assess the current knowledge about fat grafting in scalp scars and describe hair transplantation using the Follicular Unit Extraction (FUE) technique since fat grafting performed before hair transplantation can provide better graft survival. The World Congress for Hair Research (WCHR) participants already foresee the significant progress of this technique, such as stem cells and hair cloning, starting from the principle that hair transplantation offers predictable and long-lasting results. Some authors, such as Epstein,<sup>5</sup> use this graft even on the scalp without signs of scarring, as in the case of early androgenetic alopecia.

We consulted existing articles on fat grafting on Medline, with 8294 published papers; in Lilacs, with 42; and in IBECS, with 40. About hair transplantation, 1202 publications were consulted in Medline, 24 in Lilacs, and 19 in IBECS.

#### STEM CELLS

The stem cells that Kinnaird et al. found among adipose cells were matched to those in the bone marrow.<sup>6</sup> In 2019, Obara<sup>7</sup> described pluripotent cells with the potential to differentiate into multilineage in the hair follicle.

In 2004, Kinnaird et al. demonstrated that the bone marrow has stromal cells that release cytokines such as Vascular Endothelial Growth Factor (VEGF) and Basic Fibroblastic Growth Factor (bFGF), stimulating new vessels or remodeling existing ones. Normal human mesenchymal cells were cultured under normal O2 and hypoxic conditions for 72 hours. The wide genetic range was confirmed using Elisa and Immunoblot assays. Mesenchymal Stem Cells-Conditioned Media (MSC-CM) is now called Adipose-Derived Stem Cells-Conditioned Media (ADSC-CM), promoting the proliferation and migration of endothelial cells "in vitro". Anti-VEGF and anti-FGF antibodies attenuate these effects.

Pesce and Scholer<sup>8</sup> described, in 2001, the origin of stem cells Oct4 and Nanog (transcription factors), which are inside bulge cells and also in embryonic stem cells. The bulge produces cytokines - growth factors necessary for stem cell activity, such as FGF, Platelet-Derived Growth Factor (PDGF), Bone Morphogenic Protein (BMP), and VEGF. All of them need a cytokine originating from the neural crest described by Tanimura.<sup>9</sup> Epidermal stem cells are also present in the sub-bulge region to complete differentiation into a hair follicle.

Authors such as Fukuoka et al.<sup>10,11</sup> and Shin<sup>12</sup> used the ADSC protein solution on the scalp. Fukuoka applied it using the mesotherapy technique (nappage), observing satisfactory results in 12 women and 13 men. All presented increased hair strands and thickness. After four months of treatment, ADSC cells secreted cytokines – keratinocyte growth factor, vascular endothelial growth factor, platelet-derived growth factor, and hepatocyte growth factor.

Today it is known that normal adipose tissue, which can be obtained by liposuction, has similar characteristics to bone marrow stem cells. ADSC has paracrine effects with secretion, as VEGF, HGF, bFGF, PDGF, KGF, Transforming Grow Factor (TGF-beta1), insulin-like IgF-Bp, fibronectin precursors, and superoxide dismutase. These proteins have a rejuvenating effect by stimulating collagen synthesis and fibroblast migration during healing. When stem cells are subjected to the hypoxia regimen, the lesion induces an increased concentration ofVEGF-A, PDGF, and TGF-beta1.

The adipose-derived stem cell protein extract (AAPE) is a ready-to-use product from the Korean Research Team at Prostemics Co., Ltd. (Seoul, Korea), with numerous growth factors. The hair treatment adds vitamins B, H, C, and E, buflomedil, CoQ10, and cysteine. Patients received 0.02 ml to 0.05 ml injections into the scalp, totaling 3 ml to 4 ml per treatment, in four sessions lasting three to five weeks, until the hair regenerated.

Zhu<sup>13</sup> described that supplementation with adipose tissue makes a difference in hair transplantation due to the presence of Mesenchymal Embryonic Stem Cells in the adipose tissue. The author found an improvement in adipose tissue retention and also in capillary density with angiogenesis.

The 2016 literature review by Amirkhani<sup>14</sup> presented many reports showing that human bone marrow has fat tissue similar to the function of mesenchymal cells. The study observed that umbilical cord cells derive from embryonic mesenchymal stem cells and have functions similar to those of mesenchymal cells derived from adipose tissue. Epstein,<sup>15</sup> in a 2018 study, addressed mesenchymal stromal cells, which are undifferentiated until they differentiate into specialized ones. Mesenchymal stromal cells are found in the bone marrow and other tissues such as the umbilical cord, placenta, adipose tissue, dental pulp, and liver. ADSC are easily isolated and secrete several cytokines, which are growth factors with paracrine effects, such as VEGF, HGF, IGF, and PDGF. These factors play a role in neovascularization. The author also argues that fat grafting before hair transplantation has helped the grafts to settle. She also states that the antiandrogenic effect of fat comes from the Aldo-keto reductase (AKR1C2) enzyme, which converts DHT into 3-Alpha Diol through 3-alpha reductase, with no systemic effect when injected into the alopecia area.

#### FAT GRAFTING TECHNIQUE

The role of fat grafting to improve facial contours began with Coleman.  $^{\rm 16}$ 

How adipose tissue is obtained with less trauma to adipose cells, as well as processing, is essential, as described by Co-leman, Zhu, Benemond, and Gentile.<sup>17,18</sup>

The autologous fat grafting protocol comprises some phases.

- Donor region asepsis (abdomen, inner thigh, knee, hips, flanks, and/or buttocks).

- Infiltration of tumescent anesthesia with a solution containing SF, 2% Lidocaine without vasoconstrictor, 8.4% sodium bicarbonate, and 1:1000 epinephrine. Most researchers mention that these substances have no influence on the survival of fat cells and that their use reduces liposuction complications.

- Then, manual collection with 10ml syringes is performed, preserving the adipocytes' integrity by using 3 mm to 4 mm blunt cannulas. It's possible to use a 1 mm cannula, but thicker cannulas produce less negative pressure, keep the adipocytes intact, and ensure satisfactory viability. Most authors agree that fat manipulation should be as little as possible.

- The extraction of oil and blood from the liposuction can use several techniques: decanting the fat and washing two to three times with SF followed by centrifugation for 30 to 60 seconds using different speeds; mesh filtering; or the closed system Puregraft 50® (Bimini Health Tech-TX, USA-ANVISA 8058839), where the aspirated fat is injected into a sterile bag.

- The fat is injected with 3 mL syringes and 1 mm to 2 mm blunt cannulas, one hole in the tip, after the infiltration with an anesthetic solution in a ring in the area to be reconstructed.

Klinger<sup>19</sup> implanted 1 cm3 of this tissue with mesenchymal stem cells reserves from aspirated fat on a surface of 3 cm<sup>2</sup>, demonstrating that it increases the fat grafting adherence, as well as capillary density and angiogenesis. Tesauro<sup>20</sup> described tissue regeneration, showing the significance of fat transfer in 21 cases of alopecia. He proved that the best result of hair transplantation occurred in the region of scarring alopecia after fat grafting with tissue regeneration. The author suggested transplanting the follicles using the FUE technique three months after fat grafting.

#### Fat grafting reabsorption

Contrary to Tesauro,  $Doornaert^{21}$  contests fat survival, stating that its reabsorption is between 20% and 90%, with the replacement of adipose tissue by fibrosis and cysts.

The graft replacement theory has gained importance in numerous studies. Eto<sup>22</sup>, in 2012, collected rat inguinal fat and transplanted it into the scalp. He observed the areas of the periphery and center of the graft: the region that survived would present regeneration, and, in this process, adipocytes die and mesenchymal stromal cells survive. It produces pre-adipocytes, 20 times smaller than adult adipocytes, and with greater tolerance to ischemia. The study concluded that very few adipocytes survive grafting; however, "adipose-derived stromal cells" replace them. Fu *et al.*,<sup>23</sup> supported this hypothesis by finding convincing evidence that the donor vascular fraction participates in adipogenesis and angiogenesis.

Others believe that mesenchymal host cells would replace the grafted material.

#### Fat grafting in post-traumatic scarring processes

Barrera knew that in scars after third-degree burns on the scalp, when numerous procedures are performed to improve the aesthetic and physiological aspects, each surgical procedure causes more scars. For hair follicles that need microvascular anastomoses, there would be a decrease in blood flow and a consequent reduction in nutrients. However, he concluded that, due to their size, micro and mini grafts do not have many metabolic needs.

In 2013, Jung<sup>24</sup> studied 25 cases of alopecia after burns, trauma, and surgery. The donor area was the occipital region. The recipient sites were the scalp, eyebrows, lips, and eyelids. The results were excellent in 44.4% of subjects; good in 38.9%; regular in 11.1%; and poor in 5.6%. Transplantation into scar tissue is more challenging due to impaired blood circulation and tissue stiffness. Jung also noted that the results are unsatisfactory when there are deep surgical scars. Moreno Arias<sup>25</sup> performed four sessions of 6500 microtransplants in an inelastic plaque.

#### Fat grafting in bald and atrophic scalp

Hori,<sup>26</sup> 50 years ago (in 1972), observed that in cases of less than 24 hours post-mortem of men due to accidents, increased age showed a decrease in all layers of the scalp, except for the galea aponeurotica (male androgenetic alopecia pattern). In 70-year-old women, the dermis and hypodermis were more abundant than in men (24% and 44% less). It raised the question of whether the adipose layer would have any meaning for the health of the hair follicles.

#### Fat grafting in scars and scleroderma

The camouflage technique<sup>27</sup> used on the cleft lip surgery scar was cosmetically and aesthetically acceptable. Three months after the fat grafting, hair transplantation was applied using the FUE technique, with a follow-up for 12 months. Between 2008 and 2016, Riyat<sup>28</sup> conducted 746 studies in 1158 patients using fat grafting, with improvement in the scar (color, thickness, and volume), pain, and restoration of functions in affected areas after treatment. There was an improvement in pain in 567 of 966 patients.

Roh<sup>29</sup> described 20 patients with scleroderma: with two graft sessions and 12 months of controlled follow-up, he obtained 51% to 75% improvement. In 2013, Zhu<sup>30</sup> observed that different fat preparation techniques mattered: separation by gravity, centrifugation, or simultaneous washing and filtering in a closed system. He opted for the latter procedure due to reproducibility. Grafting with the elimination of supernatant oil, debris, and especially red blood cells outperforms other methods.

Cho<sup>31</sup> showed that autologous fat improves localized scleroderma, with failure in the scalp en coup de sabre, even with hair growth.

Farjo<sup>32</sup> assessed which patients have good or poor donor areas, mainly for implants in eyebrows, eyelashes, beard, and scalp. Mostly, it depends on the status of the donor area, such as good nutrition and vascularity. As for the hair receptor area, atrophy and post-burn scars are indications for prior fat grafting. Preparation is conducted three months before the hair transplantation. Farjo also mentions other non-surgical resources, such as scalp dyes and micropigmentation, colored spray, keratin microfibers, eyebrows and eyelashes makeup, fake eyelashes and eyebrows, partial or complete wigs, adhesive prostheses with hair, and combined wigs with ear prosthesis (indicated when there is hair loss behind the ear). He added that multiple transplants of hair follicles by FUE or FUT techniques require several years before satisfactory results.

#### Transplantation in two steps

Moreno and Akidag performed FUE hair transplantations, following them for 12 months. The procedures were conducted in two stages: first, the fat grafting; second, hair transplantation after three months. Epstein<sup>33</sup> advocates two procedure stages to correct the scalp: fat grafting to improve scars, atrophies, and hypertrophies, and then hair transplantation. Matsumura<sup>34</sup> observed that the hair aging process is due to the elimination of stem cells via proteolysis.

Lee, in 2020,<sup>35</sup> made an organoid culture from a TGFbeta and FGF stem cell. He obtained an organoid cyst with a stratified epidermis, fat-rich dermis, hairy and pigmented follicles with a complete sebaceous gland, and neoformation of one follicle.

#### FOLLICULAR UNIT EXTRACTION (FUE) TECHNIQUE DESCRI-BED BY SHARMA<sup>36</sup>

The surgeon will shave the patient's head immediately

before the surgery. Only around 1 mm of the hair in the donor area should be left to visualize and guide the hair strand direction. This author mentions the piloscope (endoscope) to predict how many FUs are in each hole and recommends platelet-rich plasma (PRP) one to two months after transplantation to avoid anagen effluvium.

The author of "Hair Transplant and Local Anesthetics", Lam,<sup>37</sup> mentions that many surgeons do not want to enter this field because it is overwhelmingly tedious, but it represents a perception error. When the technique is mastered, this surgery is rewarding for both the surgeon and the patient. However, this process takes a long time. The ring block marks the area to be anesthetized in the occipital and frontal regions. Buffered solutions should not be used to avoid eyelid edema. It is advisable not to reach the galea, avoiding injuries to the nerves and vessels that run alongside it.

The first consultation evaluates patients regarding the extent of the procedure, the type of alopecia, and the donor area. Laboratory tests are requested to rule out hormonal changes, autoimmune diseases, and serology for Hepatitis B, C, and HIV. Cardiac exams such as ECG, echocardiogram, and chest X-ray are also requested, in addition to photography and informed consent for FUT and FUE. Eventually, it may be necessary to switch from FUE to FUT.

#### **Prior medication**

The protocol includes antibiotics (cephalosporin, azithromycin, etc.), steroids (methylprednisolone 8 mg), and an oral antiemetic 30 minutes before surgery. The recipient area is carefully marked, considering the compromised region, the susceptible areas, and the patient's expectations. Topical anesthesia helps reduce the pain of injections, but it should be applied about two hours before surgery, with an occlusive dressing for proper action.

In the FUE technique, all the hair is shaved, leaving 1 mm in length to allow the visualization of the hair strands' orientation. After shaving, the scalp is washed with chlorhexidine degerming agent. Asepsis is performed with alcoholic chlorhexidine after monitoring vital controls and positioning the patient. Then, sterile fields are placed.

The vein is punctured, and intravenous anesthetic drugs are administered. The dosage of psychotropic medications varies according to weight, sex, and time: Fentanyl 1 mcg/kg to 3 mcg/kg, Midazolam 0.1 mg/kg to 0.5 mg/kg, Propofol 20 mg/ min to 50 mg/min, in a continuous infusion pump. Doses are distributed throughout the procedure to keep the patient calm, responsive, and without losing control and airway reflexes.

#### Graft harvesting - Donor area

Hair transplantation begins with the patient in a prone position. After sedation, tumescent infiltration is conducted inside the donor areas marking (occipital and temporal), with a solution containing 250 ml of 0.9% saline solution, 1.25 ml of epinephrine 1:1000, and 12.5 ml of 2% lidocaine without vasoconstrictor. Then, ring block anesthesia is performed. Vibration anesthesia (Blaine Labs, Santa Fe Springs CA) can be applied to mitigate the pain of the injection. The solution contains 10 ml of 1% lidocaine with 1:100,000 epinephrine, which is infiltrated subcutaneously along the lower border of the donor area. 10 ml of 1% lidocaine with 1:100,000 epinephrine is added and infiltrated to complete the anterior part of the ring. Anesthesia is infiltrated slowly, minimizing the pain. When ring anesthesia has already been administered, it is necessary to quickly inject in the subcutaneous plane of the donor area, 100 ml to 250 ml of solution with 250 ml of 0.9% SF and 1.25 ml of epinephrine 1:1000, until the tissue is rigid and whitish and achieve good tumescence, thus minimizing the transection of the neurovascular structures below the follicles.

At this point, the doctor begins harvesting the grafts. The safe donor area is situated around the occipital protuberance in the occipital midline and arches upward to approximately two fingers above the ear helix. Grafts can be removed manually, motorized, or using a robotic arm.

The punches currently used are between 0.8 mm and 1.15 mm in diameter. The most used is 0.9 mm.

In the manual method, the surgeon cuts around the hair follicle to a depth of 2.5 mm to 3 mm using a 0.9 mm punch. At greater depths, there is a risk of transection. Blunt and hybrid punches, due to their more significant dissection effect and smaller cut, can be introduced in greater depth – larger than 4 mm – with less risk of transection (Figure 1).



FIGURE 1: Harvesting the graft in the donor area

In motorized methods, the punch is attached to the motor and cuts with the sharp end, which rotates up to 20,000 rpm. It's possible to start with a speed of up to 10,000 rpm, and when reaching 2.5 mm to 3 mm in depth, the procedure is stopped and the follicle is pulled. There are the following devices: the SAFE by Harris (HSCDevelopment, Colorado, USA), the Vortex by Cole (Cole Instruments, Georgia, USA), the Ertip FUE Micromotor Silver with Nsk (autoclavable Handle), and the Artas (Restoration Robotics) just for FUE. One person pulls out the graft and places it in ice-cold saline to avoid delay. It is recommended to put a bag of ice or recyclable ice under the tub. A compress is placed to absorb the anesthetic from the holes, and the patient changes position.

ARTAS' robotic arm employs a blunt-edge punch that slides into a sharp punch. Whether manual or motorized arm, it is recommended to place the hair in the center of the sharp punch to harvest it. It goes to a depth of 2.5 mm to 3mm; then moves to another point, and so on. It's noteworthy that the instrument is as important as the surgeon's skill.

After a few grafts harvesting, the FOX test should be performed.

1. All follicular units are intact: excellent, positive Fox.

2. Significant fat loss around the bottom of the follicle or 20% amputation: good Fox.

3. Difficult emerging angle: neutral Fox.

4. Significant avulsion and amputation of surrounding fat: negative Fox.

5. Significant damage, mainly in all grafts with the upper portion of the follicles avulsed from the lower segment: Fox negative.

It may be necessary to move from FUE to FUT (Follicular Unit Transplantation) technique, but one is not superior to the other as both have their own merits and demerits. It is up to the surgeon to decide whether to continue with FUE or switch to FUT. The difference is the linear scar of FUT compared to FUE. Several surgeons prefer FUT's trichophytic closure. In the FOX test, results 1 and 2 are ideal for FUE. The transection ratio is high in results 3, 4, and 5. Often one has to switch to the FUT technique.

#### Grafts placement - Receiving area

After harvesting the grafts, the surgeon conducts the tumescent infiltration of the receptor area in the frontal region, using 30 ml of 2% lidocaine mixed with 5 ml of 0.5% bupivacaine, 30 ml of normal saline solution, 0.5 ml of adrenaline (1:1000), and 1 ml of triamcinolone 40 mg/ml (in a regular adult).

A blade 11 or a sapphire blade with a cutting edge (ophthalmic tool) is used for incisions in the receiving area. When using needles to open the implant hole, 20 G is calculated for one hair strand, 19 G for two strands, and 18 G for three strands (Figure 2). Each follicular unit is gently implanted in each cleft.



FIGURE 2: Harvested hair follicles

To introduce the graft, that is, to place the follicle in the orifice, a jeweler's tweezers with a fine and delicate tip is used, which can be placed manually. This process requires two steps: one to open and another to implant. It's possible to alternatively use the DHI (implanter from various brands such as Choi implanter Pen and Lion implanter Pen). The follicle is attached to the device, and the hole is made, leaving the follicle inside. This technique causes fewer traumas to the follicle (Figure 3). The ideal is to use 40 FUs (follicular units) per cm<sup>2</sup> to reach a satisfactory density.

#### Evolution

Most patients tolerate the procedure well. Pain is controlled with usual analgesics. Facial and periorbital swelling occurs on the third or fourth day after surgery and is esthetically unacceptable for the patient. Cold compresses, sleeping posture, intra

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FIGURE 3: Placing the grafts with the Implanter

and postoperative corticoids can help. Shampoo with minimal pressure can remove the crusts from the second or third day. The grafts can be washed with antiseptic shampoos, as folliculitis can appear after a few weeks, which is predictable. Prescription of antibiotics for folliculitis is infrequent. The postoperative period is resolved spontaneously without harming the grafts. The donor area heals but leaves hypopigmented spots

Complications include necrosis in the donor area, hair lightening due to hydrogen peroxide, and temporary sensory disturbances in the donor area. There may be anagen effluvium between one and three months after implantation.

In a period ranging from 6 to 12 months, the hair starts to grow.

Jimenez-Acosta<sup>38</sup> recommends the International Society of Hair Restoration Surgery (ISHRS) courses and defines the calculation for transplantation: the ideal is to have 40 FUs/cm<sup>2</sup> in the receiving area, but not to remove 40 FUs where there are 60 FUs/cm<sup>2</sup> or less in the donor area. The best is homogeneous extraction of about 15-20 FUs/cm<sup>2</sup>. The FUs should not be skeletonized to have good adherence. FUE is a slow technique: it takes approximately three hours to implant 1000 FUs.

#### Conclusion

The two-stage hair transplantation technique, with prior fat transplantation, is effective for scarred hairy areas, according to the reviewed articles.

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#### **AUTHORS' CONTRIBUTION:**

**Estele Yumi Odo Toledo de Barros** OCCID 0000-0002-9339-2407 Author's contribution: Data collection, analysis, and interpretation.

**Letícia Megumi Odo** ORCID 0000-0002-5754-8857

Author's contribution: Intellectual participation in propaedeutic and/or therapeutic conduct of studied cases.

#### Marina Emiko Yagima Odo DORCID 0000-0003-1982-8388

Author's contribution: Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript.

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### Microneedling in vitiligo: A systematic review

Microagulhamento no vitiligo: Uma revisão sistemática

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#### ABSTRACT

**Background:** Microneedling was initially introduced for skin rejuvenation. This review analyzes the current literature on microneedling techniques, efficacy, and safety for vitiligo treatment.

**Methods:** An extensive PubMed search was performed to identify literature on microneedling therapy for vitiligo. Case reports, case series, and clinical trials were included.

**Results:** All 14 articles evaluated showed improvement of lesions after microneedling treatment. Combination of microneedling and topical tacrolimus, 5-FU, topical calcipotriol and betamethasone, NB-UVB with or without PDT, and triamcinolone acetonide solution yielded more efficacy than microneedling monotherapy.

**Conclusion:** Microneedling is a safe and efficient technique and an adjuvant treatment for vitiligo treatment.

**Keywords:** Vitiligo; Efficacy; Evaluation of the efficacy-effectiveness of interventions; Review; Rejuvenation; Dermatology; Depigmentation; Needling

#### RESUMO

**Panorama:** Esta revisão analisa a literatura sobre técnicas, eficácia e segurança do microagulhamento, para o tratamento do vitiligo.

**Métodos:** Relatos de casos, séries e ensaios foram pesquisados no PubMed para identificar o tratamento com microagulhamento para vitiligo.

**Resultados:** Todos os artigos avaliados apresentaram melhora das lesões após o tratamento com microagulhamento. A combinação de microagulhamento e tacrolimo tópico, 5-FU, calcipotriol e betametasona tópicos, NB-UVB com ou sem TFD e solução de triancinolona acetonida apresentou maior eficácia do que microagulhamento em monoterapia. **Conclusão:** O microagulhamento é uma técnica segura e eficiente e uma terapia adjuvante para o tratamento do vitiligo.

**Palavras-chave:** Vitiligo; Eficácia; Avaliação da eficácia-efetividade das intervenções; Análise; Rejuvenescimento; Dermatologia; Despigmentação; Agulhamento

### **Review Article**

Authors:

Masoumeh Roohaninasab<sup>1</sup> Kimia Gandomkar<sup>2</sup> Azadeh Goodarzi<sup>1</sup>

- <sup>1</sup> Department of Dermatology, Rasool Akram Medical Complex Clinical Research Development Center (RCRDC), School of Medicine, Iran University of <u>Medical Sciences, T</u>ehran, Iran
- <sup>2</sup> Department of Dermatology, Rasool Akram Medical Complex, School of Medicine, Iran University of Medical Sciences- Tehran - Iran

#### Correspondence:

Azadeh Goodarzi Email: azadeh\_goodarzi1984@ yahoo.com

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#### INTRODUCTION

Vitiligo is characterized by the appearance of circumscribed depigmented spots affecting the skin, hair, and mucous membrane. The disease has a high relapsing rate and negatively affects the quality of life.<sup>1-3</sup> Patients who have vitiligo experience low self-esteem. Global prevalence of vitiligo is between 0.5% and 2%, with reported rates varying geographically, according to a self-reported survey conducted in Europe, Japan, and the United States (US), which polled participants aged 18 and up in an online global survey.<sup>1</sup> The average age of onset for this disorder is under 20, but it can strike at any age. Owing to the absence of melanocytes from the cutaneous epidermis or the inability to secrete melanin, dyschromia manifests as depigmented macules. This is caused by a lack of the tyrosine enzyme in melanocytes, which activates the pigment formation process. The psychological and emotional toll this disorder takes on patients is significant, and developing new, more appropriate treatment options is essential.<sup>2</sup> Vitiligo has complex pathogenesis, and the precise etiology is still unclear. It was suggested that different factors, especially genetic influences, stress, autoimmune predisposition, dysfunctional biochemical pathway, and trauma might act synergistically in the disappearance of melanocytes from the skin.<sup>4-6</sup>

Vitiligo is not "just a cosmetic disorder": it is challenged by social outcasting and stigmatization causing an overwhelming psychological burden in affected patients.<sup>1,2</sup> Six multiple therapeutic modalities are currently available to treat vitiligo, but none of them achieve long-term remission in this unpredictable disease. Tacrolimus (T) is one of the topical immunomodulators that inhibits calcineurin. It has been successfully used to treat vitiligo. Tacrolimus inhibits T-cell activation, and it can be used as an adjuvant or alternative to topical steroids to avoid the associated adverse events that may result from its prolonged use.7 Microneedling (Mn) enables the delivery of drugs and larger protein molecules through the epidermis. The device has fine needles to create micro channels into the skin. Moreover, Mn stimulates the release of growth factors that are essential for skin rejuvenation.<sup>8,9</sup> A recent approach using needling showed favorable degrees of repigmentation.<sup>7</sup> It can be performed using simple injection needles or microneedling devices such as manual rollers, dermarollers, automatic needle pen devices, and microneedling fractional radiofrequency devices.8,9

Microneedling is better than simple needles in controlling penetration depth, thus preventing excessive pain during injection.<sup>8</sup> It causes micro-inflammation in the epidermal layer that enhances melanocytes and keratinocyte migration and stimulates vitiligo areas repigmentation.<sup>10</sup> Additionally, it provides successful melanocytes grafting from pigmented to unpigmented areas and improves the penetration of topical agents into the skin.<sup>3, 11</sup>

Microneedling in monotherapy or combined with therapeutic injection can be a potential treatment for vitiligo. The technique has been modestly expanded in recent years without a standardized approach. Since there is no unified method to treat the causes of vitiligo, choosing the right treatment modality and predicting its efficacy is difficult. Also, microneedling has been increasingly used in clinical practice. Thus, it seemed vital to review all studies, including clinical trials, to offer better insight for physicians.

This work aims to provide a current guide for practice based on the best available evidence of microneedling for vitiligo treatment and comparing the different methods and its efficacy when accompanied with topical therapies.

#### MATERIALS AND METHODS Methods Eligibility criteria

We sought eligible studies, without limitation publication status, which met the following criteria: (i) randomized controlled trials (RCTs) involving vitiligo patients; (ii) undergoing NB-UVB therapy in the treatment group, whatever combined with other treatments or not; (iii) undergoing photo (chemo) therapy in the control group, combined with other treatments or not; (iv) measurement of re-pigmentation degree and (v) articles published in English.

#### Search strategy

Two investigators independently searched The PubMed and Cochrane libraries using the open strings "UVB", "NB-U-VB", "narrow-band ultraviolet B", "vitiligo", "random", "randomized control trial" and "RCT". Searches were conducted to cover the period from the earliest available date to November 2013. Reference lists of prior reviews, systematic reviews, and trials were also checked.

#### Study selection and data extraction

Two investigators independently screened studies for inclusion, retrieved potentially relevant studies, and determined eligible studies. Disagreements were resolved by consensus. Two investigators independently extracted data from included studies using standardized forms, and a third investigator was assigned to check the process. The data included the number and age of participants, duration, vitiligo type or stage, treatments sessions, mean sessions of the initial response, cumulative dose of total phototherapy, cumulative dose of the initial response, treatment interval, interventions of treatment group and control group, efficacy and safety.

#### Quality assessment

We used the criteria recommended by the Cochrane Collaboration Handbook to assess the methodological quality of included trials. It chiefly concentrated on description of randomization (sequence generation progress), allocation concealment, blinding, addressing incomplete outcome data, reporting of selective outcome and other potential threats to validity.<sup>11</sup> The conclusive answer for each was "Yes", indicating "low risk of bias"; "No", indicating "high risk of bias"; and "Unclear", indicating "either lack of information or uncertainty over the potential for bias".<sup>11</sup> Consensus among the third investigator resolved the disagreements.

#### **Outcome measurements**

The primary outcome was re-pigmentation degree. We estimated the trials that mentioned the number of patients who achieved 50%, 60% or 75% re-pigmentation. Secondary outcomes included: (i) adverse events; (ii) mean sessions of initial response; and (iii) cumulative dose of total phototherapy or cumulative dose of initial response.

#### Data analysis and statistical methods

Two investigators performed all statistical analyses using the duplicate data entry facility of RevMan 5.0. In addition to 95% confidence intervals (CIs), relative risks (RRs) were used for dichotomous outcomes. The I2 statistics were calculated to determine the proportion of between-study variation due to heterogeneity. The value ranges from 0 to 100%, and high values indicate strong heterogeneity. If heterogeneity was low (p40.1, I 2 550%), a fixed-effects model was used for analysis; otherwise, a random effects model or descriptive analysis was used. A funnel plot was used to detect publication bias. P50.05 was considered statistically significant between the treatment group and control group.

#### RESULTS

The authors' search identified 14 scientific articles from June 2016 to May 2020, comprising 328 patients. Most included studies were clinical trials. The level of evidence ranged from 1B (2 studies) and 1C (9 studies) to 4 (3 studies) (Table 1).  $^{12}$ 

#### Efficacy Grading scale:

Most patients were photographed pre and post-treatment using standard camera or UV light pictures. The most common measure used to assess repigmentation was the 5-grade repigmentation scale (or Physician's Global Assessment – PGA), ranking from G0 to G4<sup>11</sup>: G4 (excellent: >75% repigmentation), G3 (very good: 50%-75% repigmentation), G2 (good: 25%-50% repigmentation), G1 (satisfactory: <25% repigmentation), and G0 (poor: no repigmentation).<sup>11,13-18</sup> Visual analog scale was used in three studies.<sup>10, 18-20</sup> Other studies used the investigator's global assessment (IGA) score and the measure of repigmentation diameter.<sup>21, 22</sup>

#### Microneedling Monotherapy:

Microneedling relies on the principle of neovascularization and neocollagenesis that result from micro-injuries following needle piercing.

Two clinical trials proved that microneedling is effective to treat vitiligo using a five grading scale to assess repigmentation.<sup>14,16</sup> The study included 57 patients with localized stable vitiligo for at least three years. Topical anesthetic cream (lidocaine) was applied to the lesion. An electronic dermapen with needles varying from 1 mm or 1.5 mm to 2 mm according to the skin thickness was applied until bleeding appeared. The patient received 6 to 12 sessions at two week-interval.<sup>14,16</sup> The authors observed a clinical response in 38.5% of patients among which 17.5% had excellent repigmentation. The best response was seen on the face, followed by the trunk.<sup>16</sup>

#### Microneedling with topical tacrolimus:

Topical tacrolimus has been successfully used to treat vitiligo. Since microneedling enhances drug delivery across the skin barrier,<sup>16</sup> tacrolimus ointment was applied after microneedling under occlusive dressing for six hours, and patients were then advised to apply it once daily every two weeks.<sup>13,16</sup> All patients underwent 12 microneedling sessions (at two-week interval), except in one study where the patients received four sessions at 15-day interval.<sup>3, 15, 16</sup>

Microneedling combined with tacrolimus was more efficient than microneedling monotherapy.<sup>16</sup> The studies observed a clinical response in 83.6% (n=97) of patients receiving combined therapy.<sup>3,13,15,16,23</sup> The clinical response grades were: partial clinical response (n=10, 11.6%), G1 (n=14, 16.3%), G2 (n=24, 31.4%), G3 (n=15, 17.4%), G4 (n=4, 4.7%), G2 (n=42, 48.8%), with >24% repigmentation (n=12, 14%).

The highest repigmentation rate was observed on the face (n=12, 70% repigmentation).<sup>3,16</sup> The same study recorded excellent repigmentation (grade G4, >75% repigmentation) in three patients with vitiligo patches on the legs, but these results were not achieved on acral areas or bony prominences.<sup>3,13,16</sup> However, Ibrahim *et al.* showed excellent results in vitiligo on the elbows (n=3, 83.33% repigmentation).<sup>15</sup>

# Microneedling with topical calcipotriol plus betamethasone:

One clinical trial compared the efficacy of microneedling with calcipotriol (0.05 mg/g) plus betamethasone (0.5 mg) versus tacrolimus in vitiligo treatment. Symmetrical patches over the elbows, knees, extremities, and acral areas were treated with microneedling every two weeks for 12 sessions, and calcipotriol plus betamethasone or tacrolimus was applied immediately after the procedure.<sup>15</sup>

Microneedling with topical calcipotriol plus betamethasone was superior to microneedling with tacrolimus in treating vitiligo. It showed earlier clinical responses and needed fewer sessions. The study noted a significantly greater repigmentation in the treated extremities patches.<sup>15</sup> Excellent results were observed in elbow (n=3, 99% repigmentation) and extremities (n=8, 83.3% repigmentation), moderate results in acral areas (n=6, 50% repigmentation), and knees had the lowest repigmentation rates (n=8, 67.5% repigmentation).<sup>15</sup>

T/	ABLE 1: Scient	tific articles	from June 201	6 to May 202	ly including 328 patients. Most included studies were clinical trials						
Study (Years)	Level of evidence	Study type	Number of patients	Mean age	Disease duration and site	Treatment	Associated treatment	Scale used	Response	Adverse events	Satisfac- tions
Lima et al. (2020)	4	Case series	12 with sta- ble localized refractory vitiligo	18-48	Face, neck, Hand, and Armpit. More than 1 year	4 sessions of skin mi- croneedling and topical tacrolimus 0.1%	Topical tacrolimus 0.1%	Partial clini- cal response	Facial types showed better responses	No adverse effects reported	Most of them were satisfied (10/12)
Mina et al. (2018	1c	Compara- tive Clinical trials	25	26.4	Extremities	Micronee- dling of 2 patches of vitilgo with dermapen, then appli- cation of 5-fluorou- racil to 1 patch and tacrolimus on the other patch.		Photogra- phed	Repigmen- tation was higher in 5-fluorou- racil treated patches More than 75% repigmenta- tion in acral parts	Hyperpig- mentation and ulce- ration. In- flammation occurred in 3 patients	
Attwa et al. (2019)			27	26.7	Extremities stable for 5 years	12 sessions with a 2-week interval. Two patches were selected in each patient. One treated with mi- croneedling alone and one treated with mi- croneedling followed by topical 5-fluorou- racil		Repigmen- tation grade ranging from G0 with no res- ponse to G4 with more than 75% response	Better response in micro needling patches	Pain and itching	Not reported
Ibrahin et al. (2017)		Compara- tive study	25	23.12	Stable vitiligo for more than 3 months	Right side treated with micronee- dling and followed by topical calcipotriol plus beta- methasone ointment and left side was treated with mi- croneedling followed by topical tacrolimus		Photogra- phed	Significant difference between both sides and right side shows better res- ponse.	7 patients without any side effects, 14 patients had pain during the session and 14 patients showed ery- thema and 7 patients showed exfoliators	14 patients were very satisfied
Khashaba et al. (2017)		Compara- tive study	60	13-50	Stable more than 5 months	Patients were randomly divided in 3 groups: group 1: UVB pho- totherapy Group 2: micro- needling followed by topical triamcinolo- ne acetonide 10mg/ml Group 3: combination of group 1 and 2		No significant difference between the best outcomes.	Percentage of repig- mentation (G0-G4) The satisfaction with 40% of patient in group 3 was significantly higher than other groups	Not reported	

Study (Years)	Level of evidence	Study type	Number of patients	Mean age	Disease duration and site	Treatment	Associated treatment	Scale used	Response	Adverse events	Satisfac- tions
Khater <i>et al.</i> (2020)		Pros- pective comparati- ve study	32			Group 1 treated with trichloroa- cetic acid 70% by mi- croneedling and group 2 was received intradermal 5-fluoroura- cil injection		Physician global asses- sment	No significant difference was shown in therapeu- tic response between two groups	Burning, discomfort and infec- tion was seen in the micronee- dling group.	
Jha <i>et al.</i> (2019)		Case report	1		Acral	Dermaroller with fine microneedle with topical 5% 5-fluo- rouracil for 7 days	Oral anti- biotics and analgesic/ anti-in- flammatory for intolera- ble pain	Photogra- phed	Complete repigmenta- tion was re- ported after 6 months		
Kumar et al. (2019)		Case report	1		Neck, head and back	Maximum dose of 5-fluoroura- cil solution used in 1 session was 10 ml with using der- maroller		Photogra- phed	Repigmen- tation was uniform	No side effects	
Ebrahim et al. (2020)	1c	Randomi- zed clinical trials	90	12-60	Face, trunk, extremities and acral areas stable for more than 12 months	Patients were rando- mized in 3 groups: 1. 2. Micro- needling only both at 2-week interval for twelve sessions Micronee- dling with tacrolimus 3. Applied tacrolimus ointment 0.1% twice daily for 6 months		Three in- dependent observer assessed the photo- graphs and repor- ter the grading of repig- mentation (G0-G4)	76.6% improve- ment in combined group. Higher improve- ment in extremities in combi- ned group	Side effects were mild and tole- rable	
Lagrange et al. (2019)		Rando- mized Clinical trials	5	44.5	Nonseg- mental viti- ligo which is stable for more than 3 months	Each patient			200uM depth of micronee- dles showed optimal response for delive- ring the melanocytes into the epidermis		

Table 1 (Continued)

Study (Years)	Level of evidence	Study type	Number of patients	Mean age	Disease duration and site	Treatment	Associated treatment	Scale used	Response	Adverse events	Satisfac- tions
Giorgio et al. (2019)		Rando- mized Clinical Trials	10	19-60 y/o	Nonseg- mental	Group A: underwent micronee- dling (3 sessions) Group B: underwent the appli- cation of 5-amino- levulinic acid 10% followed by micronee- dling to reduce the penetration and covered for 2 hours and then exposed to PDT with red light for 8 minutes (3 sessions)	UVB thera- py twice a week for 3 months		No adverse efficacy sho- wed in PDT compared to micronee- dling alone		
Korobko et al. (2016)	1c	Pilot com- parative study	24	40.3	Stable for more than 3 months with symmetri- cally located lesion	Symmetrical lesions were treated with model CIT8 Dermarol- ler device with 0.5 mm needle and lata- noprost or tacrolimus for 4 mi- croneedling procedures	Latanoprost and tacroli- mus	Photogra- phed	Patients who are treated with latanoprost show better repigmen- tation than patients who are treated with tacrolimus. The diffe- rences were not statically significant. The number of lesions with more than 75% repigmenta- tion on lata- noprost was significantly higher.	No adverse effects	
Feily et al. (2020)	1c	Prospec- tive pilot study	20	30.22	Palmar and plantar lesion with more than 1 year stability	Right side of lesion re- ceived 1.5-2 mm needle length and left side of the lesion received single frac- tions with fractional CO2 laser	UVB pho- totherapy three times per week	Photogra- phed	A total of 95% of transplanted follicles survived. 0.21 mm and 0.25 mm of repigmen- tation after hypofrac- tionated CO2 laser compared with 0.08 mm and 0.17 mm in lesions treated with micronee- dling	Grade 1 erythema and grade 1 pain in both groups	Satisfied

Table 1 (Continued)

Study (Years)	Level of evidence	Study type	Number of patients	Mean age	Disease duration and site	Treatment	Associated treatment	Scale used	Response	Adverse events	Satisfac- tions
Stanimirovic et al. (2016)	1c	Pros- pective comparati- ve study	25	37	Stable for 12 years on extremities	Latanoprost and UVB photothe- rapy with and without micronee- dling		Photogra- phed using investiga- tor's global assessment scoring by independent dermato- logist and patient's global assessment scoring	Depig- mentation occurred in 9 experi- mental and 7 in control lesions. Micronee- dling did not show improve- ment in efficacy		

#### Microneedling with latanoprost and NB-UVB:

The efficacy of microneedling in combination with latanoprost and NB-UVB has been investigated on resistant vitiligo patches.<sup>21</sup> Patients were divided into two groups: microneedling (four sessions at one-week interval) combined with latanoprost and NB-UVB, and latanoprost associated with NB-UVB without microneedling. Topical latanoprost solution (0,005%) was applied immediately after microneedling. Then, the patients were prescribed NB-UVB in the period between microneedling sessions. The study showed that 37.8% of treated patches achieved satisfactory to very good repigmentation; however, there was no statistically significant difference in repigmentation between the two groups.

Another pilot study confirmed the efficacy of latanoprost combined with NB-UVB. However, the authors could not conclude whether microneedling further improved the therapeutic outcome.<sup>23</sup>

#### Microneedling in combination with 5-FU:

Two studies assessed the efficacy of Microneedling and 5-FU. Patients received 6 or 12 sessions of microneedling at two-week interval.<sup>13,14,20</sup> After microneedling, 5-FU solution (5%) was applied topically over affected areas and covered using an occlusive dressing for one day.<sup>13,14</sup> The patient was advised to apply 5-FU once daily for two weeks.<sup>13</sup>

Attwa *et al.* showed that the combination of microneedling with 5-FU yielded better results than microneedling monotherapy and increased its efficacy by 3.8 times.<sup>14</sup>

The second study aimed to compare the efficacy of microneedling with 5-FU versus its efficacy with tacrolimus. This study showed that the combination of 5-FU with microneedling has better results with excellent repigmentation and a higher number of clinical responses than the combination with tacrolimus.<sup>13</sup> The 5-FU showed excellent to good results in 40% of acral areas (repigmentation >75%) and in 57.1% of bony prominence regions (elbow and knees).<sup>13</sup>

Similar case reports showed complete repigmentation in acral, face, and back areas treated with 5-FU and micronee-dling.<sup>19,20</sup>

# Microneedling with NB-UVB and PDT, or with triamcinolone acetonide:

A randomized clinical trial assessed the additional efficacy of PDT on microneedling and NB-UVB therapy in acral areas. Since the NB-UVB is considered the gold standard in vitiligo treatment, it was applied twice a week for three months to treat vitiligo. Additionally, patients received three sessions of microneedling at three-week interval; then a group of these patients received 5-aminolevulinic acid 10% (applied under coverage for two hours) and were exposed to PDT with red light (630 nm) for eight minutes (37 J/cm2).<sup>10</sup> This study failed to prove any additional efficacy of PDT to microneedling therapy, and 40% of patients had a clinical response versus 60% in the other group (microneedling + NB-UVB).<sup>10</sup>

Another clinical study compared the efficacy of microneedling alone or with NB-UVB versus NB-UVB alone. It proved that needling and NB-UVB yielded better results when combined.<sup>17</sup> Repigmentation was seen in all patients treated with combined therapy and in 80% of patients treated with NB-UVB or microneedling monotherapy.<sup>17</sup> The grade of repigmentation in each group was: NB-UVB monotherapy: G1 (n=6), G2 (n=6), G3 (n=4); microneedling and triamcinolone acetonide solution: G1 (n=3), G2 (n=4), G3 (n=6), G4 (n=3); combination of both modalities: G1 (n=1), G2 (n=5), G3 (n=8), G4 (n=6).

#### Microneedling versus non fractioned ablative laser for autologous. cell suspension grafting in nonsegmental vitiligo:

A study comparing microneedling and non fractioned ablative Erbium laser for autologous cell suspension grafting in nonsegmental vitiligo showed that needling alone was ineffective in preparing the grafting bed, and none of the patients treated with microneedling had repigmentation.<sup>11</sup> Laser-assisted dermabrasion followed by suspension in hyaluronic acid achieved better results, where 50% of patients had excellent repigmentation.<sup>11</sup>

## Microneedling with trichloroacetic acid 70% versus 5-FU:

A prospective comparative study assessed the efficacy of trichloroacetic acid (TCA) with microneedling versus 5-FU in non-segmental vitiligo areas. In the first group, TCA was applied immediately after patients underwent microneedling until a uniform ivory white frothing appeared.<sup>18</sup> In the second group, an injection of 0.01-0.02 ml 5-FU was applied intradermally in vitiligo areas at 1 cm intervals with a maximum of 250 mg per session. Both groups received treatment every two weeks for two months.<sup>18</sup>

The study observed no significant difference between patients treated with TCA and 5-FU. In both groups, 43.8% of patients had good-to-excellent improvement (repigmentation >50%).<sup>18</sup>

## Hair transplantation and CO2 laser or microneedling followed by NB-UVB:

A pilot study compared the efficacy of hair transplantation and  $CO_2$  laser or microneedling followed by NB-UVB to treat stable and refractory palmoplantar vitiligo.<sup>22</sup> The authors compared two treatment approaches on symmetrical and comparable vitiligo lesions. Pigmented follicular grafts were harvested from the scalp and transplanted in vitiligo lesions on day 0. On days  $30\pm4$  and  $60\pm4$ , left-sided lesions received single fractions with a fractional  $CO_2$  laser, MX-7000 (10,600 nm, 100-MJ pulse energy, and 200 spots/cm<sup>3</sup> in static mode), and right-sided lesions received microneedling (1.5 mm to 2 mm) until bleeding appeared. On both sides, topical anesthesia with lidocaine-prilocaine was used before intervention. On days  $30\pm4$  and  $60\pm4$ , after the primary treatment, silver sulfadiazine ointment was applied to both sides, twice daily, for five days. Both sides received NB-UVB on day  $40.^{22}$ 

The study noted no statistically significant difference between both sides, and both had a 0.25 mm repigmentation diameter.  $^{22}$ 

#### Patient satisfaction:

Most (83.3%) patients treated with microneedling and topical tacrolimus were satisfied with the treatment outcome.<sup>3</sup> A higher percentage of patients (92%) were satisfied with topical calcipotriol and betamethasone treatment.<sup>15</sup>

The combination of microneedling with 5-FU yielded excellent results with a good satisfaction rate in Kumar *et al.* study.<sup>20</sup>

Microneedling combined with triamcinolone acetonide solution yielded a good-to-excellent satisfaction rate in 55% of patients, whereas microneedling associated with triamcinolone acetonide solution and NB-UVB raised that percentage to 75%.

The study observed high satisfaction rates in patients treated with hair transplantation and  $CO_2$  laser or microneedling followed by NB-UVB.<sup>22</sup>

#### Histological evaluation:

A skin biopsy was taken from the lesions during pre and post-treatment sessions for histological evaluation. The biopsies were stained using routine hematoxylin and eosin (H&E) and then with HMB45 to detect any pathological or immunohistochemical changes. Lesions treated with microneedling and tacrolimus had a higher expression than microneedling or tacrolimus monotherapy.<sup>16</sup> These results were consistent with the clinical outcome. A comparison between microneedling and tacrolimus and microneedling and 5-FU yielded better results in patients treated with microneedling and 5-FU.<sup>13</sup>

Also, lesions treated with microneedling with dermapen and topical calcipotriol plus betamethasone had a higher expression than those treated with microneedling and topical tacrolimus.<sup>15</sup>

#### Adverse events:

No patient presented severe adverse events related to the microneedling treatment. The post-procedure adverse events were: pain,<sup>11,14+17,22</sup> erythema,<sup>15,16,22</sup> hyperpigmentation,<sup>13</sup> it-ching,<sup>14,16</sup> ulceration,<sup>13</sup> inflammation,<sup>13</sup> and exfoliation<sup>15</sup>.

No complications were noted in 18.6 % of patients treated with tacrolimus and microneedling (n=26).<sup>3,13</sup> Only mild erythema, itching, and pain were observed in symptomatic patients.<sup>15,16,23</sup> Most patients (56.2%) treated with TCA and 5-FU had no adverse events. The adverse events reported with TCA were

blister (n=1), burning (n=2), and perilesional hyperpigmentation (n=4). Regarding 5-FU, adverse events were discomfort (n=2) and infection (n=3).<sup>18</sup>

Significantly greater pain level was noted in patients treated with laser-assisted dermabrasion compared to patients treated with microneedling.

#### DISCUSSION

Recently, there has been heightened interest in using microneedling for skin disorders. It consists of a roll with fine needles. These microneedles create micro-injuries and activate wound healing cascade, releasing several factors including platelet-derived growth factor (PGF), transforming growth factor alpha and beta (TGF- $\alpha$  and TGF- $\beta$ ), connective tissue activating protein (CTAP), connective tissue growth factor (CTGF), and fibroblast growth factor (FGF).<sup>24</sup> These factors enhance the collagen secretion by fibroblast and stimulate melanocyte migration to unpigmented patches.<sup>10</sup>

Vitiligo is a chronic disease characterized by depigmented white patches and caused by the destruction of melanocytes.<sup>4,25</sup> These patches occur mainly on extremities and are known to be resistant to conventional therapies, hence the importance of finding an effective treatment modality for these difficult-to--treat areas.<sup>26,27</sup> It has a worldwide prevalence of 1%, occurring chiefly before the age of 20 and affecting both sexes equally.<sup>4,28-31</sup>

Microneedling can treat the loss of melanocytes caused by vitiligo. It can potentially stimulate melanocytes and skin pigmentation by creating micro-injuries, leading to the release of growth factors.<sup>10,32</sup> Thus, microneedling alone can act as monotherapy for vitiligo, increasing the transdermal drug delivery of topical treatment options and, therefore, inducing a better repigmentation rate when combined with these topical treatments.

Microneedling is a relatively new treatment in dermatology and has been used for many skin disorders such as vitiligo, acne scarring, and skin rejuvenation. This article emphasized all published studies that assessed the efficacy of microneedling in vitiligo treatment. Microneedling proved to be efficient in all these studies; however, the degree of efficacy varied depending on associated therapies. There was inconstancy in scales used to assess the efficacy of microneedling monotherapy and biotherapy. Nevertheless, the combination of microneedling and topical tacrolimus, 5-FU, topical calcipotriol and betamethasone, NB-UVB with or without PDT, or triamcinolone acetonide solution was more efficient compared to microneedling monotherapy. On the other hand, microneedling was not efficient for autologous cell suspension grafting and showed no clinical response. Also, it showed no additional benefit in patients treated with latanoprost and NB-UVB.21

No life-threatening adverse events were reported. Compared to lasers, microneedling caused significantly less pain.<sup>11,33</sup>

Satisfaction rate results were not conclusive since only four studies described it. The higher satisfaction rate was seen in microneedling combined with topical calcipotriol and betamethasone, or NB-UVB and triamcinolone.

This study has many limitations. Due to the lack of uniformity of studies, a meta-analysis could not be performed, and this study was limited to a pooled data form. The high variability between scales used to measure satisfaction and repigmentation

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rate and the scarce number of patients followed up restricted our inter-study comparison. In this study, only the published data from the database mentioned were included, which is also a limitation.

The authors published many studies about vitiligo and its treatments. Therefore, microneedling in vitiligo seems to be a hot topic to work.<sup>29-37</sup>

#### CONCLUSION

Microneedling seems to be a safe adjuvant therapy besides routine treatments and is an efficient and tolerable procedure for vitiligo treatment and can be an added value in resistant patches or difficult-to-treat areas such as the extremities, especially when used in combination with topical agents.

Additional standardization of treatment dosing protocols and further randomized clinical trials are needed to establish a consensus about microneedling in vitiligo. Based on the result, the combination of microneedling and topical tacrolimus, 5-FU, topical calcipotriol and betamethasone, NB-UVB with or without PDT, or triamcinolone acetonide solution was more efficient compared to microneedling monotherapy. However, there was no specific scale between all studies to compare the results, and it we suggest further studies with a single criterion to measure the effectiveness and satisfaction of patients with the treatment.

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#### **AUTHORS' CONTRIBUTION:**

Masoumeh Roohaninasab 🜔 ORCID 0000-0002-2862-6422

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; active participation in research orientation; critical literature review; critical revision of the manuscript.

#### Kimia Gandomkar 🝺 ORCID 0000-0002-3901-6718

Approval of the final version of the manuscript; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.

#### Azadeh Goodarzi 🕩 ORC 🗈 0000-0002-1249-4429

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; active participation in research orientation; critical literature review; critical revision of the manuscript.

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# Alternatives for keloid scars treatment: an integrative review

Alternativas para o tratamento de cicatrizes queloidianas: uma revisão integrativa

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#### ABSTRACT

Keloid scars affect different populations, compromising patients' quality of life. The literature presents several treatments. The study aimed to conduct an integrative review of systematic review articles and/or meta-analyses addressing keloid treatment in the PubMed, LILACS, MEDLINE, and Cochrane databases from 2015 to 2021. After identification and following the selection and eligibility criteria, 24 articles were included for qualitative review. We observed that the difficulty in evaluating recurrence affected different keloids treatment modalities, still presenting many failure rates and the need for further studies. **Keywords:** Keloid; Scar, hypertrophic; Scar; Clinical procedures; Review; Systematic reviews as topic.

#### RESUMO

As cicatrizes queloidianas afetam diversas populações, comprometendo a qualidade de vida dos pacientes. Vários tratamentos são apresentados na literatura. O presente estudo visou a realizar uma revisão integrativa dos artigos de revisões sistemáticas e/ou metanálises que abordam o tratamento nas bases de dados PubMed, LILACS, MEDLINE e Cochrane no período de 2015 a 2021. Após a identificação, e seguindo os critérios de seleção e elegibilidade, foram incluídos 24 artigos para revisão qualitativa. Observamos que as diferentes modalidades de tratamento empregadas para os queloides são afetadas pela dificuldade de avaliar recorrência, ainda mantendo muitas taxas de insucesso e necessidade de novos estudos.

**Palavras-chave:** Queloide; Cicatriz hipertrófica; Cicatriz; Procedimentos clínicos; Revisão; Revisões sistemáticas como assunto.

### **Review article**

#### Authors:

Balduino Ferreira de Menezes Neto<sup>1</sup>

Lucas Vannuchi Magnani<sup>1</sup> Aristides Augusto Palhares Neto<sup>1</sup> Natália Parenti Bicudo<sup>2</sup> Batista de Oliveira Júnior<sup>3</sup>

- <sup>1</sup> Clinics Hospital, Medical School of Botucatu, Plastic Surgery, Botucatu (SP), Brazil
- <sup>2</sup> Fausto Viterbo's Plastic Clinic. Botucatu, São Paulo, Brazil.
- <sup>3</sup> Clinics Hospital, Medical School of Botucatu, Radiotherapy, Botucatu (SP), Brazil.

#### Correspondence:

Balduino Ferreira de Menezes Neto Email: balduinofmneto@gmail.com / alternative email: balduino.neto@ unesp.br

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#### INTRODUCTION

Keloids, named by Alibert in 1806,<sup>1</sup> were described as a growth similar to the projections of twigs or crab claws. The English word keloid derives from the Greek khele.

The main characteristics of this benign tumor are its prolonged course of activity, its ability to surpass the limits of the initial lesion, multiple specific genetic and cellular factors (many of them not yet fully elucidated), and unique pathophysiology.<sup>2</sup> At the histological level, there is a chronic inflammation of the reticular dermis, with high number of fibroblasts and collagen, especially type I, eosinophilic and hyalinized.

According to the current literature, there is lower growth and development of these tumors after menopause, being more common during pregnancy and puberty.<sup>3</sup> Also, genetics, ethnicity, and initial lesion site have been described as factors that favor the appearance of keloids.<sup>4</sup>

The literature describes several treatment techniques, which can be invasive or non-invasive. Among them, we can highlight alternatives such as compression therapy, silicone gel sheets, and onion extract.<sup>5</sup>

Pressure therapy for patients with closed wounds that tolerate pressure should be used for at least 23 hours a day, for six to 24 months, using pressure between 24 mmHg and 30 mmHg.<sup>5,6</sup> Although it shows good results, this treatment generates high costs, in addition to causing significant discomfort to patients.<sup>7</sup>

Silicone materials have been indicated as one of the main non-invasive methods, with reported improvement rates of 90%.<sup>8</sup> These materials are available as gels or sheets. Silicone sheets should be used from 12 to 24 hours a day, for three to six months, while silicone gels should be applied twice daily.<sup>5</sup> However, the literature lacks large studies that prove its effectiveness, in addition to the fact that these materials hardly reach the full resolution of scars.<sup>9</sup>

Treatment with onion extract, whose main component is quercetin – which has collagen-suppressing, antimicrobial, and anti-inflammatory properties – can also be used to reduce excess scarring.<sup>5</sup> Nevertheless, it also lacks prospective and randomized studies.

Regarding treatment, several studies attempt to prove the importance of the association of therapies but with no statistically definitive results.<sup>10</sup> However, it's noteworthy that simple surgical excision, with no adjuvant method, has high recurrence rates, close to 50%, which increases after new attempts, especially in the first four years.<sup>11</sup>

Although it remains an incurable condition, there are several types of treatments. The most classic is intralesional infiltration of drugs, such as 5-fluorouracil and corticosteroids, and several modalities of adjuvant radiotherapy (RT), such as conventional RT, electron beam RT, and single-dose RT.<sup>12</sup>

The primary mechanism of action of radiotherapy involves the inhibition of histamine release by mast cells, resulting in a decrease in fibroblast proliferation, in addition to the inhibition of TGF-Beta1, which suppresses collagen production, interfering with the formation of keloids.13

In the 1960s, studies showed that external radiation therapy failed to resolve the lesion when performed alone. Nevertheless, positive results in symptoms alleviation were obtained when the treatment was associated with surgical excision, with worse outcomes in cases of delay in performing radiotherapy after excision, generating higher recurrence rates.<sup>14</sup>

However, the risk of carcinogenesis associated with adjuvant radiotherapy was still a significant concern. A literature review conducted in 2009 described five cases of this occurrence, although it was not possible to state whether adequate adjacent tissues protection and correct doses were used.<sup>15</sup> Thus, the study concluded that the risk of carcinogenesis should not be an impediment to performing the procedure and is essential to emphasize the importance of preventive measures, such as care for the surrounding tissues and protection of the thyroid and mammary glands, especially in children and adolescents.<sup>15</sup>

A few years later, brachytherapy was developed, which performs internal or interstitial radiotherapy, further reducing these risks.<sup>16</sup> With the ability to emit more efficient and focused radiation on the lesion, this technique also requires a lower dose, resulting in reduced local radionecrosis and adverse events on adjacent healthy tissues. Nonetheless, this procedure demands higher hospital expenses due to the use of poorly available and specific materials, in addition to prolonged hospitalizations.<sup>15</sup>

Electron beam therapy has been widely used in several medical centers, considerably replacing other radiotherapy methods in the keloid treatment.<sup>17</sup> A research conducted at the Clinics Hospital of the Medical School of Botucatu (FMB-UNESP) in São Paulo (BR) highlighted its importance. Therefore, this treatment option was maintained in the current routine when approaching these lesions.<sup>18,19</sup>

Furthermore, the search for new treatments continues<sup>20</sup> and comprises the use of angiotensin-converting enzyme (ACE) inhibitors;<sup>21,22</sup> intralesional injections of calcium antagonists (such as verapamil);<sup>23</sup> intralesional injections of botulinum toxin type A;<sup>24,25</sup> electrical stimulation;<sup>26</sup> lasers; and cryotherapy,<sup>27</sup> among others.

This study aims to present an integrative literature review using only systematic reviews published in the main medical databases in the last five years to understand which treatments have been most applied and developed nowadays.

#### **METHODS**

To conduct an integrative literature review, we used the following electronic databases: PubMed, LILACS, MEDLINE, and Cochrane.

The search period was from 05/10/2021 to 05/23/2021, and we selected only articles published between January 2015 and May 2021.

Search terms and keywords

Databases were searched using the following keywords: "keloid" "and" "treatment".

Languages were restricted to English and Portuguese, and the search format was adapted to the appropriate syntax of each database.

#### Identification and selection of articles

We selected only systematic reviews and meta-analyses comprising the clinical management of pathological scars, focusing on keloids. Non-human studies and reviews focusing on other pathologies, such as burns and acne, were excluded.

#### RESULTS

According to the flowchart below (Figure 1) and the Methods section proposal, we searched articles in English and Portuguese between 05/10/2021 and 05/23/2021, using the descriptors "keloid and treatment", "keloid treatment", "queloi-de e tratamento", focusing only on systematic reviews and/or meta-analyses.

We selected four databases recognized for their visibility, information quality, and access: PubMed, LILACS, MEDLINE, and Cochrane.

In the PubMed database, we used the descriptor "keloid treatment" and filters: results by year from 2015 to 2021 and article type for systematic review and/or meta-analysis. In this initial search, we identified 46 articles. Of them, 26 were excluded: 22 did not focus on keloids, one was not in English, and three articles did not have full text available.

In the MEDLINE database, we found 20 references using the descriptors "keloid treatment systematic review and/or meta-analysis". Of them, seven articles were excluded because their abstract was incompatible with the keloid treatment topic or because they were not in English or Portuguese. The remaining 13 articles had already been identified in the PubMed database and were excluded due to duplicates.

In the LILACS database, 25 articles were found and only four were kept because the others did not focus on pathological scars, were published before 2015, or were not in Portuguese or English.

The two articles found in the Cochrane database were excluded due to duplicates, as they were already retrieved from the PubMed database.



### FIGURE 1: Flowchart for

selecting articles from the integrative review In the end, 24 systematic reviews and/or meta-analysis articles were selected: four in Portuguese and 20 in English. Two independent researchers (BFMN and AAPN) read all articles in full and divided the different treatment proposals into clinical, surgical, and radiotherapy treatments. The protocol was formulated after a discussion among the two researchers, an independent researcher from Dermatology (JVS) and another independent researcher from Radiotherapy (BOJ).

Among the selected articles, six addressed keloid treatments, four assessed the use of 5-fluorouracil associated or not with corticosteroids, three evaluated radiation therapies, and three analyzed laser technologies. Two investigated the use of verapamil, and two of bleomycin. One review article assessed fat grafting, one analyzed botulinum toxin type A, one investigated imiquimod, and one evaluated corticosteroids alone.

The four articles in Portuguese were not included as systematic reviews but were maintained as they served as references for alternative medications in the discussion of protocol formation.

#### DISCUSSION

The literature reports several methods to treat and prevent keloid scars. Because the effective and definitive treatment of this pathological scar is a great challenge, new therapeutic modalities are constantly emerging, in addition to combinations of treatments already used.

First, it is critical to emphasize that this benign tumor treatment begins with prevention. Intraoperative care is essential for all surgical procedures. However, in patients with a predisposition to keloid formation, these precautions are critical. Among them, we can mention the careful manipulation of the tissues, respect for the dissection planes when performing the synthesis, and the preferential use of absorbable sutures in the subcutaneous tissue and fascia,<sup>28</sup> thus reducing the tension on the suture lines as much as possible.

Compression therapies affect collagen degradation and fibroblast activity,<sup>29</sup> and are especially helpful in ears, as they have their pressure molds, which should not exceed 24 mmHg and 12 hours a day use.<sup>30</sup> Silicone plates and tapes also act on collagen and fibroblasts. However, in theory, they use their ability to generate a more hydrated environment for the wound.<sup>31</sup> Thus, this group of therapies is only complementary and should not be used alone.

The administration of intralesional corticosteroids is considered one of the most efficient and accessible methods to treat keloids.<sup>32</sup> As it is the first line in most services, this therapy suppresses fibroblasts and inflammatory mediators of wounds, generating collagen degradation.<sup>33</sup>

Triamcinolone acetate (TAC) in concentrations between 5 mg/mL and 40 mg/mL is the main form used, promoting the reduction of keloid volume and showing variable rates of recurrence prevention.<sup>34</sup> Skin atrophy, pain during injection, te-langiectasias, and skin pigmentation changes are among its main adverse events.<sup>35</sup>

Intralesional and topical 5-fluorouracil (5-FU) is a pyrimidine antimetabolite that interferes with RNA synthesis and inhibits the thymidylate synthase, thus inhibiting fibroblasts.<sup>36</sup> Therefore, the combination of 5-FU+TAC is safer and more effective than these drugs alone.<sup>37</sup>

Botulinum toxin (BT) type A inhibits the acetylcholine release in motor neurons by antagonizing the ionic calcium action, generating temporary muscle paralysis.<sup>38</sup> Nevertheless, there are indications that, in pathological scars, it acts directly on the activity of fibroblasts.<sup>39</sup>

Topical imiquimod 5% cream can alter the immune response by inducing the release of IFN-alpha, TNF-alpha, and interleukins 1, 6, and 8.<sup>40</sup> It presents keloid recurrence in 39% of the cases when associated with surgical excision in applications from six to eight weeks, daily or every three days.<sup>41</sup> However, some studies evaluated by this review included patients who only performed tangential excision or shaving, using closure by secondary intention, and not by layers.<sup>42</sup> This drug requires a minimum of one-week rest, especially between the second and third weeks of application, as erosion, erythema, and crust formation are frequent in 18% to 89% of patients. Therefore, topical imiquimod cream is an exceptional measure because it is unreliable.

Verapamil, a calcium channel blocker, can be applied intralesionally in doses of 2.5 mg/mL, not exceeding 2 mL per session. Sessions occur at three-week intervals and should be interrupted after the eighth procedure or when the lesion has flattened.<sup>43</sup> Although it is less effective than the 5-FU+TAC combination, its use has good clinical safety, generating fewer adverse events.<sup>44</sup> This drug increases the procollagenase synthesis, reducing the extracellular matrix production and inhibiting the fibroblast proliferation and the interleukin 6,TGF-Beta,<sup>1</sup> and VEGF expression in fibroblasts.<sup>45</sup>

Pentoxifylline is a drug derived from xanthine, a nonspecific phosphodiesterase inhibitor, which has a vasodilating effect.<sup>46</sup>

It presents significant rates of recurrence prevention of keloids in patients at high risk when administered orally, in 400 mg doses, three times a day for six months after surgical excision. Furthermore, this drug can be used intralesionally. However, few studies have addressed this possibility.<sup>47</sup>

Hyaluronidase and hyaluronic acid, drugs with antagonist actions, have been reported to treat keloids intralesionally.<sup>48</sup> Nonetheless, both drugs were used in association with corticosteroids, making it difficult to establish the real effects on pathological scars, thus requiring more research aimed at understanding its results on keloids.

Bleomycin can reduce collagen synthesis by decreasing the stimulation of TGF-Beta1.<sup>49</sup> Compared to TAC, it was more likely to generate pain, hyperpigmentation, and skin atrophy.<sup>50</sup> According to a systematic review, bleomycin seems to be as effective as TAC and its combination with 5-FU.50 This study also observed that this drug produced more pain than the others during applications. Intralesional cryotherapy with a needle achieved a reduction of up to 51% in the volume of the pathological scar.<sup>51</sup>

Currently, several treatments use laser due to the significant technological development that allowed the generation of different types of wavelengths. These treatments can be divided into non-ablative and ablative forms and vary between fractional and non-fractional configurations. Ablative forms, such as Er:YAG (waves of 2,940 nm) and CO2 laser (waves of 10,600 nm), are characterized by a longer recovery time and a considerable number of complications. Moreover, the non-ablative options, such as Nd:YAG (waves of 1,054 nm) and pulsed dyelaser (waves between 585 nm and 595 nm), eliminate some of these problems. The fractional lasers can generate microthermal zones, creating unaffected interspersed areas where tissue regenerates.<sup>52,53</sup>

The pulsed-dye laser has similar effects to those generated by TAC, but its studies presented a short follow-up, in addition to the lack of randomized and multicentric studies.<sup>53,54</sup>

The most modern and current drugs have the advantage to be applied in a laser-assisted manner, a method known as laser-assisted drug delivery (LADD).<sup>55</sup> Researchers are also trying to use this method to treat keloids,<sup>56</sup> which is possible since ablative lasers create microscopic spaces that allow drug penetration, such as BT and TAC. However, research still has low evidence, with few participants and a short follow-up period.

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Radiation therapy allows the reduction of fibroblast action in keloids in a dose-dependent manner.<sup>57</sup> Currently, after the great scientific evolution of the 20th century, it presents in two main forms: external and internal. The electron beam and X-ray are the most common ways of external application, while the most studied internal option is brachytherapy. Although some studies show the superiority of brachytherapy in preventing the recurrence of keloids,<sup>58</sup> several meta-analyses have not confirmed this result in a statistically significant way.<sup>10</sup>

When surgical excision is associated with early radio therapy, superior results are found.  $^{\rm 59}$ 

Adverse signs and symptoms of corticosteroids are similar to those of radiotherapies, such as desquamation, depigmentation, and erythema. Pain complaints are infrequent.<sup>15</sup>

#### CONCLUSION

The keloid scars treatment continues to be challenging: in addition to the peculiarities imposed by each patient, which vary according to their ethnicity, location, and size of the lesions, there is also the fact that studies can't present long and consistent follow-ups to assess the emergence relapses.

New prospective studies and knowledge about this pathology and the effects of medications need to be conducted to achieve lasting results with quality for patients.

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#### **AUTHORS' CONTRIBUTION:**

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### Balduino Ferreira de Menezes Neto 🝺 ORCID\_0000-0001-9379-4441

Study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review; critical revision of the manuscript.

Lucas Vannuchi Magnani 问 ORCID\_0000-0002-3176-9205

Preparation and writing of the manuscript; critical revision of the manuscript.

#### Aristides Augusto Palhares Neto D ORCID 0000-0002-3484-862X

Approval of the final version of the manuscript; critical literature review; critical revision of the manuscript.

Natália Parenti Bicudo DCCID\_0000-0001-8674-0349 Critical revision of the manuscript.

#### Batista de Oliveira Júnior 🝺 ORCID 0000-0003-4768-1686

Intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.

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# Loss of definition of the submental contouring: correct diagnosis and treatment algorithm

Perda de definição do contorno do submento: correto diagnóstico e algoritmo de tratamento

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#### ABSTRACT

The search for aesthetic procedures aimed at the loss of submental definition is increasing. A correct diagnosis is imperative for successful treatment and the reduction of complications. Localized adiposity, skin flaccidity, and loss of bone structure are the main findings. A treatment algorithm was discussed in this review, remembering, of course, the possibility of combined and sequential treatments for better results. **Keywords:** Deoxycholic acid; Collagen; Neck; Chin; Adipose tissue; Hydroxyapatites

#### RESUMO

A busca por procedimentos estéticos voltados para a perda de definição do submento é crescente. Um correto diagnóstico é imperativo para o sucesso do tratamento e redução das complicações. Adiposidade localizada, flacidez cutânea e perda da estrutura óssea são os principais achados. Um algoritmo de tratamento foi discutido nesta revisão, lembrando-se, claro, da possibilidade de tratamentos combinados e sequenciais para melhores resultados. **Palavras-chave:** Ácido desoxicólico; Colágeno; Pescoço; Queixo; Tecido adiposo

### **Review Article**

#### Authors:

Gladstone E. L. Faria<sup>1</sup> Clarissa L. Vilela<sup>1</sup> Alyne Queiroga Bastos<sup>1</sup> Carolina Freitas Tavares Silva<sup>1</sup> Ricardo F. Boggio<sup>1</sup>

<sup>1</sup> Instituto Boggio, São Paulo (SP), Brazil.

Correspondence: Gladstone E. L. Faria gladstonefaria@hotmail.com

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#### INTRODUCTION

The loss of definition of the submental region is popularly called a double chin. This complaint has been increasingly frequent, mainly due to changes in life habits, especially the great exposure to cameras, whether for occupational reasons, in videoconferences, or for personal motives, in social media.<sup>1</sup>

The growing search for aesthetic procedures for this region has promoted the trivialization of treatments with imprecise indications, without the correct diagnosis, and, consequently, with high rates of complications.

The definition loss of the submental contouring has several etiologies that can often be associated and, thus, be considered multifactorial.<sup>1,2</sup> To deem the etiology of the finding and then associate it with the correct treatment(s) is the key to avoiding unsatisfactory results and minimizing complication rates.

This study aims to review the literature to promote a critical analysis for a correct diagnosis of the loss of submental definition and create an algorithm to propose an adequate treatment.

The main causes of submental contour loss are localized adiposity, skin flaccidity, and bone support loss (structural).

Understanding the anatomy of the cervicomental region is crucial for the correct diagnosis and therapeutic planning. The lower border of the mandible, the anterior border of the sternocleidomastoid muscle, the submental septum, the hyoid bone, and the thyroid cartilage delimit the cervicomental region. The sternocleidomastoid muscle into anterior and posterior triangles divides this area.

In the anterior triangle, we find the submental triangle, which is a single triangle of the neck, delimited by the body of the hyoid bone and the anterior bellies of the digastric muscle. It is the most important area in defining the contour of the face and is also the most affected by aging and adipose tissue accumulation. Therefore, it is the focus of most treatments that aim to improve the cervicomental angle.<sup>1,2,3</sup>

#### Localized adiposity

The accumulation of fat in the submental region is one of the most frequent complaints of patients, and can be correlated with obesity, genetic conditions, life habits, and acquired lipodystrophies.<sup>4</sup>

Treatment consists of removing excess fat, either by surgical methods, such as liposuction (still considered the gold standard) or minimally invasive methods.

Among the minimally invasive methods, we can highlight injection lipolysis (popularly known as enzymes) and cryolipolysis.

#### Skin sagging

The natural aging process, the law of gravity, and weight fluctuations, constantly influence the skin in this region. The clinical finding is palpation without an increase in the volume of adipose tissue, but an overhanging, atrophic, and flaccid skin, causing damage to the contour of the area.<sup>5</sup>

This finding, in addition to the etiological conditions mentioned above, can also be considered secondary, resulting from treatments involving localized adiposity, which did not evolve with adequate skin retraction.

When skin flaccidity is the patient's diagnosis, minimally invasive treatments become focused on skin quality, that is, on collagen biostimulators, whether injectables, threads, or technologies.

We highlight calcium hydroxyapatite, poly-L-lactic acid, and polydioxanone (PDO) threads among the injectable collagen biostimulators. Among the technologies, we spotlight microfocused ultrasound and radiofrequency.

#### Structural

The structural cause is the etiology related to the loss of bone support. It can be congenital, due to underdevelopment of the lower third of the face, or acquired, due to the bone aging process, which becomes more accelerated with the loss of dentition.<sup>6</sup>

Poor mandibular contour and/or hypomentonism are the two major structural causes and, once again, must be properly evaluated and treated. The replacement of these segments in a minimally invasive, simpler, and safer way is done with hyaluronic acid fillers.<sup>7</sup>

Figure 1 proposes a diagnostic algorithm and its respective treatment, recognizing that multifactorial causes are often found and, therefore, should be treated together or through sequential treatment protocols.

With this algorithm, it is easy and reasonable to indicate the appropriate treatments, considering the individual experience of each professional as well as access to the different therapeutic modalities mentioned here.

## Treatment of localized adiposity with submental liposuction

Submental fat liposuction is a minor surgical method that can be performed in an outpatient setting, with local anesthesia, or in a hospital setting associated with other procedures. The surgical technique eliminates excess adipose tissue from the subcutaneous tissue of the cervical region, improving the neck's contour and definition with effective and lasting results and minimal downtime. Thus, this procedure is the gold standard.

The ideal patient for liposuction is young, has good skin quality, lacks sagging, and has loss of cervical contour secondary to the accumulation of fat in the submental and submandibular region. The patient needs to understand that liposuction does not replace weight loss. Although, unlike body indication, patients with a BMI above the ideal also benefit from the aesthetic results of liposuction in this region.<sup>8</sup>

The upper and lower margins of the fat compartment and its lateral limits must be demarcated. The limits of the sternocleidomastoid muscle (SCM) must be respected and serve as



FIGURE 1: Diagnostic algorithm for loss of submental definition and their respective treatments

an anatomical reference for vascular structures of the neck. It is also essential to define the region between the lower border of the mandible and the anterior margin of the masseter muscle, where the marginal nerve of the mandible is more superficial.3

The incisions are planned according to each patient's adiposity distribution and in most cases a single submental puncture is sufficient. Additional punctures in the insertion of the earlobe bilaterally can be used, as an exception, by more experienced professionals, due to a higher vascular risk.

Infiltration of the area is conducted with modified Klein's solution, prepared using saline solution, lidocaine, bupivacaine, and adrenaline 1:250,000. Infiltration is performed with a 2-2.<sup>5</sup> mm Klein cannula until the area becomes tumescent. It is recommended to wait 10-15 minutes before starting liposuction so that the vasoconstrictor effect of adrenaline takes place, thus reducing the risk of bleeding and bruising. The liposuction technique must respect the subcutaneous plane, always above the platysma muscle. The surgeon introduces the cannula through the hole in the neck in slight hyperextension, and guides its path with the contralateral hand, controlling its tip throughout the procedure to protect the deep planes from possible violations. Short cannulas of 2 mm to 3 mm in caliber are recommended, always with the holes facing downwards. Dermal lesions or superficial liposuctions can result in skin necrosis and surface irregularities, respectively.<sup>9</sup>

Compressive dressing and/or surgical mesh are recommended to avoid the formation of seromas and hematomas, and for adequate skin adhesion to the deep tissues. Skin retraction varies according to the individual characteristics of each patient but in the foreseeable possibility of little skin retraction and residual sagging, technologies aimed at skin tightening can be indicated for intraoperative use, such as diode laser, plasma jet, or radiofrequency.

Lymphatic drainage should be performed by a trained professional and started in the early postoperative period. Proper technique and frequency are essential for rapid recovery and to avoid complications such as fibrosis. Serious complications are rare, including marginal mandibular nerve neuropathy and vascular injuries. Bleeding, seroma, residual flaccidity, irregularities, and banding are the most frequent complications.

Submental liposuction is a simple, fast, and safe procedure,<sup>9</sup> which allows the definitive resolution of the accumulation of subcutaneous fat in the submental region and has a high level of satisfaction (Figure 2).

#### Treatment of localized adiposity with lipolytics

The two main injectable lipolytic agents are deoxycholic acid and phosphatidylcholine, which can be used separated or combined for synergistic effects. Sodium deoxycholate is a bile salt with similar detergent properties used to solubilize phosphatidylcholine. It plays a central role in the emulsification and digestion of fats in the intestine. Ionic detergents such as deoxycholate disrupt membrane integrity by introducing their polar



FIGURE 2: Submental fat liposuction: before (A) and after (B)

hydroxyl groups into the hydrophobic core of the bilayer, leading to membrane collapse into mixed micelles of phospholipids and detergent molecules.<sup>1,2</sup>

Phosphatidylcholine is a glycerophospholipid that facilitates the emulsification of fats, allowing absorption and transport of fat. The mechanism of subcutaneous fat lysis by phosphatidylcholine is still the subject of studies. It has been postulated that it stimulates lipases and breaks down triglycerides into fatty acids and glycerol.<sup>10</sup>

The combination of both has a synergistic action and causes vacuolization of the adipocyte, leading to its destruction and elimination by phagocytosis. It is speculated that deoxycholate in monotherapy promotes immediate and accentuated fat necrosis, with essential fibrotic effects, while its association with phosphatidylcholine it promotes a more organized fat necrosis. Therefore, the most common formulations comprise the two active ingredients in concentrations ranging from 2.5–5% for phosphatidylcholine and 2.5–4.7% for sodium deoxycholate.<sup>11</sup>

The selection of the ideal patient is essential for a good result. Treatment works best for soft fat compared to hard or fibrous fat. The latter is found more often found in young women and men.

The application technique is relatively simple. The fat compartment is demarcated according to the following anatomical parameters: submental sulcus anteriorly, hyoid bone posteriorly, and a line that descends from the oral commissures laterally. After the delimitation of the area, injection points equidistant 1 cm from each other are marked. A safety zone is demarcated between 1 cm and 1.5 cm from the mandibular border, a region that should not be treated, under the risk of injury to the marginal nerve of the mandible (Figure 3).<sup>12</sup>

After adequate asepsis with alcoholic chlorhexidine, injections of 0.2 mL per point in the subcutaneous plane are performed, using a 1 mL syringe and a 30 G x 13 mm needle. The bi-digital pinch of the fat increases the assertiveness of the application depth, which should be from 6 mm to 10 mm. An average volume of 3-5 mL (30-50 mg) per session is recommended, avoiding extrapolating the total volume of 10 mL in the same application (corresponding to 100 mg of deoxycholate). Three to five sessions, at least four weeks apart, should be encouraged for best results (Figure 4).<sup>13</sup>

Edema, erythema, and mild pain are frequent and start within the first five minutes post-injection and last an average of 24-48 hours. Paresthesias can last longer, like two weeks. Severe complications, such as mandibular marginal nerve injury, manifest clinically with smile asymmetry, but fortunately, most resolve spontaneously. Skin ulcerations may occur as a result of superficial applications.

#### Treatment of localized adiposity with cryolipolysis

Cryolipolysis is a technique that applies cooling to the skin surface to promote the lysis of adipocytes, in this case, pre-platysmal adipocytes. The safety of non-invasive technology is related to the higher susceptibility of adipose tissue to injury by cooling, to the detriment of other tissues such as the skin, due to its water content. Studies prove the ability to reduce the submental fat layer by around 20%.<sup>14</sup>

In vivo, histopathological studies showed that cryolipolysis induces cellular apoptosis on the third day, with an inflammatory response between the third and 14th day, and subsequent phagocytosis by macrophages between the 14th and 30th day. In the following two-three months, there is a thickening of the



FIGURE 3: Demarcation for the treatment of submental fat with lipolytics

interlobular septa and a significant loss of fat cells.

The FDA approved its use in the submental region in 2015, and studies have shown that cryolipolysis is a safe, comfortable, and effective treatment for reducing submental fat. The main adverse events are hematoma, erythema, edema, and paresthesia. Paradoxical adipose hyperplasia is an adverse event described with an incidence of 1:20,000 treatments and is more related to men, 12, and should be treated with liposuction.

#### Treatment of sagging with calcium hydroxyapatite

Injectable calcium hydroxyapatite is a valuable tool with

biostimulating properties, that is, the production of collagen and elastic fibers, in addition to an excellent ability to retract the skin. Hydroxyapatite stands out in neck treatment since it can increase skin thickness, something very desired for this region, associated with improved elasticity, especially with great safety, especially regarding the formation of nodules.<sup>15,16</sup>

The neck is usually treated with higher dilution when compared to the face. A 1:4 dilution is usually effective and safe for this procedure. A syringe containing 1.5 mL of a product receives 6 mL of diluent (a lidocaine and saline solution). Vectorized figures are drawn covering the entire region, and the application is performed through linear retroinjections in the subdermal plane using a 22 g microcannula (Figure 5).<sup>17</sup> Usually, three sessions, with intervals of 30 days, are recommended for better results (Figure 6). The massage performed immediately by the injector, associated with home self-massage twice a day for seven days, is indicated for better distribution and homogenization of the product.<sup>16</sup>

#### Treatment of sagging with poly-L-lactic acid

Poly-L-lactic acid is another tool for injectable neck biostimulation. As with calcium hydroxyapatite, neck region treatment is considered body therapy and therefore requires a higher dilution than that for facial treatment.<sup>18</sup>

The recommended dilution for neck treatment with poly-L-lactic acid provides a final total volume of 16 mL, and the protocol of prior or immediate dilution can be followed.<sup>15,16</sup> The distribution of the diluted product in the area to be treated follows the fanning-type application technique, preferably with a microcannula, in the subdermal plane. Post-application massage care follows the same criteria as previously recommended for calcium hydroxyapatite.

Nodules are the main complication regarding the injectable biostimulator, especially poly-L-lactic acid.19 Fortunately,



FIGURE 4: Treatment of submental fat with lipolytics: before (A) and after (B) - four sessions with 30-day intervals



FIGURE 5: Demarcation of the application of calcium hydroxyapatite in the neck at a dilution of 1:4 with the use of vectorized figures

most are more palpable than visible and self-limiting without any treatment. Visible nodules can be treated with a vigorous massage, intranodular injection of distilled water with or without lidocaine, associated with massage to dilute the product, and, in refractory cases, intranodular injection of 5-fluorouracil and corticosteroids. Granulomas manifest as inflammatory nodules and are even rarer.

#### Treatment of sagging with polydioxanone (PDO) threads

PDO threads (polydioxanone monofilament) are absorbable sutures that will be absorbed while stimulating collagen production, once positioned in the tissue. The traction threads have cones that anchor the skin and subcutaneous tissue, thus allowing lateral traction of the submentum sagging also generating a biostimulus as they are reabsorbed. Its positioning in the correct plan in this region requires the professional's high degree of expertise. Otherwise, irregularities and skin pinch may occur in addition to the risk of damage to noble structures in the subplatysmal plane.<sup>20</sup>

On the other hand, straight threads applied in a juxtadermal plane in hashtag or parallel have the sole objective of collagen biostimulation and are used increasingly in this region due to their ease of application. However, it is noteworthy that the results are directly proportional to the number of threads per region.

The most frequent complications are hematoma, infection, irregularity, migration, and even extrusion. Less experienced professionals can also cause injury to deep structures in the neck.

The careful selection of the candidate patient for the threads is an essential point for the success of the treatment. Patients with low BMI, whose only change in the cervical region is flaccidity, are excellent candidates, while obese patients with large volumes in the submentum will have limited results.<sup>21</sup>

#### Treatment of sagging with microfocused ultrasound

Microfocused ultrasound is a non-invasive device that promotes thermal injury and repair in the tissue through the ultrasound wave directed to the target tissue, resulting in collagen stimulation, tissue-lifting effect, and increased thickness of the local skin. Direct visualization allows higher safety in the treatment, in addition to more promising results by adequately reaching the target tissue.<sup>22</sup>

Numerous studies prove the device's effectiveness for the neck region, promoting the improvement of fine wrinkles, sagging, texture, and skin retraction, both in monotherapy and associated with calcium hydroxyapatite. When treatments are combined, the effects are synergistic and can be performed on the same day, starting with technology.<sup>22,23</sup>

#### Radiofrequency treatment of saging

Radiofrequency is another device capable of improving skin quality and stimulating collagen. Its mechanism of action is the transformation of radiofrequency, applied to the skin, into thermal energy in the different layers of the skin through the frictional heating of molecules exposed to the electromagne-



FIGURE 6: Treatment of submental skin sagging with calcium hydroxyapatite. One syringe per session. Total of two sessions. A - pre-treatment; B - one session; and C - two sessions (observe adequate skin retraction)

tic field. Different tissues conduct electrical currents differently and, therefore, have different impedances, mainly related to the degree of hydration. Fat tissue has high electrical resistance and, as such, responds by generating more heat. Heat induces tissue damage, activates the inflammatory system, and the lesion repair process culminates in collagen production and skin quality improvement.<sup>24</sup>

There are several radio frequency options available: monopolar, bipolar, and multipolar, each with or without temperature control. Kinney, in 2018, demonstrated that, for the neck, the preferred protocol would be multipolar radiofrequency, with temperature control, protocoled with at least five sessions.<sup>24,25</sup>

Finally, the neck region benefits from a valuable technique that uses radiofrequency associated with microneedling. This association makes it possible to deliver radiofrequency energy directly to the area to be stimulated at a predetermined depth. It reaches better results, achieving higher temperatures and more safety, minimizing the adverse events of epidermal heating.<sup>26</sup>

#### Submental contour loss of the structural origin

The structural cause is determined by the lack of support underlying the skin, especially the jawbones. When there is not adequate support, the skin becomes redundant, resulting in apparent excess skin. A correct diagnosis of the cause of double chin is essential because, despite simulating sagging skin, which would be treated with collagen biostimulators, the cause lies in the lack of stretching of this skin and should, therefore, be treated with improved bone support.<sup>4,5,7</sup>

The lack of bone support can be congenital, due to a deficiency in the development of the mandibular bones, especially in mouth breathing patients. However, the bone resorption process inherent to the aging process can also cause it.<sup>6</sup>

The origin of the structural loss can be divided. In most cases, hypomentonism is observed and stretching and/or projection of the chin with hyaluronic acid fillers is indicated. In certain situations, the treatment of the chin can be associated with the mandibular contour improvement, promoting the three-dimensional stretching of the skin of the submental region. Individual characteristics between genders should receive special attention before filling in these regions to avoid dysmorphisms and stigmas.<sup>27,28,29</sup>

Figure 7 shows a treatment protocol for a patient diagnosed with a double chin with structural origin. In this case, stretching and projection of the chin were performed, associated with mandibular contour improvement. Supraperiosteal bolus points with high G-prime and high normal strength hyaluronic acid were used for the projection (pink points – bolus). Treatments in the subcutaneous plane were associated with stretching the chin (filling in the labrum-mental groove) and oral support at the pre-jowl level (in a triangle in Figure 7), which contributes to better mental projection, in addition to filling the body



**FIGURE 7:** Submental loss of contour definition of structural origin. **P** - treatment schedule with hyaluronic acid filler. Before (**A**) and after (**B**)

and ramus of the jaw. Figure 7 describes the doses and these points, collaborating to stretch the redundant skin in a three-dimensional way.

It is noteworthy that any patient with loss of contour of structural origin may be a candidate for definitive treatment with orthognathic surgery and this possibility should be considered before the cosmiatric procedure.

#### CONCLUSION

The popularly called "double chin" is something much more complex and deserves much more respect than what it has been approached recently. Neglecting this anatomical region, especially when treated by non-qualified professionals, can lead to a higher incidence of complications, which are often avoidable. A correct diagnosis and an adequate therapeutic indication, often with the creation of sequential protocols, are essential conditions for the best results.  $\bullet$ 

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#### **AUTHORS' CONTRIBUTION:**

#### Gladstone E. L. Faria D ORCID 0000-0002-0754-2019

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Clarissa L. Vilela D ORCID 0000-0003-2077-1614

Approval of the final version of the manuscript; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; critical literature review; critical revision of the manuscript.

#### Alyne Queiroga Bastos D ORCID 0000-0002-1020-4221

Approval of the final version of the manuscript; active participation in research orientation; critical revision of the manuscript.

**Carolina Freitas Tavares Silva** ORCID 0000-0003-3224-5099 Approval of the final version of the manuscript; critical revision of the manuscript.

#### **Ricardo F. Boggio** (D ORCID 0000-0002-5139-0243

Approval of the final version of the manuscript; active participation in research orientation; critical revision of the manuscript.

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# Clean beauty - literature review of new trends in cosmetics

Clean beauty: artigo de revisão sobre a nova tendência em cosméticos

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#### ABSTRACT

In recent years, there has been an increasing trend toward the search for nature-friendly cosmetics without chemical or synthetic ingredients, thus boosting sales of products within this market niche. Currently, the term clean beauty refers to products that do not contain ingredients with unknown impacts on our bodies or that are potentially harmful to the environment. However, the definition of green beauty products, as well as vegan, natural, or organic products, is not regulated by ANVISA. Therefore, this study aimed to review these definitions to facilitate the medical understanding of the subject. **Keywords:** Beauty; Cosmetics; Beauty products; Green chemistry Technology

#### RESUMO

Nos últimos anos, cresce a tendência pela busca de cosméticos "amigos da natureza", sem ingredientes químicos ou sintéticos, impulsionando as vendas de produtos pertencentes a este nicho de mercado. Atualmente, o termo clean beauty refere-se a produtos que não contenham ingredientes sobre os quais não se conheça o impacto que terão em nosso organismo ou seu potencial dano ambiental. Entretanto, a definição do que é um cosmético verde, bem como vegano, natural e orgânico, não é regulamentada pela Agência Nacional de Vigilância Sanitária (Anvisa), sendo o objetivo deste artigo fazer uma revisão das definições para facilitar o entendimento médico sobre o tema.

Palavras-chave: Beleza; Cosméticos; Produtos para beleza; Química verde

## **Review article**

#### Authors:

Célia Luiza Petersen Vitello Kalil<sup>1</sup> Artur Stramari de-Vargas<sup>2</sup> Flávia Pereira Reginatto Grazziotin<sup>1</sup> Valéria Barreto Campos<sup>3</sup> Christine Rachelle Prescendo Chaves<sup>4</sup>

- <sup>1</sup> Federal University of Fronteira Sul (UFFS), Dermatology, Passo Fundo (RS), Brazil
- <sup>2</sup> Farmatec, Development of Cosmetics, Porto Alegre (RS), Brazil.
- <sup>3</sup> Jundiaí School of Medicine, Dermatology, Jundiaí (SP), Brazil.
- <sup>4</sup> Farmatec Research and Development Porto Alegre (RS) Brazil

#### **Correspondence:**

Célia Luiza Petersen Vitello Kalil E-mail: celia@celiakalil.com.br / Alternative email: formato2s cientific.com.br

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#### INTRODUCTION

In recent years, a trend has been observed in the search for a skincare routine with products of natural origin and without chemical or synthetic ingredients, boosting sales of products belonging to this market niche.<sup>1</sup> The report "Global Natural and Organic Personal Care Products Industry", from Ecovia Intelligence (a company specialized in the research, consulting, and training focused on ethical products), projects global sales of natural and organic personal care products at US\$ 12 billion between 2021 and 2026. China represents the largest market in this segment in Asia, while in Germany, in Europe, these products already represent 10% of the market.

The term clean beauty emerged in the 1970s as a reference to clean, makeup-free skin. In the 2000s, the word got a new meaning with the launch of skincare lines products that do not contain ingredients with uncertain long-term impact on human health – whether by ingestion, application, cross-contamination, or because it is a potential environmental pollutant after its disposal. It impacts the entire production chain since, from the raw materials used to the production, distribution, sale, and disposal of waste, they must be within the "clean" concept. These choices can benefit the user's health and the environment but do not necessarily mean a "cleaner" or even safer product, as natural products can also cause contact dermatitis or even phytophotodermatitis.<sup>2</sup>

In Brazil, the registration of a natural, vegan, or organic product is subject to the same requirements as conventional cosmetics, and there is no distinction between them before the national regulatory body, Anvisa.3 Thus, most cosmetics companies request national or international certification bodies to validate their product as natural, vegan, or organic. The seal of these certification bodies, given to the products, can generate a false sense of security in the consumer since the product meets their expectations regarding these concepts and visions. However, the selection of ingredients considered "harmful" without adequate scientific support has been confusing both in the medical field and the cosmetic, pharmaceutical, and consumer industries. Thus, it is crucial to analyze what benefits the consumer and the environment within the "clean beauty" nomenclature.

#### OBJECTIVE

This study aims to review the definitions of current concepts of "clean beauty", differentiating natural, organic, and vegan cosmetics, to facilitate the medical understanding of the difference between these products, which are growing market trends.

#### Natural, organic and vegan

So far, there is no official regulation in Brazil distinguishing natural products from organic or vegan ones. Thus, the identification of these products is currently made by the presence of seals from certification bodies, such as COSMOS, ECOCERT, Brazilian Vegan Seal (*Selo Vegano Brasileiro - SBV*), and Biodynamic Institute for Rural Development (*Instituto Biodinâmico de Desenvolvimento Rural - IBD*).

#### Natural products

A natural cosmetic does not have chemical or synthetic additives in its composition. Raw materials of animal, vegetable, or mineral origins are used to manufacture it, excluding products such as petrolatum and silicones or preservatives, dyes, and fragrances of synthetic origin, for example. In addition to its composition, the product packaging must be designed within this concept, using recyclable, biodegradable, or reusable materials. It is a concept that aims to preserve the environment through the use of raw materials that cause less impact on ecosystems and human health. Although certification bodies cover the presence of a certain amount of organic raw materials in natural formulations, they also allow small amounts of synthetic products, which may vary according to the agency (in general, it is required that 95% of the raw materials used are of natural origin; the other 5% of the composition may contain synthetic substances, provided they are released).

#### **Organic products**

The cultivation and use of organic products relate to the attempt to reduce the negative impacts of agriculture on the environment and human health.<sup>4,5</sup> The manufacture of organic cosmetics comprises sustainable raw materials with minimal impact on ecosystems, animals, and humans. Pesticides and synthetic fertilizers are prohibited in the cultivation of raw materials. Organic cultivation is based on crop rotation, cover crops, and appropriate choice of species for crop rotation, in addition to biological and natural pesticides. It has a positive impact on reducing greenhouse gas emissions, improving biodiversity, reducing water consumption, and improving soil, water, and air quality.<sup>4</sup>

For most organic cosmetics certification bodies, at least 95% of raw materials must be of organic origin, and the product must not contain raw materials of synthetic origin to receive organic certification.

#### Vegan products

Veganism is a philosophy that aims to abolish the use and exploitation of animals for any human activity, mainly motivated by the increase in health and ethics.<sup>6</sup>Vegan cosmetics do not use ingredients of animal origin, such as beeswax or lanolin. Also, they have a cruelty-free philosophy, prohibiting products from having their efficacy or safety tested on animals.

It is noteworthy that a vegan cosmetic does not have the same definition as a natural or organic one, although they are concepts that can work together. If a cosmetic has 100% synthetic ingredients, it is vegan, as there are no ingredients of animal origin in its formulation. However, it is not considered natural or organic.

#### Renewable sources x biodegradable product

Terms such as "produced with raw material from a renewable source" or "produced with biodegradable raw material" are widely applied to packaging as a marketing appeal. However, these concepts are often confusing to those who buy the product.

The concept of a renewable source is related to the time and possibility of renewing this material. As with renewable energies, renewable raw materials have a renewal cycle on a human time scale, that is, they are always available and do not run out. Examples of renewable raw materials are those derived from agricultural plants, such as corn, soybeans, or cassava, unlike those derived from petroleum, which is non-renewable. However, not all plant sources are renewable. The plant's growth time and how extractivism is conducted can make it a non-renewable source since the consumption of the product becomes higher than the amount produced. An example is the exaggerated extraction of jaborandi (*Pilocarpus microphyllus*) in the state of Maranhão, in northeastern Brazil.

Mainly for pilocarpine extraction, the use of the plant is leading to the depletion and threat of extinction of the natural populations of this plant resource.<sup>7</sup>

The concept of biodegradability concerns the decomposition of the product after its use and disposal. Microorganisms can naturally consume the biodegradable product, converting it into biomass, carbon dioxide, and water in a maximum period of six months. It is a great advantage when compared to products that persist in nature for hundreds of years after being discarded. Biodegradable polymers, such as plastics and resins, are produced from natural raw materials, usually from renewable sources.

However, each product must be well analyzed to be characterized as biodegradable or as a renewable source. Polyethylene-type plastic produced from sugarcane ethanol has the same chemical property as polyethylene obtained from petroleum but is not biodegradable. However, it comes from a renewable source, which is sugarcane.

Something crucial to consider is that these products are categorized asbiodegradable through laboratory tests, which are often not transferable to the conditions found in the environment. Specific substrate, temperature, and humidity conditions are required for microorganisms to degrade polymers. When these parameters are not ideal, such as when the plastic material ends up in the sea, the disintegration time of the products can be much longer.<sup>8</sup>

Much has been said about the impact of microplastics on the environment and human health. Microplastics are plastic particles measuring between 100 nanometers and 5 millimeters.9,10 These residues have already been found all over the world, in water, soil, air, and food. These small plastic particles have an irregular shape and a large surface area compared to their small volume. Due to their lipophilic nature, many hazardous pollutants, such as polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs), and dichlorodiphenyltrichloroethane (DDT), end up binding to the surface of microplastics, making them a source of pollutants in high concentration.<sup>11,12</sup> Microplastics can originate by addition to products (such as personal hygiene products) or by the fragmentation of macroplastics present in the environment.13 Among the sources of microplastics, cosmetics represent a considerable portion. Products such as exfoliants, soaps, toothpaste, sanitizing gels, sunscreens, and shampoos may contain microplastic in their composition. Usually, these particles are used as an abrasive agent or a decoration, in the case of glitter.<sup>10,14</sup>

Currently, there are many alternatives for microplastic, both as abrasive and exfoliating agents and as decoration, in the case of glitter. Abrasive agents derived from plants, such as ground fruit and cereal seeds, or derived from natural rocks, are a biodegradable, non-polluting replacement for plastic beads. In the case of plastic glitter, there is the possibility of using natural materials of mineral origin, such as mica, diamond powder, pearl powder, or other mineral derivatives

Another issue of great relevance to consumers is organic sunscreens in photoprotective compositions. Many cosmetics, mainly sunscreens, use organic filters to protect the skin against the damage of ultraviolet radiation (UVR). They are also present in other personal care products, such as oxybenzone, avobenzone, and octocrylene, among others, mainly because of their effectiveness and low cost.<sup>15</sup> These substances have already been detected in inhabited and uninhabited coastal waters and ecosystems, such as the Arctic and Antarctic, contaminating marine animals,16 thus making its use a concern. In Brazil, benzophenone, ethylhexyl methoxycinnamate, ethylhexyl salicylate, and octocrylene filters have already been identified as contaminating pre- and post-treatment waters.17 These substances reach the environment by directly rinsing off skin products during recreational activities, mainly on beaches, or indirectly by overflowing from landfills and as effluent from sewage treatment plants, which usually do not efficiently remove them from the water before return to the rivers and seas.15 This difficulty is mainly due to the chemical characteristics of the filters since they are poorly soluble in water and have high lipid solubility, and because the effluent treatment is mainly developed to remove particulate matter from the water. Many organic filters are considered persistent pollutants with potential for bioaccumulation.<sup>18</sup> A systematic review observed that the risk posed by the contamination of ecosystems by these substances is low when the average concentrations found in the environment are analyzed. However, it becomes high when assessing the maximum concentrations found in some ecosystems. Also, toxicity data to establish predicted no-effect concentration (PNEC) values for the ecosystem are scarce. There is still a lack of data evaluating effects at different trophic levels, what are the toxic mechanisms of action of substances, and what variables, such as temperature, salinity, or acidification, can interfere with toxic effects.19

#### CONCLUSION

Currently, consumers are increasingly aware of the composition of products consumed in their daily lives. This concern about knowing the composition before purchase is quite consolidated in food, but has been migrating to cosmetics. The main positive point is that clean beauty has been encouraging both the cosmetic and raw material industries to conduct better safety studies of actives and better select the products and packaging used in production. Another essential point is that consumers of clean beauty products demand transparency from manufacturers. It has caused a movement in the global cosmetics market towards more open communication about product components and their impact on the skin and the environment.

As there is no regulation or legal or official definition, each product brand defines clean beauty according to the company's internal policy and marketing. It brings heterogeneity of raw materials and products that may not match the proposal to be a product free of toxic ingredients. Although there are already lists of components not allowed in products with this marketing appeal, the lack of regulation means that these lists are respected within the budget of the manufacturing industry. The fact is that there are numerous scientific articles demonstrating the toxic potential of cosmetic actives, whether for the environment or even for humans. However, most of these studies are in vitro, in small numbers, with high variability of results, or with methodologies that pre-

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vent a meta-analysis. Thus, the dermatologist must be careful when prescribing products under a clean beauty appeal since it is not a guarantee that the patient will not have any complications with their use. •

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#### AUTHORS' CONTRIBUTION:

**Célia Luiza Petersen Vitello Kalil** ORCID\_0000-0002-1294-547X Approval of the final version of the manuscript; study design and planning; active participation in research orientation; critical revision of the manuscript.

Artur Stramari de-Vargas D ORCID 0000-0001-5773-8039 Preparation and writing of the manuscript; critical literature review.

**Flávia Pereira Reginatto Grazziotin** <sup>D</sup> ORCID\_0000-0002-8189-2375 Approval of the final version of the manuscript; active participation in research orientation; critical revision of the manuscript.

Valéria Barreto Campos D ORCID 0000-0002-3350-8586

Approval of the final version of the manuscript; active participation in research orientation; critical revision of the manuscript.

Christine Rachelle Prescendo Chaves 问 ORCID\_0000-0001-8861-6499

Preparation and writing of the manuscript; critical literature review; critical revision of the manuscript

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# Snail flap as an option to reconstruct a nasal defect: a series of two cases

Retalho em caracol como uma opção de reconstrução de defeito nasal: uma série de dois casos

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#### ABSTRACT

Basal cell carcinoma (BCC) is the most common skin cancer. When located in the nasal region, reconstructing the defect resulting from its exeresis can become very challenging for the dermatological surgeon. The snail flap (SF) technique can be used to correct defects, mainly on the nose's lateral wall, but we use it in a modified way to close the nasal wing injury. In both cases, the results were satisfactory, cosmetically and functionally.

Keywords: Carcinoma basal cell; Surgical flaps; Nose

#### RESUMO

Carcinoma basocelular (CBC) é o câncer de pele mais comum. Quando localizado na região nasal, a reconstrução do defeito resultante de sua exérese pode se tornar muito desafiadora para o cirurgião dermatológico. A técnica do retalho em caracol (RC) pode ser utilizada para defeitos, principalmente na parede lateral do nariz, mas também a utilizamos de maneira modificada para fechamento de lesão da asa nasal. Nos dois casos, os resultados foram satisfatórios, tanto pela cosmética quanto pela funcionalidade.

Palavras-chave: Carcinoma basocelular; Retalhos cirúrgicos; Nariz



#### Authors:

- Rogerio Nabor Kondo<sup>1</sup> Gabriela Bernardi Maia<sup>1</sup> Leticia Amstalde Bertoncini<sup>1</sup> Suellen Tormina da Silva<sup>1</sup>
- <sup>1</sup> Universidade Estadual de Londrina, Department of Internal Medicine, Londrina (PR), Brazil.

#### Correspondence:

Rogerio Nabor Kondo Email: kondo.dermato@gmail. com / Alternative E-mail: kondo. dermato@gmail.com

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#### INTRODUCTION

Basal cell carcinoma (BCC) is the most common type of skin cancer.<sup>1</sup> Sometimes, complete excision of this type of tumor requires a flap to close the resulting defect, especially those larger than 10 mm.<sup>1,2</sup> Reconstructions in the nasal region are challenging for dermatological surgeons due to their local characteristics, such as rigid structure and little mobility.<sup>3</sup>

The snail flap (SF) is a rotation flap in which part of the pedicle makes a folding movement over itself, resembling a snail shell. It is generally used to correct circular defects in the lower nasal wall, where the adjacent skin above and laterally to the defect is used to provide higher mobility to the flap.<sup>4</sup>

We report two cases who underwent reconstruction with SF after excision of nasal BCC: one patient had a lesion in the nose's lower lateral wall (where the flap is most often used), and the other presented a lesion in the nasal wing (where it's rarely performed). Both had a satisfactory aesthetic result. This study aims to exemplify the SF and demonstrate an option of the technique to correct defects in the nasal wing, with easy execution and a good level of patient satisfaction.

#### METHOD

Two patients with BCC in the nasal region were treated: **Patient 1:** A 80-year-old man, skin phototype III, from Londrina (PR), presented a pearly plaque, 12 mm x 9 mm, on the lower left lateral dorsum of the nasal region, compatible with BCC by biopsy. The lesion was excised with safety margins of 5 mm. The resulting defect was 17 mm in the longest axis, and RC was chosen (Figures 1, 2, and 3).

**Patient 2:** A 73-year-old woman, skin phototype III, from Londrina (PR), presented an erythematous plaque, 6 mm x 5 mm, in the nasal wing to the left of the nasal region, compatible with BCC by biopsy. The lesion was excised with safety margins of 5 mm. The resulting defect was 11 mm in the longest axis, and RC was chosen (Figures 4, 5, and 6).

Description of the technique used for Patient 1: (Figures 1 and 2):

- A) Patient in horizontal supine position;
- B) Marking with methylene blue or surgical pen of the lesion with a 5 mm margin and flap incision si-



FIGURE 1: A - Marking the lesion with a 5 mm margin and flap incision sites. The three portions of the flap: (1) alar portion, (2) body, and (3) tail. B - Defect.



FIGURE 2: A - Flap incision. 2B. Flap positioned and sutured.

tes: an arch starting from the defect in its upper portion and extending to the homolateral nasogenian groove. From there, a retrograde incision (back-cut) was performed. This flap had three portions: (1) alar, (2) body, and (3) the tail (Figure 1A).

- C) Antisepsis with topical 10% polyvinyl iodine;
- D) Placement of surgical drapes:
- E) Infiltrative anesthesia with 2% lidocaine and vaso-constrictor;
- F) Lesion incision using blade 15 and round block excision of the piece;
- G) Hemostasis;
- H) Flap incision, starting from the defect, making an arc in its upper position, passing through the malar region to the nasogenian groove (as previously marked). From that point, a retrograde incision was made;

- I) Flap detachment;
- J) Positioning the flap and other sutures with 5.0 mononylon, using single stitches. The alar portion folds over itself (with a "curled" aspect), resembling a snail shell (Figures 2A and 2B);
- K) Local cleaning with saline;
- L) Occlusive dressing.

Description of the technique used for Patient 2 (Figures 4, 5 6A):

The differences between the techniques of patients 1 and 2 are in items b, h, and j (the sequences described above: a, c, d, e, f, g, i, k, and l of the two techniques remained the same).

B) Marking with methylene blue or surgical pen of the lesion with a 5 mm margin and incision sites of the flap: an arch starting from the lower region of the defect, outlining it in a spiral until the homolateral nasogenian groove in a retrograde incision



FIGURE 3: A - One month after the operation. B - Four months after the operation.



FIGURE 4: A -Patient 2. Marking the lesion with a 5 mm margin. B - Marking the flap incision sites.

(Figures 4 and 5);

- H) Flap incision, starting from the lower region of the defect, making a spiral arch up to the nasogenian groove (as previously marked);
- J) Positioning the flap and other sutures with 5.0 mononylon, using single stitches. The portion proximal to the defect folds over itself (with a "curled" aspect), resembling a snail shell (Figures 4B, 5B and 6A).

#### RESULTS

**Patient 1:** The patient evolved uneventfully in the first postoperative days. There was good healing and accommodation, with a satisfactory aesthetic result in the late postoperative period (Figure 3B).

**Patient 2:** The patient evolved uneventfully in the immediate postoperative period. There was good healing and accommodation, with a satisfactory aesthetic result in the late postoperative period (Figures 6A and 6B).

#### DISCUSSION

SF is a rotation flap technique, but it can also be considered an "island" flap as it maintains vascularization in its central region. It is used to correct circular defects in the lower nasal wall, and it is considered a good alternative for nasolabial interpolation since it can be performed in a single surgical time.<sup>4</sup>

FS is neither exclusive to the nasal wall nor restricted to the nose area. When applying a flap that folds over itself, resembling a snail shell, it is an SF. Christopoulos et al. described an SF



Figure 5: A - Defect. B - Flap incision



FIGURE 6: A - Flap positioned and sutured. B - Four months after the operation.

technique for reconstructing scalp defects,<sup>5</sup> and Aksu *et al.* used it for the external auditory canal.<sup>6</sup>

In the case of patient 1, we performed the classic SF. We incised an arch that started from the upper region of the defect to the homolateral nasogenian sulcus, and, from that point on, we made a backward cut incision. This flap had three portions: (1) alar, (2) body, and (3) tail. The alar portion reconstructed the alar region of the defect and was the same size as that area. The flap's body and tail were the same size as the vertical dimension of the entire defect and covered the old position of the alar portion<sup>4</sup> (Figures 1A and 2B).

In the case of patient 2, we applied the modified SF to the nasal wing defect. The beginning of the flap incision was in the lower region, making an arch almost parallel to the defect for better accommodation, so there was no lifting of the nasal wing. Not only the end of the flap fold over itself, but nearly half of it spiraled (Figures 5B and 6A) The reason why SF is rarely used in the nasal wing region may be due to other existing techniques (grafting, advancement island flaps, transposition). In addition, if the SF is made in the same proportions and incisions as its classic model (that is, without being modified), it can cause local deformities, such as lifting the nasal ala.

In addition to the nasal wall (patient 1), another location where SF could be applied would be the nasal ala (patient 2). The technique for this last location differs from the first in that it uses practically half of the flap (not just the end) to fold over itself. For better results, the present authors advise not to perform surgical defects larger than 15 mm, due to the risk of alar nasal anatomical distortion.

#### CONCLUSION

SF can be a good option for resolving defects in the lateral wall and nasal wing regions.  ${\ensuremath{\bullet}}$ 

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#### **AUTHORS' CONTRIBUTION:**

#### Rogerio Nabor Kondo D ORCID 0000-0003-1848-3314

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Gabriela Bernardi Maia D ORCID 0000-0002-3730-8207

Approval of the final version of the manuscript; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.

#### Leticia Amstalde Bertoncini D ORCID 0000-0002-4687-8332

Approval of the final version of the manuscript; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.

#### Suellen Tormina da Silva D ORCID 0000-0003-1175-0571

Approval of the final version of the manuscript; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.

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# Adverse reaction to isotretinoin: alteration of the hair shaft structure

Reação adversa à isotretinoína: alteração do formato capilar

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#### ABSTRACT

Although little reported in daily practice, the use of systemic retinoids can cause changes in the shape, color, and texture of hair shafts. We report a case of a patient treated with isotretinoin for acne vulgaris who experienced new growing curly hair. Such hair changes are recognized during therapy with oral retinoids; however, isotretinoin-induced modifications on the hair fiber curvature are extremely rare. **Keywords:** Hair; Isotretinoin; Pharmacological treatment

#### RESUMO

Embora pouco frequente na prática clínica, o uso de retinoides sistêmicos pode provocar alterações no formato, na coloração e textura das hastes capilares. Relatamos o caso de um paciente tratado com isotretinoína para acne vulgar que experimentou mudança do tipo capilar, de liso para encaracolado. Tais modificações são possíveis ao longo da terapia com retinoides orais; entretanto, a mudança do formato dos fios induzida pela isotretinoína é um fenômeno extremamente raro na literatura.

Palavras-chave: Cabelo; Isotretinoína; Tratamento farmacológico

### **Case Report**

#### Authors:

Rodrigo Lousada<sup>1,2</sup> Edilbert Pellegrini Nahn-Júnior<sup>1,2</sup> Hudson Dutra Rezende<sup>3</sup> Liana Moura de Almeida<sup>2,4</sup> Ana Paula Moura de Almeida<sup>2,4</sup> Maria Fernanda Reis Gavazzoni Dias<sup>5</sup>

- <sup>1</sup> Universidade Federal do Rio de Janeiro, Department of Dermatology, Macaé (RJ), Brazil.
- <sup>2</sup> Faculdade de Medicina de Campos, Department of Dermatology, Campos dos Goytacazes (RJ), Brazil.
- <sup>3</sup> Centro Universitário Lusíada (UNILUS), Department of Dermatology, São Paulo (SP), Brazil.
- Hospital Escola Álvaro Alvim,
  Department of Dermatology,
  Campos dos Goytacazes (RJ), Brazil.
- <sup>5</sup> Universidade Federal Fluminense, Department of Dermatology, Niterói (RJ), Brazil.

#### **Correspondence:**

Edilbert Pellegrini Nahn-Júnior Email: doutorpellegrini@yahoo. com.br / Alternative email: doutorpellegrini@yahoo.com.br

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#### INTRODUCTION

Changes in the shape, color, and texture of hair are reported with the use of systemic retinoids, although they are rarely observed in clinical practice. The pathophysiological mechanisms that justify the physical alterations of the hair shafts in this context are partially understood. Still, they seem to be related to the duration of the treatment, the systemic retinoid used, and the doses used.

#### **CASE REPORT**

A 20-year-old man started treatment with oral isotretinoin for acne vulgaris in 2018, with a daily dose of 0.5 mg/kg/ day, obtaining an accumulated dose of 12,820 mg in 11 months. The patient reported a gradual change in hair shape, from straight to wavy, especially noticed in the last two months of treatment (Figure 1). No additional complaints were mentioned. In his last assessment, in December 2020, the hair changes persisted.

#### DISCUSSION

Among the hair changes related to systemic retinoid use, the literature reports interferences in the hair cycle and changes in the shafts' color, shape, and texture.<sup>1,2,3</sup> The literature describes changes in hair shaft shape leading to a more wavy hair in patients treated with etretinate, acitretin, and, less commonly, isotretinoin.<sup>1,3</sup> Although the mechanism that leads to hair strand changes is not fully elucidated, it is known that retinoids affect the differentiation of follicular and epidermal keratinocytes and their pattern of keratin expression.<sup>4</sup> In 2009, Seckin *et al.* observed the hair waving of a 70-year-old woman under treatment with acitretin for psoriasis vulgaris. The author proposed that the phenomenon was linked to the hair follicle's inner root sheath's (IRS) keratinization deterioration.<sup>2</sup> As a note, IRS is a structure of great importance in determining the shape of hair fibers by acting as an intrafollicular structural mold during the growth of new hairs.<sup>3</sup>

In line with the observations of Seckin, Westgate et al. suggested that hair's shape, type, and color are determined not only by genetic mechanisms during embryogenesis but also repeatedly in each hair cycle.<sup>3</sup> Thus, such characteristics would be subject to the influence of external and environmental factors.

With the advance of more complex studies on the human genome, more evidence points to the influence of developmental genes on the formation of wavy hair.<sup>3</sup> Ectodysplasin receptors, for example, related to hair shape and thickness, are not detected only in hair follicles during their morphogenesis but also at puberty and throughout the phase changes of the hair cycle.<sup>3</sup>

The retinoid action on the pilosebaceous unit, reducing volume and glandular activity, also represents a possible link with the hair shape change. Interestingly, and according to observations by Westgate et al., when studying the straight hair of Asian patients, evolutionary glandular changes may have acted as a driving force behind the penetration of new genes that determine the shape of human hair.<sup>3</sup>

As in this case report, alterations in the curvature of hair strands after the systemic use of isotretinoin is not unprece-



**FIGURE 1:** Hair shape before treatment and alteration of hair shape, with waving, after treatment with oral isotretinoin

dented in the literature<sup>2,4,5</sup> and is in line with the mechanisms of action of systemic retinoids on the IRS and the sebaceous glands. To date, there are no data on the duration of hair changes caused by retinoids. Regarding the infrequency of this adverse event in dermatological practice, the capillary changes induced by isotretinoin may be uncommon given its temporary use and in low doses, as commonly applied in the treatment of acne vulgaris.<sup>4</sup>

#### CONCLUSION

We hope that this report will contribute to the list of possible rare adverse events that isotretinoin may cause in the body during its use. The dermatologist would be prepared for more complete and refined care by recognizing infrequent adverse events related to everyday drugs. •

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#### **AUTHORS' CONTRIBUTION:**

#### Rodrigo Lousada D ORCID 0000-0002-5690-5584

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Edilbert Pellegrini Nahn-Júnior (D ORCID 0000-0003-1656-3441

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Hudson Dutra Rezende D ORCID 0000-0002-7039-790X

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Liana Moura de Almeida D ORCID 0000-0002-7183-6900

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Ana Paula Moura de Almeida D ORCID 0000-0003-1297-9298

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Maria Fernanda Reis Gavazzoni Dias D ORCID 0000-0001-7397-7478

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

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## Unexpected riziform bodies

Corpos riziformes em localização inusitada

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#### ABSTRACT

Riziform bodies are structures in the synovial fluid or attached to the synovium, which macroscopically resemble rice grains. They are common in patients with rheumatoid arthritis and result from a chronic inflammation. They are found in 25% of aspiration procedures or joint surgery. However, there are still no publications reporting its presence in the subcutaneous tissue. We report for the first time the occurrence of riziform bodies in the subcutaneous plane of the palmar region in a patient with rheumatoid arthritis, confirmed by sonographic and anatomopathological examination, successfully treated with surgical drainage, without recurrences after two years of follow-up.

Keywords: Abscess; Rheumatoid arthritis; Dermatopathies; Hand dermatoses; Outpatient Surgical Procedures; Surgical Diagnostic Techniques

#### RESUMO

Corpos riziformes são estruturas que podem ser encontradas no líquido sinovial ou aderidas à sinóvia, que se assemelham macroscopicamente a grãos de arroz. São frequentes em pacientes com artrite reumatoide e decorrem de resposta inflamatória crônica. São encontrados em 25% dos procedimentos de aspiração ou cirurgias das articulações. Porém, ainda não existem publicações relatando sua presença no subcutâneo. Relatamos, pela primeira vez, a ocorrência de corpos riziformes no subcutâneo da região palmar em paciente com artrite reumatoide, confirmados por exames ultrassonográfico e anatomopatológico, tratados com sucesso com drenagem cirúrgica, sem recidivas após dois anos de seguimento. **Palavras-chave:** Abscesso; Artrite reumatoide; Dermatopatias; Dermatoses da mão; Procedimentos cirúrgicos ambulatoriais; Técnicas de diagnóstico por cirurgia

### **Case Report**

#### Authors:

Isabella Zurita Dehó<sup>1</sup> Jayme de Oliveira Filho<sup>2</sup> Irina Andrea Pires Afonso<sup>2</sup> Anna Rita Ferrante Mitidieri de Oliveira<sup>1</sup>

- <sup>1</sup> Hospital Sírio Libanês, Department of Dermatology, São Paulo (SP), Brasil.
- <sup>2</sup> Tez Dermatologia, Department of Dermatology, São Paulo (SP), Brasil.

#### Correspondence:

Isabella Zurita Dehó Email: isazdeho@gmail.com / isazdeho@gmail.com

Financial support: None. Conflict of interest: None.

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#### 1

#### INTRODUCTION

Riziform bodies are structures found in the synovial fluid or adhered to the synovia. They receive this name because they macroscopically resemble rice grains.<sup>1</sup> These agents occur due to a chronic and nonspecific synovial inflammatory response.<sup>2</sup> They are composed of an acidophilic center of collagen types I, II, and IV, encapsulated in the periphery by fibrin.<sup>3,4</sup>

These structures were described for the first time in 1895 in a patient with tuberculous arthritis.<sup>1</sup> They were later described in association with other diseases, such as rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), osteoarthritis, tenosynovitis associated with brucellosis, joint infection by mycobacteria and fungi, or even idiopathically, in patients without comorbidities.<sup>1,3</sup>

They are currently more frequently associated with rheumatoid arthritis than seronegative arthritis. Its removal ensures clinical improvement for patients, reduction of synovitis, and the possibility of investigating infectious causes.<sup>5</sup>

Riziform bodies are found in 25% of aspiration procedures or joint surgeries.<sup>3,4</sup> However, there are still no publications reporting their presence in the subcutaneous plane, even in patients with rheumatoid arthritis. In this article, we report, for the first time, the occurrence of riziform bodies in the subcutaneous tissue of the palmar region in a patient with rheumatoid arthritis, confirmed by ultrasound and pathological examinations. They were successfully surgically drained, with no recurrences after a two-year follow-up.

#### CASE REPORT

A 67-year-old woman, skin phototype II, born and resident in São Paulo, sought medical care for three weeks complaining of pain and difficulty opening her right hand (Figure 1). Dermatological examination revealed an erythematous tumor, poorly delimited, measuring 2.7 cm in its longest axis, surmounted by hyperkeratotic areas in the right palmar region, at the level of the metacarpophalangeal joints, between the second and fourth fingers (Figures 2A and 2B).

She had a personal history of hepatitis C, *diabetes mellitus*, sickle cell anemia, rheumatoid arthritis, and kidney transplantation 26 years ago. The patient was in use of ribavirin, NPH human insulin, azathioprine, folic acid, B complex, alpha epoetin, and prednisone 5 mg/d.

The differential diagnoses included cutaneous abscess, tenosynovitis, epidermal inclusion cyst, adnexal tumor, and Dupuytren's contracture.

Given that the clinical characteristics suggested the diagnosis of abscess, we chose treatment with oral ciprofloxacin 500 mg 12/12h for ten days and requested exams, including imaging. After a week, the patient returned with the results of the exams, and the lesion still looked the same.

The ultrasound of the right hand showed tendons with an extensive circumscribed collection, walls, and hypoechoic content associated with thick suspension debris surrounding the tendons (Figure 3).



FIGURE 1: Contracture present in the first consultation



FIGURE 2: A - Dermatological examination: erythematous tumor, poorly delimited, surmounted by hyperkeratotic areas in the region of the metacarpophalangeal joints of the right hand. B - Oblique view: erythematous tumor surmounted by hyperkeratotic crust. C - Surgical drainage: visualization of multiple granular structures, pearlescent,

with fibroelastic consistency and smooth surface.

**D** - Drainage of the entire content of the lesion







**FIGURE 4: A** - Surgical drainage: visualization of multiple granular structures, pearlescent, with fibroelastic consistency and smooth surface. **B** - Drainage of the entire content of the lesion

We conducted the surgical drainage of the lesion. During the procedure, we observed the presence of a fibrous nodule adhered to the deep planes, associated with the emergence of multiple granular, cystic structures, with fibroelastic consistency and smooth surface (Figures 4A and 4B).

The material was sent to the anatomopathological exam (Figures 5A, 5B, 5C, and 5D), which showed granular material represented by hyalinized collagen, intermingled with cells with elongated or ovoid nuclei and rare mononuclear elements, and presence of foci of dystrophic calcification. In the periphery of the lesions, we observed the presence of fibrin and macrophages,



FIGURE 5: A - Material sent for anatomopathological study.
 B - Anatomopathological: general view. C- Image with microscopic magnification of 40 times, showing hyalinized collagen intermingled with cells with elongated or ovoid nuclei and rare mononuclear elements. Presence of foci of dystrophic calcification. In the periphery of the lesions,

there is the presence of fibrin and macrophages. **D** - 70-fold magnification on optical microscopy, showing hyalinized collagen intermingled with cells with elongated or ovoid nuclei and rare mononuclear elements. Presence of dystrophic calcification foci. In the periphery of the lesions, there is the presence of fibrin and macrophages



**FIGURE 6: A** - Follow-up three weeks after the procedure. **B** - Follow-up two months after surgical drainage. **C** - Image after two years of follow-up, showing no recurrence in the site or in other joints

some of them phagocytizing a light brown pigment with the characteristics of hemosiderin. There was an absence of signs of malignancy. These features confirmed the diagnosis of "riziform bodies".

One month after the drainage, the patient returned for consultation, presenting clinical improvement; however, she still had difficulty flexing her fingers (Figure 6A).

Two months after the drainage, the patient returned with significant clinical improvement, including the ability to flex her fingers, which was previously difficult to perform (Figure 6B).

The patient evolved with complete wound healing and no recurrence after a two-year follow-up (Figure 6C).

This article presents the complete clinical picture and the follow-up of the lesions within one month, two months, and two years after the procedure.

#### DISCUSSION

Riziform bodies are prevalent in patients with rheumatoid arthritis. Previous studies have already demonstrated its presence in 72% of the joint effusions of these patients.<sup>5</sup> On average, they appear in rheumatoid arthritis with six to nine years of evolution. Still, they can occur both at the onset of the condition and in later stages, without association with the disease severity.<sup>5</sup>

Its pathogenesis remains uncertain. It is believed that these bodies are the end product of an inflammatory and proliferative process in the synovia, associated with ischemia with subsequent degeneration and desquamation of the same, encapsulated by fibrin.<sup>6</sup> In this article, the patient had a previous diagnosis of rheumatoid arthritis. On the other hand, other authors reported the presence of riziform bodies before the diagnosis of inflammatory arthritis, highlighting the importance of following up on these patients for at least one to two years for etiological investigation.<sup>2</sup>

Riziform bodies have already been isolated in chronic infectious arthritis of the hands, mainly caused by *Mycobacterium marinum* and *M. avium*.<sup>7</sup> However, it is the first article to report their occurrence in this location, associated with rheumatoid arthritis.

Furthermore, during surgical drainage, we observed that they originated from the subcutaneous tissue of the patient's palmar region, unlike what is expected in rheumatoid arthritis, in which they predominantly occur within the bursa, with the subacromial being the most affected. This subcutaneous occurrence was previously reported only in tenosynovitis caused by mycobacteria.<sup>8</sup>

In patients with rheumatoid arthritis, consideration of concomitant infection is essential, especially in patients using immunosuppressants and corticosteroids.<sup>7</sup>

As shown the particles are characterized, macroscopically, by a smooth, light, yellow surface. However, it has already been demonstrated that riziform bodies can present several morphological variations: color (between white and yellow), consistency (smooth or rough), and size (from less than 2 mm to greater than 7mm).<sup>5</sup>

In this case, the patient had complete remission of the lesion after surgical drainage without the need for additional treatments. Other authors have reported similar results after treatment but with a shorter follow-up time than described in this article.<sup>2</sup> The improvement with drainage seems to be due to the removal of fibrin deposits that make up the riziform bodies since this substance presents the ability to perpetuate the inflammatory stimulus in the joints.<sup>5</sup> Thus, in addition to being curative, surgical drainage reduces the recurrence risk, as observed during the two-year follow-up of our patient.<sup>9</sup>

Another measure associated with surgical treatment is the clinical control of underlying arthritis with specific pharmacological therapy, and, in cases of associated infection, antimicrobial therapy should be introduced.

#### CONCLUSION

What most caught our attention in this patient was the rarity we came across similar cases.

The diagnosis was made through physical examination combined with ultrasound examination and confirmed by pathological examination. Along with the unique characteristics of the surgical finding, we concluded this unusual and rare diagnosis.

In this case, we believe that the etiology is rheumatoid arthritis. As the clinical evolution has been satisfactory, we did not conduct other tests, nor the proposal in the literature for the excision of the affected tendon sheath. However, we are closely following the evolution of the clinical picture, which continues without recurrences and with good recovery of joint movements after two years of follow-up.

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#### AUTHORS' CONTRIBUTION:

**Isabella Zurita Dehó** Dercip ORCID 0000-0002-2884-7073 Preparation and writing of the manuscript.

Jayme de Oliveira Filho D ORCID 0000-0003-0239-0981

Approval of the final version of the manuscript; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.

Irina Andrea Pires Afonso D ORCID 0-000-0001-6787-8529

Author's contribution: Approval of the final version of the manuscript; preparation and writing of the manuscript.

Anna Rita Ferrante Mitidieri de Oliveira (D) ORCID 0000-0002-5551-7440 Approval of the final version of the manuscript.

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# Pemphigus vegetans: surgical approach as a complementary treatment

Pênfigo vegetante: abordagem cirúrgica como tratamento complementar

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#### ABSTRACT

Pemphigus vegetans is considered a rare clinical variant of Pemphigus vulgaris and is associated with recurrent lesions that can evolve into extensive vegetative plaques that are difficult to resolve. Surgery may be an alternative in the complementary treatment of lesions resistant to classical therapy. There is a shortage of literature that shows the surgical technique and the postoperative results of the approach to pemphigus vegetans, making the communication of this case relevant. We present the case of a patient with the Hallopeau type of pemphigus vegetans successfully treated with tangential exercisis followed by secondary intention healing of large retroauricular projections.

Keywords: Pemphigus; Dermatologic surgical procedures; Treatment outcome

#### RESUMO

O pênfigo vegetante é considerado uma rara variante clínica do pênfigo vulgar e cursa com lesões recorrentes que podem evoluir para placas vegetantes extensas de difícil resolução. A cirurgia pode ser uma alternativa no tratamento complementar de lesões resistentes à terapêutica clássica. Há escassez de literatura que evidencie a técnica cirúrgica e os resultados pós-operatórios da abordagem do pênfigo vegetante, tornando relevante a comunicação deste caso. Apresentamos o caso de um paciente com pênfigo vegetante de Hallopeau, tratado com sucesso por meio da exérese tangencial seguida da cicatrização por segunda intenção de grandes projeções retroauriculares.

Palavras-chave: Pénfigo; Procedimentos cirúrgicos operatórios; Resultado do tratamento

### **Case Report**

**Authors:** 

- João Felipe Rossival-Preto<sup>1</sup> Ingrid Stresser-Gioppo<sup>2</sup> Flávia Fajardo<sup>1</sup> Marina Carrara-Camilo-Barbosa<sup>1</sup> Ivander Bastazini-Junior<sup>1</sup>
- <sup>1</sup> Lauro de Souza Lima Institute, Dermatology, Bauru (SP) Brazil.
- <sup>2</sup> Hospital Geral de Curitiba, Dermatology, Curitiba (PR) Brazil.

#### **Correspondence:**

João Felipe Rossival-Preto Email: jfpreto@hotmail.com / Alternative email: jfpreto@hotmail. com

Financial support: None. Conflict of interest: None.

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#### INTRODUCTION

Pemphigus is a group of diseases that manifest with blistering lesions on the skin and/or mucosa and differ among them according to their clinical, histopathological, and etiological characteristics.<sup>1</sup> Pemphigus vegetans is a clinical variant of pemphigus vulgaris considered the rarest, representing about 1% to 2% of all cases of pemphigus.<sup>2</sup>

The literature describes two subtypes of pemphigus vegetans: the Hallopeau, a mild form that, at first, is characterized by pustular lesions that erupt, fuse, and gradually evolve into vegetative erosions that expand centrifugally; and Neumann's, a more recalcitrant type, which usually starts with vesicles and blisters similar to pemphigus vulgaris, but they erupt and form vegetative exudative masses and hypertrophic erosions.<sup>1,3</sup>

The treatment of pemphigus vegetans is similar to that of pemphigus vulgaris and includes the remission-inducing phase of the lesions and the maintenance phase. It is often prolonged, lasting, on average, five to 10 years. Some lesions, however, may be refractory to the initial treatment, requiring another type of procedure for their resolution,<sup>1,4</sup> such as surgical approach.

#### **CASE REPORT**

We report the case of a 62-year-old man who was initially followed up in the Dermatology Department due to pemphigus vulgaris. The lesions later evolved with retroauricular and forehead pustules that culminated in the local appearance of vegetating, papillomatous, well-defined, and irregular plaques, in addition to erosive lesions in seborrheic areas on the back and thorax. Considering the clinic, the results of the biopsies for anatomopathological study, and the direct immunofluorescence exam with a deposit of intercellular IgG in the epidermis, we defined the diagnosis of pemphigus vegetans, Hallopeau subtype. Remission of lesion activity was achieved with the use of dexamethasone and dapsone (remaining stable with a reduced and continuous dose of dexamethasone 0.75 mg every other day and dapsone 100 mg daily). However, residual vegetative plaques persisted. We tried adjuvant therapy with serial triamcinolone acetonide injections, with some improvement of the lesions on the forehead, but no regression of the retroauricular plaques. Noting the refractoriness of the vegetating plaques with the therapy, the stability of the lesions, and the patient's frustration with the disfiguring appearance in the retroauricular region, we chose a surgical approach (Figure 1).

We performed tangential excision followed by electrocoagulation of the base of the lesions under local anesthesia and healing by secondary intention (Figures 2, 3, and 4). The patient had a good evolution, with no recurrence of the lesions (Figure 5).

#### DISCUSSION

Classically, the use of systemic corticosteroids is recommended to treat pemphigus vulgaris and, consequently, pemphigus vegetans. Immunomodulatory, immunosuppressive, or



FIGURE 1: Irregular, papillomatous, and verrucous vegetating plaques in the left retroauricular region – lateral view



FIGURE 2: Marking of the area to be excised



FIGURE 3: Tangential excision of the retroauricular vegetating plates

immunobiological drugs can be used to mitigate the adverse events of corticosteroid therapy and contribute to controlling the recalcitrant lesions. After controlling the activity of the condition, periodic reassessment and treatment are maintained with the minimum dosage of medications necessary to keep the inactive disease until, if possible, they are weaned.

However, hypertrophic vegetations of pemphigus vegetans may persist, and the use of extracorporeal photopheresis and carbon dioxide laser as effective alternatives are recommended. More recently, the literature has described skin grafting as an option. Intralesional corticosteroid infiltration is also mentioned, although suggested for more localized forms.<sup>2</sup>

The literature does not explore much the surgical approach of the lesions. A search in the PubMed database using the terms "Pemphigus Vegetans Surgery", without adding filters, found 35 results, but no studies with perioperative images of the surgical approach to vegetating lesions. More studies focusing on the surgical technique and postoperative outcomes are needed for this treatment modality to gain more space in the clinical practice of dermatologists who treat pemphigus vegetans.

Surgery for this type of lesion involves complications due to the disease itself and the prolonged use of corticosteroids, such as delayed wound healing and risk of infection.<sup>5</sup> It is proposed to meet the criterion of stable disease and vegetating lesions that do not regress with other treatments. Also, a good postoperative follow-up is necessary.



FIGURE 4: Immediate postoperative appearance after tangential excision and electrocoagulation of the base of the lesions



**FIGURE 5:** Appearance on the 133rd postoperative day after healing by secondary intention. Evolution without adherence or recurrence of lesions

The authors advocate that surgery should be more widely used as a form of treatment for cases with aesthetic and functional impairment, given the impact it can have on patients' quality of life and well-being. The procedure can be performed under local anesthesia, followed by healing by secondary intention, with satisfactory aesthetic results. Compared to other modalities described for unsightly lesions, such as CO<sub>2</sub> laser and grafting, it is a lower-cost therapy, widely available, with a postoperative period well tolerated by the patient.

#### CONCLUSION

We concluded that surgery proved to be a safe and viable option for managing refractory disfiguring lesions, extending to those that may generate functional impairment.

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#### **AUTHORS' CONTRIBUTION:**

#### João Felipe Rossival-Preto D ORCID 0000-0002-7883-1555

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Ingrid Stresser-Gioppo (D ORCID 0000-0001-9520-7888

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Flávia Fajardo (D) ORCID 0000-0002-8239-8440

Data collection, analysis, and interpretation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases.

#### Marina Carrara-Camilo-Barbosa i ORCID 0000-0001-8906-0242

Intellectual participation in propaedeutic and/or therapeutic conduct of studied cases.

#### Ivander Bastazini-Junior D ORCID 0000-0003-0300-1263

Approval of the final version of the manuscript; preparation and writing of the manuscript; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.

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# Scalp microneedling as a complementary therapy for female pattern hair loss

Microagulhamento do couro cabeludo como terapia complementar no tratamento da alopecia de padrão feminino

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#### ABSTRACT

Female pattern hair loss (FPHL) is one of the most frequent complaints in dermatological practice. It affects up to 50% of climacteric and postmenopausal women. Despite multiple therapies available nowadays, some patients are refractory to conventional treatments, requiring the association of second-line therapies to obtain good aesthetic results. This paper aims to show the advantages of microneedling of the scalp for such cases by reporting the case of a 48-years-old patient who failed to the association of topical minoxidil and oral finasteride therapy.

Keywords: Alopecia: Attachment disorder; Combined modality therapy; Hair diseases

#### RESUMO

A alopecia de padrão feminino figura dentre as queixas mais frequentes no consultório dermatológico e afeta até 50% das mulheres no climatério e na pós-menopausa. Apesar da existência de múltiplas terapias hoje disponíveis, algumas pacientes mostram-se refratárias aos tratamentos convencionais, sendo necessária a associação de tratamentos de segunda linha para a obtenção de bons resultados estéticos. Este trabalho ilustra as vantagens do microagulhamento nesse cenário por meio do relato de uma paciente de 48 anos de idade que não apresentou boa resposta clínica à associação do minoxidil tópico à finasterida oral.

Palavras-chave: Alopecia; Doenças dos anexos; Terapia combinada.

## **Case report**

Authors: Pedro Colli Rocha Dias<sup>1</sup> Hudson Dutra Rezende<sup>2</sup>

- <sup>1</sup> Clínica Pedro Colli Dermatologia, Dermatology, Botucatu (SP), Brazil.
- 2 Centro Universitário Lusíada, Dermatology, Santos (SP), Brazil.

#### Correspondence:

Pedro Colli Rocha Dias pedrocolli@hotmail.com / Alterna tive E-mail:: contato@hudsondtra. com.br

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It is estimated that 50% of climacteric and postmenopausal women have some degree of female pattern hair loss (FPHL).<sup>1</sup> Although equivalent in practice, the term FPHL has been used more often than androgenetic alopecia (AGA) for women since the participation of dihydrotestosterone in the pathophysiology of follicular miniaturization has significant implications in the disease evolution in men, but it is still questionable in women.<sup>2</sup>

The Food and Drug Administration (FDA) authorizes only two treatments for FPHL: topical minoxidil and Low-Level Laser Therapy (LLLT).<sup>3</sup> Due to the refractoriness to first-line therapies of some cases, new treatments for FPHL have been proposed, such as microneedling, drugs infusion into the scalp, and platelet-rich plasma (PRP) injection, which is currently prohibited in Brazil by the Federal Council of Medicine.<sup>4</sup>

### **CASE REPORT**

A 48-year-old woman, menopausal, with no other morbid history, presented a clinical and dermoscopic diagnosis of FPHL. She used topical minoxidil 5%, once daily, and finasteride 5 mg orally for a year. However, she chose to discontinue the treatment due to facial hypertrichosis associated with minoxidil. After six months without the medication, the patient underwent four sessions of microneedling with an electrical device (pen) using twelve 1.5 mm needles and a 90 Hz frequency. The stipulated interval between sessions was 15 days.

The sessions were performed after local antisepsis with an alcoholic chlorhexidine solution. The frontal and vertex regions were treated, and each session lasted the period necessary to produce small bleeding spots (Auspitz sign). Pre-treatment and post-treatment photographic control was performed with clinical images of the scalp and dermoscopic images corresponding to the area of intersection of the coronal and sagittal lines.

Fifteen days after the 4th session, there was increased capillary density in the frontal and vertex regions, with decreased visualization of the scalp (Figure 1). At dermoscopy, we observed increased capillary density, mainly due to the decreased difference in the hair diameter, the increased general diameter of the hair shafts, and the quantitative reduction of miniaturized hair (Figure 2).

### DISCUSSION

As a chronic condition with high rates of treatment dropout, FPHL presents a challenge to clinical practice.<sup>5</sup> The FDA officially authorizes few therapeutic options for FPHL management, such as topical minoxidil and LLLT.<sup>3</sup>

Despite its proven effectiveness, the unwanted effects of topical minoxidil therapy, such as itching, hypertrichosis, and increased scalp oiliness, lead to poor patient compliance.<sup>5</sup> LLLT is an option that has shown satisfactory results but does not replace first-line treatments and cannot yet be considered a widely available and affordable option.<sup>6</sup> Thus, microneedling can compose the therapeutic arsenal for cases resistant to standardized therapies or for those patients in which, for some reason, first-line therapies are not applicable.

Our case exemplifies the advantages of microneedling for refractory FPHL. The limitation of this report is the small



FIGURE 1: Global image before (A) and after 15 days (B) of the last microneedling session (total of four sessions)



FIGURE 2: Dermoscopic image before (A) and after 15 days (B) of the last microneedling session showing increased capillary density (manual dermoscope, 10x)

variation in standardization between the first and second clinical photos, which can distort the global perception of capillary gain. However, dermoscopic photos support the improvement in hair removal and hair diameter after treatment.

Microneedling produces controlled dermal microperforations that stimulate angiogenesis, promote vasodilation, and subsequent release of cytokines and interleukins, also stimulating the expression of genes related to hair growth.<sup>7</sup> Part of this action is due to the activation of cellular regeneration mechanisms arising from the follicular the bulge stem cells activation and the Wnt3a/B-catenin pathway activation, which directly signals the maintenance of the anagen phase, hair growth, and stem cell recruitment.<sup>7,8,9,10</sup> The minor bleeding induced by the technique also releases growth factors derived from platelets, involved in the activation of the tissue repair process, and vascular endothelium growth factor (VEGF), involved in follicular growth secondary to the increase in the local angiolymphatic network, improving the dermal papilla vascularization.<sup>8,10</sup> In the technique, the needle length, varying from 0.25 mm to 2.5 mm, defines the depth of the cutaneous microperforations.<sup>10</sup> Although there is no rigid protocol defining the best needle length for the alopecia treatment, many authors opt to use 1.5 mm needles as they provide moderate bleeding and are well tolerated by patients.<sup>8,9,11</sup> The number of sessions ranges widely in the literature, but few publications propose less than three sessions in the FPHL.<sup>7</sup>

The complementary character of microneedling in FPHL treatment is also reinforced by the possible formation of minimal cumulative fibrosis in the scalp in the recovery of tissue damage caused by needles.<sup>10</sup> The long-term impact of this phenomenon on the alopecia treatment is still unclear but sufficient to not recommend microneedling as a compulsory and indistinct practice in trichology.

### CONCLUSION

Few studies reveal the real contribution of microneedling alone in FPHL. The demonstration of effectiveness as a short-term monotherapy encourages the rational use of the technique as an auxiliary method in the search for better results, whether in the management of refractory cases or patients with limitations in the standardized prescription.  $\bullet$ 

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### **AUTHORS' CONTRIBUTION:**

### Pedro Colli Rocha Dias 🕩 ORCID 0000-0002-6987-5177

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

### **Hudson Dutra Rezende** D ORCID 0000-0002-7039-790X

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.



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# Cutaneous sarcoidosis and facial filling: a possible triggering event?

Sarcoidose cutânea e preenchimento facial: um possível evento desencadeante?

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### ABSTRACT

Sarcoidosis is a systemic granulomatous disease with skin involvement in 10% to 25% of cases. This skin condition has been associated with previous trauma, including the use of skin fillers. We present the case of a patient with an erythematous plaque on the nasal dorsum with 12 months of evolution and a history of previous facial fillings with polymethylmethacrylate and hyaluronic acid. Skin biopsy showed a granulomatous inflammatory process with an epithelioid pattern and multinucleated giant cells, characteristic of cutaneous sarcoidosis. Sarcoidosis can occasionally manifest without systemic involvement and may be associated with the previous use of long-term tissue fillers.

Keywords: Hyaluronic acid; Dermatology; Polymethyl methacrylate; Dermal fillers; Sarcoidosis

### RESUMO

A sarcoidose é uma doença granulomatosa sistêmica com envolvimento cutâneo em 10 a 25% dos casos. O quadro cutâneo tem sido frequentemente associado a traumas prévios, incluindo o uso de preenchedores cutâneos. Apresenta--se caso de paciente com placa eritematosa em dorso nasal com 12 meses de evolução e histórico de preenchimentos prévios com PMMA e ácido hialurônico. A biópsia cutânea evidenciou processo inflamatório granulomatoso de padrão epitelioide e células gigantes multinucleadas, características de sarcoidose cutânea. As reações granulomatosas tardias podem estar associadas ao uso de preenchedores, tanto pelo trauma provocado pelas cânulas quanto pelos antígenos dos preenchedores utilizados.

**Palavras-chave:** Ácido hialurônico; Dermatologia; Polimetil metacrilato; Preenchedores dérmicos; Sarcoidose

### **Case Report**

### Authors:

lago Gonçalves Ferreira<sup>1,2</sup> Gustavo Bottene Ribolli<sup>2</sup> Luyze Homem de Jesus<sup>2</sup> Fabiane Cristina Lersch<sup>1</sup> Mariele Bevilaqua<sup>1</sup>

- <sup>1</sup> Santa Casa de Misericórdia de Porto Alegre, Dermatology Service, Porto Alegre (RS), Brazil.
- <sup>2</sup> Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre (RS), Brazil.

### Correspondence:

lago Gonçalves Ferreira Email: iago\_goncalves14@hotmail. com / Alternative email: iago\_ goncalves14@hotmail.com

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Sarcoidosis is a systemic granulomatous disease involving multiple organs – including lungs, lymphatic system, and skin. It has a higher prevalence among adults, black individuals, and women.<sup>1</sup> This condition may present cutaneous involvement in about 10% to 25% of cases, occasionally manifesting without associated systemic implication, affecting only the skin.<sup>2</sup>

The use of cutaneous fillers can cause early adverse events, such as erythema or hematomas,<sup>3</sup> or late complications, such as immune-mediated inflammatory disorders and non-infectious granulomatous disorders.<sup>4,5</sup> Late granulomatous reactions occur mainly in the form of foreign body granulomas. However, in some rare cases, granulomatous lesions can occur through sarcoid reactions, characterizing cutaneous sarcoidosis (CS).<sup>1,5,6</sup> These granulomas do not have well-defined pathophysiology and etiology, and they are associated with skin trauma caused by perforation of cannulas regarding the antigens of the fillers used.<sup>1,3,4,7</sup> Given the relevance of complications related to aesthetic procedures, this report aims to discuss a case of CS in a patient with previous skin filling.

### **CASE REPORT**

A 50-year-old woman patient reported an erythematous plaque on the nasal dorsum with an asymptomatic evolution for about a year and a half. She described a history of previous aesthetic procedures: malar filling with polymethylmethacrylate (PMMA), brand not mentioned, in 2014, and filling of the orbicularis fossa with hyaluronic acid (HA-Emervel Touch<sup>®</sup> Galderma Brasil, São Paulo, Brasil) 1 ml, in 2018. All procedures occurred with no acute reactions. The patient had no joint pain, respiratory changes, lymphadenopathy, gastrointestinal, cardiological, ophthalmological, or neurological changes.

Dermatological examination revealed a well-defined erythematous plaque with an orange background, regular borders, and thin linear vessels at dermoscopy (Figure 1). Complementary investigation showed negative serological markers for rheumatological and infectious diseases. Chest tomography



**FIGURE 1: A** - Nasal lesion in an erythematous-orange plaque with an "apple jelly" appearance. **B** - Dermoscopy showing telangiectatic vessels, on an erythematous-orange base, with hypochromic linear structures and central scar from a previous biopsy

revealed normal parenchyma, with no typical lymph node enlargement. Soft tissue ultrasound revealed hyperechoic deposits with "mini-comet-tail" reverberation artifacts in the region of the nasolabial folds, extending from the height of the mid-nasal third to the labial commissures, suggestive of PMMA deposits in the dermis (Figure 2).

The histopathology of the skin biopsy showed a chronic inflammatory process with the formation of epithelioid pattern granulomas and the presence of multinucleated giant cells in the superficial and deep dermis. There was no evidence of necrosis (Figure 3) and negative AFB, thus confirming the diagnosis of CS.

### DISCUSSION

The application of cutaneous fillers can lead to early and self-limited complications, such as hematomas, edema, and erythema, or late complications, such as the Tyndall effect, surface irregularities, hypersensitivity reactions, or even granulomatous lesions, as CS.<sup>6</sup> Among the late complications, CS has occasionally been reported after trauma, cutaneous surgery, and aesthetic procedures, such as venipuncture and injections of fillers, a condition described in the case.<sup>7</sup>

Although sarcoid-like lesions do not necessarily occur at puncture sites, but also appear in other locations, it is postulated that cutaneous trauma could evidence underlying systemic sarcoidosis and trigger CS in predisposed individuals.<sup>1,4</sup> However, other factors may be involved. Etiologic factors have also been associated with CS, such as exposure to insecticides, metals, fungi, drugs, and infection by microorganisms such as Mycobacterium tuberculosis and Herpes simplex virus,<sup>1</sup> the latter was also present in the history of this patient, who had recurrent oral herpes.

CS can present several clinical forms, which include spots, papules, lupus pernio, infiltrations in tattoos, or previous scars, as well as psoriasiform, lichenoid, ichthyosiform, and verrucous lesions.<sup>1,7</sup> Regarding the plaques, the presentation seen in this case, they tend to reveal diameters smaller than or equal to 1 cm, colorations ranging from red, violet, brown, or even hypopigmentation, affecting extremities, areas of trauma, or the central region of the face, as in the patient.<sup>7</sup>

It is believed that the pathogenesis of CS is associated with an abnormal immune response to different antigens, of a Th1 pattern, with the involvement of mediators such as interferon-gamma and tumor necrosis factor (TNF), resulting in the formation of non-caseating granulomas.<sup>7</sup> Given the morphology similar to other dermatoses, CS is frequently diagnosed through skin biopsies, which should exclude other causes of granulomatous reactions, including foreign body granulomas.<sup>8</sup> The histopathology of sarcoidosis reveals epithelioid, non-caseating, well-delimited granulomas of circular shape, located in the dermis.<sup>1</sup>

Due to their long permanence in tissues, non-biodegradable fillers have been more related to late adverse events, and PMMA is a significant culprit.<sup>4</sup> On the other hand, PMMA is a synthetic, biocompatible polymer with antigenic potential, for-



**FIGURE 2:** Soft tissue ultrasound of the face showing hyperechoic deposits with "comet tail artifact" reverberation in the nasolabial folds



FIGURE 3: A - Interstitial lymphohistiocytic inflammatory infiltrate with formation of epithelioid granulomas, without necrosis, associated with well-developed lymphocytic mantles (Hematoxylin & eosin 20x). B - Asteroid body (arrow) surrounded by epithelioid granuloma with lymphohistiocytic infiltrate (Hematoxylin & eosin 40x)

merly widely used to correct nasolabial folds and glabellar and frontal rhytids.<sup>5,9</sup> However, due to late complications related to its use – allergic reactions, formation of foreign body granulomas, and subcutaneous nodules – PMMA has been falling into disuse.<sup>9</sup>

The occurrence of adverse events with HA reveals lower incidence rates – about 0.05% to 0.15% of cases.1 Biodegradable fillers, such as HA, are less prone to late complications due to their higher biocompatibility and lower immunogenicity.<sup>1,6</sup>

In this case, it is not possible to say that any of the fillers acted as the primary agent of the sarcoid lesion. However, they may have worked as triggers.

Also, the appearance of CS in the patient's nasal wall was observed seven years after the application of PMMA and three years after the application of HA. According to Tholken et al., the prolonged time between application and the clinical presentation of the lesions proves to be a positive predictive factor for the diagnosis of isolated CS.<sup>1</sup> The therapeutic approach to CS is diverse. In localized forms, topical medications such as corticosteroids (clobetasol, halobetasol, betamethasone), calcineurin inhibitors (tacrolimus and pimecrolimus), retinoids are used, in addition to intralesional corticosteroids (triamcinolone).<sup>7</sup> Alternative topical therapeutic options include photodynamic therapy, phototherapy, laser, and surgical excision of lesions. Most treatments show relevant results about two to three months after starting the medications.<sup>7</sup> In our patient , we chose topical therapy with mometasone and tacrolimus due to the limited extent of the lesion, achieving significant improvement after six months.

Severe and relapsing cases may require systemic therapy, which includes the use of antimalarials, tetracycline antibiotics, pentoxifylline, apremilast, and retinoids.<sup>2,7</sup> Immunobiologicals, such as TNF inhibitors, specifically adalimumab and infliximab, have shown important responses in chronic, recalcitrant, and severe forms of CS, including ulcerative sarcoid lesions, lupus pernio, and forms unresponsive to systemic corticosteroid therapy.<sup>7</sup>

### CONCLUSION

This case report presents an alert for the emergence of late reactions to cutaneous fillers regarding early identification and prompt treatment establishment. We highlight the importance of differential diagnosis of CS with other dermatoses, given its varied clinical presentations and the appearance of cutaneous sarcoid-like lesions in places that were not necessarily the application sites. Furthermore, the histopathological differentiation between sarcoid granulomas and other granulomatous diseases must be performed, especially foreign body granulomas, often associated with the use of fillers. As seen in the case and reported in the literature, the response to the available therapeutic options has been positive, showing no serious evolution of the conditions.

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### **AUTHORS' CONTRIBUTION:**

### Iago Gonçalves Ferreira D ORCID 0000-0002-4695-1982

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review; critical revision of the manuscript.

#### Gustavo Bottene Ribolli D ORCID 0000-0001-7302-6461

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review; critical revision of the manuscript.

### Luyze Homem de Jesus D ORCID 0000-0002-4200-7310

Author's contribution: Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review.

### Fabiane Cristina Lersch D ORCID 0000-0003-3590-4344

Approval of the final version of the manuscript; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.

### Mariele Bevilaqua D ORCID 0000-0001-5689-1162

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.



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# Cutaneous diffuse large B-cell lymphoma, leg type - a typical case

Linfoma cutâneo difuso de grandes células B, tipo perna: sobre um caso típico

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### ABSTRACT

Cutaneous diffuse large B-cell lymphoma, leg type, is a rare, aggressive, and poorly prognostic neoplasm. It corresponds to 10-20% of cutaneous B-cell lymphomas and mainly affects the lower limbs of older women. We report the case of an 81-year-old woman with painful, fast-growing nodules and tumors in her left leg. Histopathological and immunohistochemical findings, associated with the absence of extra-cutaneous involvement during staging, concluded the diagnosis of cutaneous diffuse large B-cell lymphoma, leg type. The rarity of this limphoma, its typical clinic and epidemiology, and the excellent response to treatment motivated this report.

**Keywords:** Immunohistochemistry; Diffuse; Lymphoma non Hodgkin; Lymphoma large B-cell, Neoplasms; Therapeutics

### RESUMO

O linfoma cutâneo difuso de grandes células B, tipo perna, compreende uma neoplasia rara, agressiva e de mau prognóstico. Corresponde a 10-20% dos linfomas cutâneos de células B e afeta principalmente membros inferiores de mulheres idosas. Relatamos o caso de mulher de 81 anos, com nódulos e tumorações dolorosos, de crescimento rápido em perna esquerda. Os achados histopatológicos e a imuno-histoquímica, associados à ausência de comprometimento extracutâneo no estadiamento, concluíram o diagnóstico de linfoma cutâneo difuso de grandes células B, tipo perna. A raridade, a clínica e a epidemiologia típicas e a excelente resposta ao tratamento motivaram este relato.

**Palavras-chave:** Imuno-histoquímica; Linfoma difuso de grandes células B; Linfoma não Hodgkin; Neoplasias; Terapêutica

### Case report

### Authors:

Flávia Regina Ferreira<sup>1,2</sup> Mariana Oliveira Fernandes<sup>1</sup> Marina Thereza Fogo Pereira<sup>1</sup> Fernanda da Rocha Gonçalves<sup>3</sup>

- <sup>1</sup> Hospital Municipal Universitário de Taubaté, Dermatology Service, Taubaté (SP), Brazil.
- <sup>2</sup> Universidade de Taubaté, Dermatology, Taubaté (SP) Brazil.
- <sup>3</sup> Hospital do Servidor Público Estadual, Pathology, São Paulo (SP), Brazil.

### Correspondence:

Flávia Regina Ferreira Email: dermagica@uol.com.br

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Primary cutaneous lymphomas are defined as a heterogeneous group of lymphoproliferative malignancies that affect the skin, with no evidence of extracutaneous involvement at the time of diagnosis.<sup>1</sup>

Cutaneous B-cell lymphomas (CBCL) account for 20% to 25% of all primary cutaneous lymphomas and are more common in women.<sup>1,2</sup>

According to clinical, histopathological, immunohistochemical, and molecular criteria, CBCLs are classified by the World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) - 2018, as centrofollicular and diffuse large B cells, leg type; the latter represents only 4% of all cutaneous lymphomas.<sup>1</sup>

The rarity of this type of lymphoma, its typical clinic and epidemiology, and the excellent response obtained to treatment motivated this report.

### **CASE REPORT**

A Caucasian, 81-year-old woman came to the Dermatology Outpatient Clinic complaining of fast-growing "lumps" on her left leg, with one-month evolution. Dermatological examination revealed vegetating nodules and tumors, with an erythematous-yellow fibrinoid surface and the presence of blackened crusts (Figure 1). There was no lymph node enlargement or visceromegaly. The lesions were painful, and the patient denied any systemic symptoms. She mentioned previous trauma as a triggering factor. Also, she had peripheral venous insufficiency and type II *diabetes mellitus* as comorbidities. The hypotheses put



FIGURE 1: A: Left leg: vegetating nodules and tumors, sometimes covered by a blackened crust. B: Greater detail: medial face

forward were squamous cell carcinoma, amelanotic melanoma, cutaneous metastases, and cutaneous lymphoma. Incisional biopsies were performed in two points. The histopathological study showed ulcerated epidermis with areas of necrosis and the presence of dense and diffuse lymphocytic infiltrate consisting of large cells in the superficial and deep dermis, sometimes with nuclei with irregular contours and abundant mitotic figures (Figure 2). The immunohistochemical panel was positive for Bcl-2, CD20, and MUM1 (Figure 3) and negative for CD3, CD10, and cyclin D1 (Figure 4), concluding a B-cell non-



FIGURE 2: Superficial and deep dermis with presence of dense diffuse lymphocytic infiltrate of large cells, sometimes with irregularly contoured nuclei, and abundant mitotic figures (Hematoxylin & Eosin 40x, 400x)



FIGURE 3: Immunohistochemistry: MUM-1 positive



FIGURE 4: Immunohistochemistry: CD3, CD10, and cyclin D1 negative

Hodgkin lymphoma diagnosis. Bcl-6 was not performed. The proliferative index by Ki-67 was 90%, and C-MYC was positive in about 30% of the cells (Figure 5).

The patient was referred to the Hebe Camargo Cancer-Fighting Network, where she was staged and diagnosed with diffuse cutaneous large B-cell lymphoma, leg type, T2bN0M0 (Table 1).

We instituted therapy with R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and scheduled surgical intervention, which was not performed due to the excellent evolution of the patient (Figure 6). Currently, the patient has only dyschromic cicatricial areas and is under joint follow-up with Dermatology and Oncology.

### DISCUSSION

Diffuse cutaneous large B-cell lymphoma, leg type, comprises a rare, aggressive neoplasm with a poor prognosis.<sup>1,3</sup>

It corresponds to 10-20% of CBCLs and has a 5-year survival rate of 50%.<sup>1,3,4</sup> It mainly affects women of advanced age (70-82 years).<sup>1,3,5</sup> Clinically, it manifests as nodular, infiltrative, single, or multiple lesions, which may be located in different sites (lower limbs are the most common). It also presents a rapid pro-



**FIGURE 5:** Immunohistochemistry: C-MYC positive in 30% of cells

gression, agreeing with what was observed in this case. Phlogistic signs and pruritus may be present.<sup>1,3</sup>

The development of extracutaneous lesions is common, especially among patients who have involvement in the lower limbs, with bone marrow, lymph nodes, and central nervous system is the most affected sites.<sup>1,5,6</sup>

TABLE 1: Tumor classification according to the EORTC/ISCL for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome	
Tumor	
T1	Only a skin lesion:
	T1a. The lesion size is up to 5 cm in diameter
	T1b. The lesion size is greater than 5 cm in diameter
T2	Two or more skin lesions. They can be in a single region of the body or nearby region:
	T2a. All skin lesions can be placed within a 15 cm diameter circle
	T2b. The circle needed to round all lesions is between 15 and 30 cm in diameter
	T2c. The circle needed to round all skin lesions is greater than 30 cm in diameter
T3	Skin lesions in different regions of the body or at least three different regions:
	T3a. Many injuries involving two regions of the body, distant from each other
	T3b. Many injuries involving three or more regions of the body.

Source: American Cancer Society

EORTC/ISCL: European Organization for Research and Treatment of Cancer/ International Society for Cutaneous Lymphomas



FIGURE 6: Scar dyschromic areas after chemotherapy with R-CHOP regimen

The diagnosis is made by clinical, histopathological, and immunohistochemical findings.<sup>1,2</sup>

In histopathology, it is characterized by a dense infiltrate of large cells in the dermis and subcutaneous tissue, separated from the epidermis by a narrow band of collagen called the grenz zone (not observed in the present case). <sup>2,5</sup> Often, this infiltrate tends to be more intense in the deep dermis, called a "bottom-heavy pattern".<sup>2</sup> The positivity of the markers Bcl-2, Bcl-6, MUM1, and FOXP1 is characteristic of this type of lymphoma.<sup>1,5</sup> The positivity of C-MYC seems to be related to a worse prognosis.<sup>7,8</sup> Other indicators of poor prognosis include lower limb location, multiple injuries, and age over 75 years.<sup>6</sup>

The treatment of the more aggressive types of CBCL, mainly the leg type, includes chemotherapy with a CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone). The association of rituximab (R-CHOP) may lead to better results, as observed in this patient, and increased survival.<sup>1,2,9</sup> Surgical excision and radiotherapy are among the first-line therapies for solitary lesions. However, due to the high recurrence rates, more recently, the literature recommends treating even so-litary and localized lesions with the R-CHOP regimen in the first line, followed by radiotherapy with a safety margin and/or surgery as adjuvant therapies.<sup>9</sup>

Considering the rapid growth, the high proliferative index, and the reserved prognosis of diffuse cutaneous large B-cell lymphoma, leg type, we emphasize the importance of knowing its multiple clinical manifestations, especially its classic form in the lower limb, which allows the early diagnosis and adequate treatment, positively impacting patient survival.

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### **AUTHORS' CONTRIBUTION:**

Flávia Regina Ferreira DOCOD 0000 0001 5679 4282 Approval of the final version of the manuscript; preparation and writing of the manuscript; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

Mariana Oliveira Fernandes (D) ORCID 0000 0002 3134 7096 Approval of the final version of the manuscript; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.

**Marina Thereza Fogo Pereira** D ORCID 0000 0002 3185 4653 Approval of the final version of the manuscript; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases.

**Fernanda da Rocha Gonçalves** D ORCID 0000 0003 2933 2845 Intellectual participation in propaedeutic and/or therapeutic conduct of studied cases.



## Surgical & Cosmetic Dermatology

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# Microneedling for female pattern hair loss: case report and histopathological changes

Microagulhamento para tratamento de alopecia de padrão feminino: relato de caso e alterações histopatológicas

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### ABSTRACT

Microneedling has traditionally been used to induce collagen formation. Scalp microneedling has been seen to stimulate the capillary cycle and anagen phase, but studies demonstrating histopathological changes after this procedure are lacking. Here we present the case of a 37-year-old woman with a 15-year history of female pattern alopecia, with diffuse hair thinning prominent in the frontoparietal region and hair miniaturization seen in dermoscopy. The patient's condition remained stable for seven years with use of spironolactone and topical minoxidil. The patient underwent three scalp microneedling sessions at monthly intervals. Histopathological analysis was conducted before the sessions and one month after the last session. Despite slight clinical and dermoscopic improvement, the alopecia pattern remained the same, without significant changes in follicle count after the interventions. Neither inflammation nor fibrous tracts were observed after the procedure. The histopathological analysis is essential to assess the safety of scalp microneedling in the short and long term, investigate signs such as inflammation and fibrosis, and determine the effectiveness of this procedure in treating alopecia. Studies with a more significant number of cases are necessary.

Keywords: Alopecia; Pathology; Treatment outcome

### RESUMO

O microagulhamento tem sido tradicionalmente usado para induzir a formação de colágeno. No couro cabeludo, foi observado que estimula a fase anágena e o ciclo capilar, mas faltam estudos que demonstrem as alterações histopatológicas após o procedimento. Relatamos o caso de uma mulher de 37 anos com história de alopecia de padrão feminino há 15 anos, com rarefação difusa proeminente na região fronto-parietal e miniaturização capilar observada à dermatoscopia. A condição permaneceu estável por 7 anos com uso de espironolactona e minoxidil tópico. A paciente foi submetida a três sessões de microagulhamento no couro cabeludo em intervalos mensais. A análise histopatológica foi realizada antes das sessões e um mês após a última sessão. O padrão de alopecia permaneceu o mesmo, sem alterações significativas na contagem de folículos após as intervenções, apesar de discreta melhora clínica e dermatoscópica. Não foram observados tratos fibrosos ou inflamação após o procedimento. A análise histopatológica é importante para avaliar a segurança do microagulhamento do couro cabeludo em curto e longo prazo, para investigar sinais como inflamação e fibrose, bem como para determinar a eficácia deste procedimento no tratamento da alopecia, e estudos com maior número de casos são necessários.

Palavras-chave: Alopecia; Patologia; Terapêutica

### **Case report**

#### Authors:

- Flávia Machado Alves Basilio<sup>1</sup> Fabiane Mulinari Brenner<sup>1</sup> Betina Werner<sup>2</sup>
- <sup>1</sup> Federal University of Parana, Department of Dermatology, Curitiba (PR) Brazil
- Federal University of Parana, Department of Pathology, Curitiba (PR), Brazil

#### Correspondence:

Flávia Machado Alves Basilio Email: flavia\_mab@yahoo.com.br / Alternative Email: flavia\_mab@ yahoo.com.br

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Microneedling has traditionally been used for collagen induction in facial scars and skin rejuvenation. Microwounds induce the healing process and create transdermal microchannels across the stratum corneum, increasing permeability for small molecule drugs. Recently, regeneration of hair follicles and resumption of the anagen phase has also been observed after this therapy.<sup>1,2</sup>

Hair regeneration is essential for alopecia treatment and in wound healing and skin regeneration. Epidermal stem cells from hair follicles are a significant supplier of keratinocyte proliferation in wounded skin.<sup>3</sup> Wound regeneration is delayed when hair follicles are absent and is faster in the skin with anagen than with telogen hairs.<sup>3</sup>

These findings have led to the use of microneedling to stimulate hair follicle growth in androgenetic alopecia (AGA) and possibly modulate the hair cycle. But so far, no study has documented histopathological changes after scalp microneedling for AGA.

### **CASE REPORT**

Our 37-year-old female patient had a 15-year history of progressive hair thinning. She also had pernicious anemia and hypothyroidism and received vitamin B12 and levothyroxine. Diffuse hair thinning was prominent in the frontal and parietal areas. Trichoscopy demonstrated miniaturization, an increase in single hair follicular units, and yellow dots in the frontal area (compared to the occipital area). Pull test was negative. Hair thinning was stable after treatment with spironolactone 150 mg/ day and topical minoxidil 5% for seven years. However, the patient was unhappy with her hair density. Scalp microneedling with a 2.0 mm roller device was performed at monthly intervals.

Slight clinical and dermoscopic improvement was observed after three sessions, as shown in figures 1A and 1B. We conducted two 4 mm punch biopsies in the central and parietal scalp before the treatment, and another near the first site one month after the third session. Histopathological examination of all samples using transverse sections did not demonstrate significant changes in the follicular count before and after the intervention, and the standard female androgenetic alopecia pattern persisted (low terminal:vellus hair ratio). We observed a slight inflammatory lymphocytic infiltrate in the superficial dermis around the follicles after the microneedling procedures but no significant fibrosis (Figures 2A, 2B, 2C, 2D).

### DISCUSSION

Microneedling is believed to increase hair regrowth in alopecia by increasing platelet-derived growth factor, epidermal growth factors, and bulge activation.1 Overexpression of Wnt proteins has also been seen after microneedling.<sup>4</sup> Activation of the Wnt/b-catenin signaling pathway is essential to initiate and maintain hair morphogenesis.<sup>5</sup> Wnt10b is responsible for proliferation and maintenance of trichogenesis-promoting ability. At the same time, Wnt3a is involved in hair follicle growth and melanocyte homeostasis. In AGA, androgens downregulate secreted factors involved in normal hair follicle stem cell differentiation by inhibiting the Wnt signaling pathway.<sup>5</sup> Microneedling has been considered to increase long-term clinical results in AGA. Weekly microneedling associated with daily application of minoxidil 5% topical solution was proven to increase hair growth after 12 weeks. When the procedure was associated with 1 mg finasteride and 5% minoxidil, it demonstrated persistent results after 18 months of follow-up.4,6 However, it is still unknown



FIGURE 1: A - Diffuse hair thinning is prominent in the frontal and parietal areas before microneedling. B - Slight clinical improvement was observed after three sessions of microneedling. However, a similar pattern was maintained in figure B



**FIGURE 2:** Histopathological study of scalp before (**A** and **B**) and after microneedling treatment (**C** and **D**). A. Two hair units with three follicles and sebaceous glands. H.E. stain. Original magnification 10x. B. One of the follicles is a vellus hair. H.E. stain. Original magnification 20x. **C.** Three hair units with five follicles and sebaceous glands. H.E. stain. Original magnification 10x. **D**. Only terminal hairs are seen, and some lymphocytes are noted in the adjacent dermis. H.E. stain. Original magnification 20x. No significant changes in average hair count and hair diameter before and after the procedure were noticed.

whether microneedling alone can elicit the desired therapeutic response in AGA.

One concerning adverse event on the scalp is perifollicular fibrosis, which could hinder hair growth.<sup>2</sup> In the case reported here, microneedling did not lead to unequivocal clinical or dermoscopic improvement. Slight clinical improvement was not correlated with average hair diameter and hair count on histopathological evaluation. Nevertheless, neither significant inflammation nor scarring tracts were detected after the procedure, in this case disproving the hypothesis that microneedling could induce fibrosis.

Further studies with a more significant number of cases are needed to demonstrate the therapeutic effect of microneedling in AGA. Histopathological assessments as part of these studies can help determine the safety and efficacy of this procedure on the scalp during the short and long terms.

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### **AUTHORS' CONTRIBUTION:**

### Flávia Machado Alves Basilio 🕩 ORCID 0000-0001-7426-9879

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

### Fabiane Mulinari Brenner D ORCID 0000-0001-7970-522X

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

### Betina Werner D ORCID 0000-0002-9671-5603

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.



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### Applicability of the Limberg Flap: a case series

Aplicabilidade do retalho de Limberg: uma série de casos

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### ABSTRACT

Local flaps are an excellent option for repairing the excision of skin tumors, where the primary closure of the defect would cause aesthetic and functional impairment. The rhomboid (Limberg) flap is a simple and versatile transposition flap that can be applied widely with good cosmetic and vascularization results. The retrospective analysis of a case series using the Limberg flap to reconstruct defects resulting from tumor resections proved to be easy to perform, with excellent evolution and vascular viability. **Keywords:** Carcinoma basal cell; Skin neoplasms; Surgical flaps; Surgical oncology

### RESUMO

Retalhos locais constituem uma excelente opção para o reparo da excisão de tumores cutâneos, em que o fechamento primário do defeito acarretaria prejuízos estético e funcional. O retalho romboidal (de Limberg) é um retalho de transposição simples e versátil, que pode ser aplicado amplamente com bons resultados cosméticos e de vascularização. A análise retrospectiva de uma série de casos em que o retalho de Limberg foi utilizado para reconstruir defeitos resultantes de ressecções de tumores demonstrou tratar-se de técnica de fácil execução, com ótima evolução e viabilidade vascular. **Palavras-chave:** Carcinoma basocelular; Neoplasias cutâneas; Oncologia cirúrgica; Retalhos cirúrgicos

### **Case report**

#### Authors:

- Anelise Darabas dos Santos<sup>1</sup> Douglas Haddad Filho<sup>2</sup> Flávia Fenólio Nigro Marcelino<sup>3</sup> Luiza Vieites<sup>4</sup>
- <sup>1</sup> Universidade de Santo Amaro, Dermatology, São Paulo (SP), Brazil.
- <sup>2</sup> Universidade de Santo Amaro, Plastic surgery, São Paulo (SP), Brazil.
- <sup>3</sup> Universidade de Santo Amaro, Dermatology, São Paulo (SP), Brazil.
- <sup>1</sup> Universidade de Santo Amaro, Medicina, São Paulo (SP), Brazil.

### Correspondence:

Anelise Darabas dos Santos Email: anelisedarabas@gmail.com

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Skin cancer is the most incident worldwide, with basal cell carcinoma (BCC) being the most common malignant neoplasm. Its incidence has increased over the last few years, influenced by population aging and accumulated sun exposure. BCC has low mortality but can cause significant morbidity, mainly due to local tissue destruction.<sup>1</sup>

The clinical and histological presentation of BCC is quite variable and includes the nodular, superficial, infundibulocystic, fibroepithelial, and desmoplastic subtypes, with different characteristics.<sup>1,11</sup> Due to its low metastatic power, BCC treatment aims mainly at local control. Anatomical location is a known risk factor for BCC recurrence, and areas in the H-zone of the face, which encompasses the nose, temples, ears, periocular, periauricular, and upper lips, are considered high-risk regions, regardless of tumor size. Surgical resection with adequate safety margins of the lesion is the mainstay of treatment for this neoplasm. However, it causes aesthetic and/or functional damage, requiring the use of local reconstruction techniques to close the resulting cutaneous defects.<sup>1</sup> A thorough evaluation of each lesion and each patient chooses surgical method to have a better result regarding surgical recovery and the aesthetic outcome.

Skin flaps are classified according to the movement of the skin towards the receptor area. They can be advancement, rotation, transposition, or interpolation flaps.<sup>3,4</sup> The Limberg flap is a straightforward and versatile type of transposition flap since its geometric design can be constructed from any of the four corners of the rhomboid design.<sup>5,6</sup>

It is called "transpositional" because it is elevated and mobilized towards an adjacent defect and transposed by an incomplete bridge of skin.<sup>3</sup> Alexander A. Limberg first described its use in 1946, based on the Euclidean definition of the geometric figure of the rhomboid design, a parallelogram with four equal sides, equal opposite acute angles, and equal opposite obtuse angles.<sup>4,7</sup> The traditional rhombic flap using the Limberg design is performed with 60 and 120 degrees angles of equal length sides.<sup>3</sup>

Subsequently, Dufourmentel and Webster performed modifications to the original technique.<sup>3</sup> Dufourmentel proposed its alteration using a 90 degree angle, allowing a smaller rotation arc and less tension at the flap tip.<sup>4,6,8</sup> Webster projected the construction of a 30 degrees angle, increasing the pedicle base, combined with M-plasty, decreasing the rotational deformity of the edges and reducing tension at the donor site.<sup>4,9</sup>

### **METHODS**

We conducted a retrospective analysis of a series of cases involving 20 outpatient surgeries, in which local anesthesia with 1% lidocaine and epinephrine solution 1:200,000 was used. The flaps were made considering the size and location of the original defect, as well as lines of force, and elasticity of the adjacent tissues. They were performed with 0.5 cm safety margins on the sides and across the entire thickness of the skin.

From the defect resulting from the resection, a diamond was drawn with internal 60 degrees and 120 degrees angles (Figure 1A). The marking must be idealized with two equilateral triangles with 60 degree angles aligned base to base, so that all sides of the defect have the same length, which, in practice, is equal to the smallest diagonal. The first side of the flap is an extension out of the defect of the smallest diagonal along its own length; the second side is marked with a line the same size as the first one, adjacent to the diamond defect, creating a 60 degree angle at the apex of the flap.

The final configuration of the flap scar, in all cases, is predictable, as figure 1B shows.<sup>10</sup> In dermatological surgery, the rhomboidal flap is very useful in the forehead, periocular re-



FIGURE 1: Schematic drawing of the Limberg flap

gions, nasal tip, malar region, chin, and neck, and can be applied to other regions of the body.<sup>4</sup>

For each defect, four rhomboid flaps can potentially be made. Then, according to the lines of tension and expression of the skin, orientation, and location, the flap that best adapts to the defect is chosen. The undermining of all lesion edges, the flap edges, and the flap base is performed, providing an adequate approximation of the tissues, without tension in the closure.<sup>10</sup>

### **CASE SERIES**

We assessed a series of patients diagnosed with BCC in which the Limberg flap was used for post-excision reconstruction of the lesions. All patients were Fitzpatrick skin phototype II. We highlight that, from the selected series, in four cases the flap was performed on the face and, in another patient, on the left thoracic region (Figure 6), which demonstrates the versatility of using this flap. All cases progressed well, with excellent tissue perfusion. Figures 2, 3, 4, and 5 illustrate other cases in the present series.

### DISCUSSION

Local flaps are an excellent option for the excision repair of tumor skin lesions, where primary closure of the defect would cause aesthetic and/or functional damage, with the possibility of distortion of the structures. They are preferred to grafts as they present better color and texture correspondence with the recipient skin area since they are in the same region. Also, they don't need a homogeneous receptor bed for good integration since



FIGURE 2: Immediate pre and post-operative



FIGURE 3: Immediate pre and post operative



FIGURE 4: Immediate pre and post-operative



FIGURE 5: Immediate pre and post-operative



Figure 6: Immediate pre and post-operative

they have their vascular pedicle.<sup>2</sup> A well-planned and executed local flap allows the acquisition of excellent results and minimal distortion of facial lines.<sup>3</sup>

The safety of the rhomboid flap has made its use increasingly widespread, and it can be applied on a large part of the body surface.<sup>12,13</sup> Local facial flaps, especially on the forehead, malar region, temple, and lower part of the chin and lip, are ideal locations for vector transposition using the rhomboid flap according to Langer's lines.<sup>4</sup> The literature also reports the use of the Limberg flap to reconstruct defects after resection of large lesions in the trunk,<sup>13</sup> as in the present series, and also in the pilonidal cyst,<sup>14</sup> lumbosacral meningomyelocele correction,<sup>15,16</sup> burns sequelae, such as bands and synechiae, antecubital region,17 and even in breast reconstructions.<sup>18,19</sup> The choice of using this flap in patients with trunk injuries considers the limitation of edge--to-edge closure, extensive scarring, excess tension, and increased possibility of complications. The Limberg flap is versatile, and up to four flaps can be elevated from the rhomboid design if necessary, which cannot be seen in advancement or bilobed flap, for example. It can be applied in single or multiple formats, with vascular viability and good cosmetic results.<sup>5</sup>

### CONCLUSION

We can conclude that the Limberg flap presented good aesthetic and functional results in the cases described, illustrating its great versatility both in facial lesions and in extensive injuries in the trunk, proving to be a safe flap with good vascularization and easy to perform.

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### AUTHORS' CONTRIBUTION:

Anelise Darabas dos Santos D ORCID 0000-0002-4957-9688 Preparation and writing of the manuscript; critical literature review.

Douglas Haddad Filho D ORCID 0000-0001-9304-4739

Approval of the final version of the manuscript; study design and planning; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.

**Flávia Fenólio Nigro Marcelino** D ORCID 0000-0003-4057-5143 Preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review.

Luiza Vieites D ORCID 0000-0003-0647-8104 Preparation and writing of the manuscript.



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### Acral amelanotic melanoma

Melanoma amelanótico acral

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### ABSTRACT

Acral amelanotic melanoma is rare and can mimic many entities, such as eccrine poroma, squamous cell carcinoma, plantar wart, and chronic ulcers. Due to the variety of possible differential diagnoses, it is a challenging and frequently late diagnosis. Dermoscopy features can help in early diagnosis. The derma-tologist should keep this diagnosis in mind when faced with a pink, progressively growing, irregularly shaped lesion, mainly if located on the hands and feet.

**Keywords:** Dermoscopy; Melanoma amelanotic; Skin neoplasms; Oncology; Foot ulcer Financial support: None

### RESUMO

O melanoma amelanótico acral é raro e pode mimetizar muitas entidades, como poroma écrino, carcinoma de células escamosas, verruga plantar e úlceras crônicas. Devido a esta variedade de possíveis diagnósticos diferenciais, é um diagnóstico difícil e, muitas vezes, tardio. As características da dermatoscopia podem ajudar no diagnóstico precoce. O clínico deve ter esse diagnóstico em mente ao se deparar com uma lesão rosada, de crescimento progressivo e formato irregular, principalmente se localizada nas mãos e nos pés.

Palavras-chave: Dermoscopia; Melanoma Amelanótico; Neoplasias Cutâneas; Oncologia; Úlcera do Pé

### **Case report**

### Authors:

- Marina Riedi Guilherme<sup>1</sup> Bruna Cristina Mendes dos Santos<sup>1</sup> Osvaldo Szenczuk<sup>1</sup> Ligia Márcia Mário Martin<sup>1,2</sup> Cássio Rafael Moreira<sup>1,2</sup>
- <sup>1</sup> Autarquia Municipal de Saúde, Dermatology, Apucarana (PR), Brazil.
- <sup>2</sup> Universidade Estadual de Londrina, Dermatology, Londrina (PR), Brazil.ation.

### Correspondence:

Marina Riedi Guilherme Email: mariedigui@gmail.com

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Amelanotic melanoma is a subtype of cutaneous melanoma that shows no or little amount of pigment at macroscopy, dermoscopy, and histology.

Approximately 2–8% of melanomas are amelanotic. The final diagnosis is usually late due to the delay in identifying signs of malignancy.<sup>1</sup> Dermoscopy is an essential tool for anticipating these findings, allowing early suspicion, biopsy, and treatment. We present a case of acral amelanotic melanoma with typical dermoscopic findings, and we highlight the importance of the diagnostic suspicion.

### CASE REPORT

A 74-year-old man came to the Dermatology Outpatient Clinic complaining of a tumor in the right plantar region with five months of evolution. He was being followed up at the Basic Health Unit due to the hypothesis of chronic vascular ulcer. However, as the lesion showed growth and local pain, he was referred to the Dermatology Specialty Center. Dermatological examination revealed an oval-shaped ulcerated tumor in the right plantar region, with well-defined and elevated edges, and no signs of secondary infection (Figure 1). Dermoscopic examination showed a milky-red background, with vascular polymorphism combining dotted vessels and irregular linear vessels, and the presence of textile fibers (Figure 2). We referred the patient for an excisional biopsy of the lesion. The histopathology revealed the epidermis with hyperplasia, irregular acanthosis, and hyperkeratosis (Figure 3A), in addition to the presence of the pagetoid component (Figure 3B), mitoses, and lentiginous aspect of the lesion (Figure 3C). Immunohistochemistry was positive for MELAN-A (Figure 3D) and HMB-45 (Figure 3E), concluding that it was an amelanotic malignant melanoma, with a Breslow index of 8.6 mm.

The patient was referred to the Oncology Service of the municipality for staging and margin expansion. The investigation evidenced the presence of pulmonary and inguinal lymph node metastases. Clinical treatment with carbo-taxol was started, but the patient did not tolerate it and died seven months after the diagnosis of the lesion.

### DISCUSSION

Amelanotic melanoma can be divided into two subtypes according to the clinic and dermoscopy of the lesions: "true" and hypomelanotic. True amelanotic melanoma does not show pigment either clinically or on dermoscopy. Some authors even add histology, with less than 5% of tumor cells with melanin. Hypomelanotic melanoma has no pigment in the clinic but shows small pigmented areas on dermoscopy.<sup>2</sup>



Figure 1: Ulcerated lesion on plantar region, oval in shape, well-defined borders.



Figure 2: Dermoscopy with a milky-red background, vascular polymorphism, combining dotted vessels and irregular linear vessels, and presence of textile fibers.



### Figure 3:

A - Epidermis with hyperplasia, irregular acanthosis, and hyperkeratosis (Hematoxylin & eosin, 10x). **B** - Pagetoid component (Hematoxylin & eosin, 40x). C - Lentiginous appearance (Hematoxylin & eosin, 40x). **D** - Positive immunohistochemistry for MELAN-A. E - Positive immunohistochemistry for HMB-45.

Any subtype of cutaneous melanoma can be amelanotic, but it is more common in subungual (25%) and desmoplastic melanoma. The literature suggests three primary clinical forms of amelanotic melanoma: erythematous macula with epidermal changes, which occurs more commonly in photoexposed areas; normochromic dermal plaque without epidermal changes; and papular-nodular form, responsible for 58% of cases of amelanotic melanoma.<sup>3</sup>

In the absence of pigment, vascularization helps in the dermoscopic examination of amelanotic melanoma. Dermoscopy is difficult because the vessels may disappear depending on the pressure placed between the dermoscope and the lesion.<sup>4</sup> In general, there are six vascular patterns: dotted vessels, comma vessels, regular or irregular linear vessels, glomerular vessels, hairpin-like vessels, and arboriform vessels.<sup>5</sup>

The literature considers as dermoscopic features with the highest positive predictive value for suspected melanoma the presence of brown spots or globules of irregular size or distribution, multiple blue-grey spots, irregular depigmentation, blue--white veil, more than one shade of pink, milky-red areas, vessels mainly in the central region of the lesion, vascular polymorphism combining mainly dotted, irregular linear, and hairpin-like vessels. Some additional criteria are white areas of regression, ulceration, white structures, and inverted network.

On the other hand, characteristics with the highest negative predictive value for melanoma are more than three milia-like cysts, the predominance of comma-shaped vessels in the lesion, and arboriform vessels only.<sup>6,7,8</sup>

In the case reported, the initial diagnostic hypothesis of the primary care physician was a chronic ulcer with a probable vascular origin, which is one of the differential diagnoses of plantar ulcers, as well as plantar warts, eccrine poroma, plantar perforating ulcer, squamous cell carcinoma (SCC), and acral melanoma. The dermoscopic examination allowed assessing the characteristics suggestive of amelanotic melanoma and provided the best possible follow-up for the case, which emphasizes the importance of the dermatologist in the evaluation of skin lesions for the early diagnosis of potential malignancies, as well as the relevance of dermoscopic examination knowledge to increase the specialist's diagnostic accuracy.

### CONCLUSION

Amelanotic melanoma is a rare condition; however, it has a high mortality rate, mainly due to late diagnosis. The dermoscopic examination has become an essential ally to anticipate the diagnosis of these lesions and improve the prognosis. The presence of vascular polymorphism and milky-red background in a pink lesion should raise suspicion of malignancy and prompt biopsy.

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### **AUTHORS' CONTRIBUTION:**

**Marina Riedi Guilherme** D ORCID 0000-0003-4765-2180 Study design and planning; preparation and writing of the manuscript; critical literature review.

**Bruna Cristina Mendes dos Santos** D ORCID 0000-0002-6789-5836 Preparation and writing of the manuscript.

**Osvaldo Szenczuk** D ORCID 0000-0002-2002-2990 Critical revision of the manuscript.

**Ligia Márcia Mário Martin D** ORCID 0000-0002-4293-9580 Approval of the final version of the manuscript; critical revision of the manuscript.

**Cássio Rafael Moreira** DORCID 0000-0002-8781-1505 Approval of the final version of the manuscript; active participation in research orientation.



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# Merkel cell carcinoma: multiple primary skin lesions in the lower limb

Carcinoma de células de Merkel: múltiplas lesões cutâneas primárias no membro inferior

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### ABSTRACT

Merkel cell carcinoma is a rare and aggressive neuroendocrine skin tumor usually presenting as a single lesion in the head or neck region. We report a case of atypical topography and presentation, with multiple and simultaneous tumors on the left leg of rapid progression associated with palpable inguinal lymphadenopathy and diagnostic confirmation by histopathology and immunohistochemistry. Exeresis of the left inguinal lymph node and skin lesions with a safety margin was performed. **Keywords:** Carcinoma Merkel cell; Merkel cells; Merkel cell polyomavirus

### RESUMO

Carcinoma de células de Merkel é um tumor neuroendócrino raro e agressivo de pele que usualmente apresenta-se como lesão única na região de cabeça ou pescoço. Relata-se um caso de topografia e apresentação atípicas, com presença de múltiplos e simultâneos tumores na perna esquerda de rápida evolução, associados à linfonodomegalia inguinal palpável, com diagnóstico confirmado por meio de histopatologia e imuno-histoquímica. Realizada exérese de linfonodo inguinal esquerdo e das lesões cutâneas com margem de segurança.

Palavras-chave: Carcinoma de Célula de Merkel; Células de Merkel; Poliomavírus das Células de Merkel

### **Case report**

### Authors:

Bruna Margatho Elias<sup>1</sup> Giovanna Curi Campos<sup>1</sup> Hudson Dutra Rezende<sup>1</sup> José Roberto Paes Almeida<sup>1</sup> Karla Calaça Kabbach Prigenzi<sup>1</sup> Sandra Lopes Mattos Dinato<sup>1</sup>

<sup>1</sup> Centro Universitário Lusíada (UNILUS), Dermatology, Santos (SP), Brazil.

### Correspondence:

Marina Riedi Guilherme Email: bruelias15@gmail.com / Alternative email: bruelias15@ gmail.com

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Merkel cell carcinoma (MCC) is a rare form of non-melanoma skin cancer of neuroendocrine origin, more common in elderly white men.<sup>1</sup> In general, it manifests as an asymptomatic papule or nodule, pink or bluish-red, with a rapid increase in size, in weeks to months.<sup>2</sup> The most affected sites are the photoexposed areas of the head and neck.<sup>3</sup> The pathogenesis of MCC is still unknown, despite the association with several chromosomal abnormalities, growth signaling, and apoptotic pathways, in addition to the possible involvement of polyomavirus in tumor carcinogenesis. Even today, MCC represents a diagnostic and therapeutic challenge in clinical practice.

### CASE REPORT

A Caucasian 70-year-old man, born and residing in Santos, retired, came to the Dermatology Sector complaining of multiple fast-growing lesions on the left leg, four months ago. The lesions were painful, with colorless exudation. The patient reported swelling, color change in the region, and difficulty walking. He denied any systemic symptoms, despite using atenolol and sinvastatin. Dermatological examination revealed multiple papules, nodules, tumors (diameters ranged from 1 cm to 6 cm) with exudate. The lesions had a slightly soft consistency on palpation (Figure 1). Painless, nonadherent bilateral inguinal lymph nodes were palpable, and edema was present in the compromised limb. Dermoscopy showed multiple irregular, polymorphic vessels, bright white areas without structures, and milky-red areas. Also, we observed a lesion clinically compatible with basal cell carcinoma (BCC) in the presternal region.



Figure 1: Merkel cell carcinoma: multiple primary skin lesions on the lower limb Biopsy of a solitary papular lesion near the left medial malleolus revealed proliferation of atypical small cells in the dermis, with a high nucleus/cytoplasm ratio, a high mitotic index (>30 mitoses/10CGA), and numerous apoptotic bodies, arranged in chordal pattern or solid blocks, which sometimes outlined rosettes. It indicated a high-grade malignant neoplasm, suggesting a small cell neuroendocrine carcinoma (Figure 2). Immunohistochemistry revealed immunoexpression of cytokeratin 5/6, chromogranin, synaptophysin, and CK20 in a "dotted" pattern, confirming epithelial histogenesis and neuroendocrine differentiation of neoplastic cells, compatible with the diagnosis of MCC (small cell neuroendocrine carcinoma). Markers indicative of squamous differentiation, melanocytic histogenesis, and pulmonary and gastrointestinal primary site were also performed and were negative.

Given the rarity of the case and its atypical topography and presentation, we searched immunosuppression, which was negative. Thus, the differential diagnosis with neuroendocrine carcinoma of another primary site was questioned. Additional evaluation with computed tomography (CT) scans of the chest, abdomen, and pelvis did not reveal disease in other sites nor lymph node enlargement. CT of the left leg showed exophytic skin lesions that maintained continuity with the subcutaneous tissue, without presenting a clear cleavage plane with the underlying muscle fasciae and without infiltrating deeper muscles or planes. Plasma investigation by qualitative PCR for polyomavirus was negative.

The patient was referred to oncological surgery and underwent excision of the left inguinal lymph node, which was sent for intraoperative and subsequent histopathological frozen section, with a negative result. Then, excision of the skin lesions was performed with a safety margin (Figure 3).

Due to the extensive exposed area, with the impossibility of primary closure and difficulty to conduct flaps due to the skin condition, a dressing was made with silver sulfadiazine and Rayon bandage, opting for healing by secondary intention (Figure 4).

### DISCUSSION

MCC is a rare and aggressive condition that affects white men in the 7th and 8th decades of life, coinciding with the profile of the presented patient.<sup>1</sup> Classically, it involves photoexposed skin of the cervicofacial region in 29–53% of cases, according to current literature. Approximately 1/3 of cases (35–38%) affect the extremities, 21% upper limbs, and only 14–24% lower limbs.<sup>4</sup>

The case reported here was observed in a region of rare involvement. Regarding the clinical presentation, it varies widely; however, it's typically characterized by a single, persistent, and asymptomatic erythematous-violaceous nodular lesion, often smaller than 2 cm, with rapid growth, reaching 20 cm in months.<sup>1,5,6</sup> In almost 1/3 of the cases, there are other simultaneous skin neoplasms, such as basal cell carcinoma (BCC), which agrees with our patient.<sup>3</sup> The pathogenesis is uncertain, but the polyomavirus seems to have some role, as it is detected in



Figure 2: Histopathology of Merkel cell carcinoma. **A** - Atrophic epidermis; in the dermis, proliferation of small, hyperchromatic cells is observed, extending to the hypodermis (Hematoxylin & eosin, 40x). **B** - Detail of small cells arranged singly or in chordal arrangements or rosettes (Hematoxylin & eosin, 100x). **C** - Nuclei are oval-shaped, similar in size to a mature lymphocyte, with chromatin in a "salt-and-pepper" pattern, with nuclear molding, apoptotic bodies, and mitotic figures (Hematoxylin & eosin, 400x)



Figure 3: Multiple cutaneous Merkel cell carcinoma: surgical approach.

most cases (80%) and frequently among patients with acquired immunodeficiency syndrome and transplanted immunosuppressed individuals. Also, it is integrated into the genome before the clonal expansion of tumor cells, suggesting that it is a factor that contributes to the development of the tumor.<sup>4,5</sup> The patient in question did not have immunosuppression or positive serology for the virus.

Due to the usually nonspecific clinical picture, imaging investigation is necessary, helping to diagnose and differentiate MCC from metastases from other neuroendocrine carcinomas, such as small cell lung cancer. The diagnosis is based on a thorough examination of the skin and lymph nodes, biopsy, and histological evaluation by an experienced dermatopathologist.<sup>6</sup> Histologically, it presents as small, uniform basophilic cells that



**Figure 4:** Multiple cutaneous Merkel cell carcinoma: 15th postoperative day

fill the dermis with scant cytoplasm, "dusty" chromatin, and nuclear molding. The cells are organized in nests, spreading to the reticular and subcutaneous dermis, with eventual epidermal involvement. The MMC has neuroendocrine and epithelial characteristics, expressing some markers, and CK20<sup>4</sup> is a very specific and sensitive marker when found in the paranuclear "dotted" pattern, which can be confirmed in the case presented.

It is a highly aggressive and metastatic tumor, with a disease-specific 5-year survival rate of 64% and a 3-year mortality rate of 33% after diagnosis.<sup>1,4</sup> It is known that 2/3 of patients with MCC present only local disease but nodal or metastatic condition at the time of diagnosis is not uncommon and local recurrence is around 25-33%.<sup>5</sup> A sentinel lymph node biopsy, performed in this case, should be considered for all patients, as 1/3 of individuals with clinically localized disease at the time of presentation has occult lymph node involvement,<sup>6</sup> and hematogenous and/or distant lymphatic metastases may occur involving mainly the liver, bones, brain, and skin.<sup>1</sup>

As for MCC treatment, there is no consensus. Surgical excision is the standard therapy for primary lesions smaller than 3 cm and adjuvant radiation therapy for lesions larger than 2 cm. Some studies recommend 2 cm margins for tumors larger than 2 cm and 1cm margins for tumors smaller than 2 cm. However, there are no controlled studies comparing different excision mar-

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gins, considering the rarity of the disease.<sup>1,4</sup> Also, there is evidence for the use of radiotherapy exclusively for unresectable disease, but not for chemotherapy, reserved for cases of metastatic disease.<sup>1,4</sup>

### CONCLUSION

Although rare, the incidence of MCC is increasing due to the aging of the population, increased sun exposure, and the high number of immunocompromised individuals.<sup>7</sup> As it is an aggressive tumor, atypical presentations must be considered since early recognition makes it possible to improve quality of life and prognostic perspectives.<sup>4,7,8</sup> •

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#### **AUTHORS' CONTRIBUTION:**

Bruna Margatho Elias D ORCID 0000-0003-2615-5775

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review.

**Giovanna Curi Campos D** ORCID 0000-0002-8155-4499 Preparation and writing of the manuscript; critical literature review.

### Hudson Dutra Rezende 🜔 ORCID 0000-0002-7039-790X

Approval of the final version of the manuscript; preparation and writing of the manuscript; ; active participation in research orientation; critical literature review; critical revision of the manuscript.

### José Roberto Paes Almeida D ORCID 0000-0002-3869-6715

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.

**Karla Calaça Kabbach Prigenzi** D ORCID 0000-0002-8264-8972 Preparation and writing of the manuscript; critical literature review.

### Sandra Lopes Mattos Dinato D ORCID 0000-0002-4547-0474

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.



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# Primary cutaneous adenoid cystic carcinoma in the scalp with pulmonary metastases: a case report

Carcinoma adenoide cístico cutâneo primário no couro cabeludo com metástases pulmonares: um relato de caso

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### ABSTRACT

Primary cutaneous adenoid cystic carcinoma (PCACC) is a rare tumor with an estimated incidence rate of 0.23 cases/1,000,000 people per year. A 60-year-old man presented a scalp lesion in 2017. Initially, it was not possible to perform a histopathologic diagnosis. In 2018, surgical biopsy and immunohis-tochemistry of the local skin recurrence indicated a diagnosis of PCACC (treatment was surgery and radiotherapy). In 2020, a new local tumor recurred and was surgically resected. The patient had systemic metastases (pulmonary metastases) and underwent chemotherapy. Currently, the pulmonary metastases are stable. The PCACC has progressed to pachymeninges.

Keywords: Carcinoma adenoid cystic; Scalp; Neoplasm metastasis; Skin neoplasms

### RESUMO

O carcinoma adenoide cístico cutâneo primário (CACCP) é um câncer extremamente raro, com uma taxa estimada de ocorrência de 0,23 caso/1.000.000 de pessoas ao ano. Paciente do sexo masculino, 60 anos de idade, apresentou lesão no couro cabeludo em 2017. Inicialmente, não foi possível realizar o diagnóstico histopatológico. Em 2018, biópsia e imuno-histoquímica indicaram tratar-se de CACCP (tratamento realizado com cirurgia e radioterapia). Em 2020, ocorreu nova recidiva local, sendo realizada ressecção cirúrgica. Paciente apresentou recidiva sistêmica (metás-tases pulmonares). Foi realizado tratamento quimioterápico. Atualmente, as metástases pulmonares estão estáveis e o CACCP progrediu para paquimeninges.

Palavras-chave: Carcinoma Adenoide Cístico; Couro Cabeludo; Metástase Neoplásica; Neoplasias Cutâneas

### Case report

### Authors:

Rafael Everton Assunção Ribeiro da Costa<sup>1</sup>

Fergus Tomás Rocha de Oliveira<sup>1</sup> Eugênio de Sá Coutinho Neto<sup>2</sup> Carlos Eduardo Coelho de Sa<sup>3</sup>

- <sup>1</sup> Universidade Estadual do Piauí, Health Sciences Center, Teresina (PI), Brazil.
- <sup>2</sup> Hospital do Coração de Messejana, Radiology, Fortaleza (CE), Brazil.
- <sup>3</sup> Hospital Macrorregional de Caxias Dr. Everaldo Ferreira Aragão, Caxias (MA), Brazil.

### **Correspondence:**

Rafael Everton Assunção Ribeiro da Costa Email: rafaelearcosta@gmail.com

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Adenoid cystic carcinoma (ACC) is a rare cancer that commonly originates from the salivary glands and may also arise from lacrimal, sweat, and Bartholin glands. Although its clinical course is slow, there is a tendency for an early invasion of blood vessels and peripheral nerves, which causes a high rate of local recurrence and metastases, especially to the lungs, bones, and liver, resulting in a worse prognosis.<sup>1</sup>

Primary cutaneous adenoid cystic carcinoma (PCACC) is an extremely rare type of ACC. A 30-year epidemiological study of PCACC estimated an incidence rate of 0.23 cases per million people per year.<sup>2</sup> A recent survey of PCACC cases showed a total of only 114 cases reported in the English-language literature.<sup>3</sup> PCACC presents a lower degree of malignancy among ACCs, and the occurrence of metastases is very infrequent, despite the high incidence of local recurrence.<sup>4</sup>

Given the rarity of metastatic PCACC and the scarcity of literature on the subject, this study aims to describe a case of PCACC in the scalp with lung metastases.

### CASE REPORT

In April 2017, a 60-year-old man arrived at the Service with a small lesion on the scalp (<1.0 cm). The lesion presented a rough surface and a light brown color, located in the region corresponding to the posterior part of the sagittal suture, with bilateral involvement of the temporal bones. The surgical resection, biopsy, and anatomopathological study indicated it was a neoplasm with characteristics of malignancy, without the possibility of histopathologic diagnosis.

The patient presented an erythematous-violaceous nodule, with fibroelastic consistency, measuring 1.2 cm on the scalp, compatible with local recurrence of the primary lesion, in March 2018 (Figure 1). Magnetic resonance imaging (MRI) indicated a lobulated diplopic lesion with heterogeneous enhancement in the posterior portion of the sagittal suture, partially involving the superior sagittal sinus and with intra and extracranial extension.

We decided to perform a bilateral parietal craniotomy. Figure 2 shows the surgical field after the removal of the parietal bones. Biopsy and anatomopathological study were performed, in addition to immunohistochemistry, and the results were compatible with PCACC in the scalp, with bone infiltration (p63 and CD117 positive). The patient was referred for adjuvant radiotherapy for three months (total dose of 50 Gy in 20 applications) and periodic clinical follow-up.

In March 2020, the patient presented a new lesion on the scalp. MRI showed signs of surgical manipulation characterized by bilateral median and paramedian parietal craniotomy and an extra-axial expansive lesion, with intense uptake by homogeneous contrast in the right parietal region, underlying the craniotomy. It suggested a recurrence of 2.1 cm, promoting an impression on the right parietal lobe without changing its sign. Brain parenchyma showed preserved morphology and signal intensity. A new bilateral parietal craniotomy was performed in July 2020, with no indication for radiotherapy due to the high risk of brain parenchyma necrosis.

In November 2020, chest computed tomography showed multiple irregular pulmonary nodules in both lungs, the largest measuring 1.1 cm, and 1.3 cm, compatible with neoplastic metastases. Figure 3 depicts the most eminent nodules.

In January 2021, adjuvant chemotherapy with cisplatin and 5-fluorouracil was started, with some adverse events (headache, nausea, and vomiting). Currently, the lung metastases are stable, and the patient is on a chemotherapy pause. However, there was a progression from PCACC to pachymeninges. The case was sent to the Neurosurgery team to study the possibility of a new craniotomy.

The Research Ethics Committee of the State University of Piauí, Teresina (PI), Brazil, approved the present study under CAAE n. 44847121.1.0000.5209. All precepts contained in resolution 466/12 of the National Health Council and international documents were respected.



**FIGURE 2:** Bilateral parietal craniotomy for surgical treatment of the first local recurrence.



**FIGURE 1:** First local recurrence of primary cutaneous adenoid cystic carcinoma on the scalp.



**FIGURE 3:** Computed tomography of lung metastases from primary cutaneous adenoid cystic carcinoma.

### DISCUSSION

There are few conclusive studies in the literature on PCACC's clinicopathological aspects and survival due to its rarity, and there is still no consensus on a standard treatment to be adopted in these cases.

Behbahani *et al.* published perhaps the more extensive study on PCACC in 2020, including 201 patients diagnosed between 2004 and 2016.<sup>5,6</sup>

The survival analysis performed by Behbahani *et al.* showed an overall 5-year and 10-year survival rate of 87.0% and 76.0%, respectively. The same study also showed a mean age at diagnosis of 57.7 years and a higher occurrence of PCACC in women (57.7% of the 201 cases). Also, the primary tumor site was the ear (58.2%), followed by the scalp/neck (25.9%). Most cases were localized tumors (65.8%).<sup>6</sup>

In addition to PCACC rarity, the patient in this study presented a series of discrepancies regarding what is expected in a case of this nature. First, PCACC is far less common in men, occurring less frequently on the scalp. Furthermore, PCACC tends to have a much less aggressive course than other types of ACC, showing good overall survival rates with a predominance of localized cases.<sup>1-6</sup>

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Regarding treatment, although there is still no consensus, the chief modality adopted is local surgical resection, and radiotherapy is also widely used.<sup>6</sup> In this case, we performed surgical resection and radiotherapy. However, there were local recurrences and, later, systemic recurrence (pulmonary metastases). The patient underwent chemotherapy achieving stability of the metastatic neoplastic disease in the lungs. However, PCACC continued to progress locally, affecting pachymeninges.

### CONCLUSION

A 60-year-old man presented a rare case of PCACC on the scalp, with a very aggressive course. Surgical treatment was performed in combination with radiotherapy, with a 4-year follow-up. However, the patient had local recurrences and lung metastases and underwent chemotherapy. Currently, the patient has stable metastatic neoplastic disease in the lungs, but PCACC has progressed locally to pachymeninges.

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### **AUTHORS' CONTRIBUTION:**

### Rafael Everton Assunção Ribeiro da Costa in ORCID 0000-0002-0798-890X

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review; critical revision of the manuscript.

### Fergus Tomás Rocha de Oliveira D ORCID 0000-0001-6869-9709

Approval of the final version of the manuscript; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review; critical revision of the manuscript.

### Eugênio de Sá Coutinho Neto D ORCID 0000-0002-0806-3933

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

### Carlos Eduardo Coelho de Sá 问 ORCID 0000-0002-9610-8010

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.



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### Agminated blue nevus over acne scars: coincidence or pathophysiological relationship?

Nevo azul agminado sobre cicatrizes de acne: coincidência ou relação fisiopatológica?

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### ABSTRACT

Blue nevus is a benign lesion arising from dermal melanocytes containing large amounts of melanin. The agminated variant presents a cluster of blue nevus lesions with linear or blaschkoid distribution. We report two cases of patients with agminated blue nevus that developed on previous acne scars, and dermoscopy helped a lot in the differential diagnosis. This is the first occurrence found in the literature of agminated blue nevus that appeared on a previous scar, which may have occurred by chance or as a result of the collagen remodeling process inherent to the healing process. **Keywords:** Scar; Collagen; Dermoscopy; Nevus blue

### RESUMO

Nevo azul é uma lesão benigna originada de melanócitos dérmicos contendo grande quantidade de melanina. A variante agminada apresenta-se como um agrupamento de lesões de nevo azul com distribuição linear ou blaschkoide. Relatamos dois casos de pacientes com nevo azul agminado que surgiu sobre cicatrizes prévias de acne, sendo a dermatoscopia de grande auxílio para diagnóstico diferencial. Esta é a primeira ocorrência relatada de nevo azul agminado sobre cicatrizes prévias, o que pode ter ocorrido ao acaso ou em decorrência do processo de remodelamento do colágeno, próprio do processo cicatricial.

Palavras-chave: Cicatriz; Colágeno; Dermoscopia; Nevo Azul

### **Case report**

### Authors:

- Deborah Heloisa Cezar Dourado<sup>1</sup> Nathália Bacni Garcia<sup>1</sup> Marilda Aparecida Milanez Morgado de Abreu<sup>1</sup> Vinícius de Souza<sup>2</sup> Ana Claudia Cavalcante Esposito<sup>12</sup>
- <sup>1</sup> Universidade do Oeste Paulista, Medical School, Presidente Prudente (SP), Brazil.
- <sup>2</sup> Universidade Estadual Paulista "Júlio de Mesquita Filho", Department of Dermatology, Medical School of Botucatu, Botucatu (SP), Brazil.

### Correspondence:

Ana Claudia Cavalcante Esposito Email: anaclaudiaesposito@gmail. com

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The blue nevus is a benign lesion, usually asymptomatic, originated from dermal melanocytes that present large amounts of melanic pigment.<sup>1</sup> It can be congenital or acquired, and the literature describes several histological variants.<sup>2-4</sup> The most common clinical form is the solitary (single lesion), but it can also manifest as a cluster of lesions with a linear or blaschkoid distribution usually less than 10 cm in length, referred to as agminated blue nevus.<sup>5</sup>

We report two rare cases of patients with agminated blue nevus that arose over previous acne scars on the face.

### **CASE REPORT**

### Case 1

A 39-year-old woman, Fitzpatrick's skin phototype IV, sought dermatological care reporting acne on the face between 12 and 19 years old with the formation of pustules and nodules. At the time, she did not undergo treatment and evolved with the emergence of multiple scars. Ten years ago, she reported the appearance of a blackened and asymptomatic spot in the right buccinator muscle region, which concerned her. She denied recent growth of the lesion and comorbidities or the use of any medications.

On dermatological examination, the patient presented multiple icepicks and box acne scars in the malar, buccinator, zygomatic, and mandibular regions, bilaterally. In the right buccinator muscle region, there was a blue-black macula measuring 4 cm by 3.5 cm, with increased pigmentation at the bottom of the acne scars (Figure 1). There were no palpable lymph nodes in the head and neck chains. Non-polarized light dermoscopy showed homogeneous pigmented lesions with a blue-gray color and absence of structures, interspersed with areas of healthy, slightly erythematous skin with intermingled telangiectasia (Figure 2). Polarized light dermoscopy showed blue-gray pigmented lesions with areas without structures in addition to bright white lines and smudges with a scar pattern, probably resulting from the scar reorganization typical of the scarring process (Figure 3).



**FIGURE 2:** Non-polarized light dermoscopy: homogeneous pigmented lesions with a blue-gray hue and absence of structures, interspersed with areas of healthy, slightly ery-thematous skin with intermingled telangiectasia.



**FIGURE 1:** Multiple ice picks and box scars in the malar, buccinator, zygomatic, and mandibular region, on the right. Presence of a blue-black macula measuring 4 cm by 3.5 cm in the right buccinator region, with increased pigmentation at the bottom of acne scars.



**FIGURE 3:** Polarized light dermoscopy: blue-gray pigmented lesions with areas without structures plus bright white scar-patterned lines and smudges.

The clinical hypotheses were agminated blue nevus, with a differential for extrinsic pigmentation (tattoo-like), exogenous ochronosis, superficial extensive melanoma, and Reed nevus. Incisional biopsy was performed under local anesthesia (4 mm punch) in two areas. The anatomopathological examination showed normal epidermis, with elongated melanocytes in the dermis, with a variable quantity of cytoplasmic melanin, without nuclear atypia or mitosis. The histological findings were defined to diagnose blue nevus, agminated variant, which developed over previous acne scars.

### Case 2

An 18-year-old man reported acne since he was 12 years old. Two years ago, he noticed a blue-black spot in the right buccinator muscle region. On dermatological examination, the patient presented closed comedones, erythematous papules, rare pustules, and icepicks and box acne scars (in smaller amounts) on the face, especially in the zygomatic, buccinators, and mandibular areas. In the right buccinator region, he had a blue-black macula measuring 4 cm by 2 cm (Figure 4A). At dermoscopy (non-polarized light), the lesion was composed of homogeneous blue-grey pigmentation, with no structures, interspersed with areas of erythematous healthy skin (Figure 4B). The clinical and dermoscopic hypothesis was agminated blue nevus that developed over acne-affected skin (including scars). The patient is under clinical follow-up without any surgical approach to the pigmented lesion.

### DISCUSSION

Blue nevi are bluish macules, papules, plaques, or nodules. The agminated form was described for the first time only in 1947. Since then, the literature has gathered just over 30 cases of this variant, which justifies the rarity of the present case.<sup>5</sup>

Agminate lesions have a linear or blaschkoid distribution, and their pathogenesis is unknown. There are different theories to justify the segmental distribution, such as the development of lesions from peripheral nerves; dermal melanocytes resulting from an interruption during neural crest migration towards the epidermis; and, finally, clonal growth from a single cell.<sup>2,5,7</sup>

While the common blue nevus has a predilection for the limbs and face, the agminated form has a similar distribution between the trunk, extremities, head, and neck, in addition to affecting men and women equally.<sup>1,2,5,8</sup> One hypothesis is that the agminated lesion tends to appear in an area of cutaneous trauma, with implantation of melanocytic cells in the deep dermis, or excessive sun exposure.<sup>3</sup> In the reported patients, the lesion developed in a photoexposed area previously subjected to an intense inflammatory process resulting from acne.

The literature describes blue nevus agminated associated with nevus spilus, melanoma, dermatomyositis, Darier disease, and Carney complex. However, these are the first reports of the lesion appearing over the scar area.<sup>3-5,8,12</sup> The lesion on the previous site of an acne scar may have occurred by chance, or the inflammatory process and collagen remodeling, typical of scar formation, may have facilitated the migration of melanocytes to the upper dermis.

Histologically, the agminated blue nevus more frequently corresponds to the common variant, where melanocytes – bipolar dendritic melanocytes or stellar with long dendrites – are located in the dermis, and may also aggregate around the skin appendages and neurovascular bundles.<sup>69</sup>

Activation mutations in GNAQ or GNA11, whose protein products signal through the MAPK pathway, are present in more than 83% and 7%, respectively, of blue nevus cases.<sup>10,11</sup> In



**FIGURE 4: A** - Blue-black macula measuring 4 cm by 2 cm in the right buccinator region. **B** - Dermoscopy (non-polarized light): homogeneous blue-gray pigmentation, without structures, interspersed with areas of erythematous healthy skin.

the case of agminated blue nevus, only one article assessed mutations identified in GNAQ.<sup>5</sup> The two present reports did not perform mutation research.

The diagnosis of agminated blue nevus, in general, is a major clinical challenge.<sup>6</sup> Given the complexity of the lesions, dermoscopy becomes a crucial tool, especially to differentiate melanoma from ochronosis.<sup>4,13</sup> Dermoscopic findings in blue nevus include a homogeneous pattern melanocytic lesion, with few structures, bluish-gray amorphous areas, and there may be globules and spots.<sup>14</sup> The blue color results from the Tyndall effect caused by the incident light in the deep melanin deposits melanin (dermis), which refracts and spreads.<sup>15</sup> Despite the significant contribution of dermoscopy, the definitive diagnosis of blue nevus is histological.

#### CONCLUSION

The rarity of agminated blue nevus and its similarity to other dermatological lesions make its diagnosis challenging. These are the first reported cases of agminated blue nevus that have developed over a previous scar area. The inflammatory process and collagen remodeling, typical of the healing process, may have facilitated the migration of melanocytes to the upper dermis.

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#### **AUTHORS' CONTRIBUTION:**

#### Deborah Heloisa Cezar Dourado D ORCID 0000-0003-3611-5048

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review; critical revision of the manuscript.

#### Nathália Bacni Garcia (D ORCID 0000-0002-2539-5163

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review; critical revision of the manuscript.

#### Marilda Aparecida Milanez Morgado de Abreu 🝺 ORCID 0000-0001-9099-6013

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review; critical revision of the manuscript.

#### Vinícius de Souza D ORCID 0000-0001-8819-6906

Approval of the final version of the manuscript; preparation and writing of the manuscript; analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Ana Claudia Cavalcante Esposito D ORCID: 0000-0001-9283-2354

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.



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# External vascular compression by hyaluronic acid injection via pneumatic microjet device

Compressão vascular externa por ácido hialurônico injetado por dispositivo a vácuo

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#### ABSTRACT

Filling with hyaluronic acid using a pen that injects with vacuum pressure in the lips region became popular due to not using needles, but it presents risks like any minimally invasive procedure. We present a case of injection of hyaluronic acid with this device in the labial region, which resulted in a subocclusion of the inferior labial artery. It is known that the use of pressure can offer a lower precision than the methods already used classically. Therefore, it is important to warn about the risks of this device, which despite not using needles, presents the same risks of complications. **Keywords:** Dermal fillers; Hyaluronic acid; Lip

RESUMO

O preenchimento com ácido hialurônico por meio de caneta que o injeta com pressão a vácuo na região dos lábios popularizou-se por não usar agulhas, porém apresenta riscos como qualquer procedimento minimamente invasivo. Relatamos um caso de injeção de ácido hialurônico com esse dispositivo na região labial que teve, como consequência, uma suboclusão da artéria labial inferior. Sabe-se que o uso da pressão pode oferecer uma precisão menor do que os métodos já classicamente utilizados. Portanto, é importante alertar acerca dos riscos desse dispositivo que, apesar de não empregar agulhas, apresenta os mesmos riscos de complicações.

Palavras-chave: Ácido hialurônico; Lábio; Preenchedores dérmicos

# **Case report**

#### Authors:

Alexandra Brugnera Nunes de Mattos<sup>1</sup> Gabriela Martins Fim<sup>1</sup> Gabriela Quadri Bortoll<sup>1</sup> Caroline Erthal<sup>1</sup> Márcio Guedes Brandão<sup>2</sup>

- <sup>1</sup> Faculdade Meridional (IMED), Dermatology, Passo Fundo (RS), Brazil
- <sup>2</sup> Radiological clinic, Passo Fundo (RS), Brazil

#### Correspondence:

Alexandra Brugnera Nunes de Mattos anunes12@hotmail.com / E-mail alternativo: alexandra.mattos@ imed.edu.br

Financial support: None Conflict of interest: None

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With the popularization of hyaluronic acid fillers, there was an increase in cases of vascular complications, such as compression, vascular obstruction, and tissue necrosis, which intrigues patients and physicians.<sup>1</sup> The hyaluronic acid pen uses pneumatic pressure to administer hyaluronic acid into the skin. Thus, it is presented as a needle-free device that, theoretically, would make the procedure safer. However, like any minimally invasive aesthetic technique, it presents vascular risks. This study aims to report a case of vascular compression by a vacuum device and discuss the risk of this method.

#### **CASE REPORT**

A 31-year-old woman sought dermatological care reporting significant lip edema three hours after undergoing lip filling with two syringes of hyaluronic acid using a needle-free pneumatic injection device. Before the procedure, the patient had already ingested 80 mg of prednisone and 180 mg of fexofenadine on her own, as she had already presented an episode of lip edema four months ago, after the application of 1 ml of hyaluronic acid with a needle. At the time, she underwent an allergic test to lidocaine and mepivacaine anesthetics, both negative. On physical examination, she presented significant diffuse edema, with a hardened appearance of the lips and ecchymosis, but no pallor (Figure 1). We referred the patient for urgent ultrasound examination, which showed changes in flow amplitude and vascular resistance between the right and left inferior labial arteries, with reduced systolic velocity peaks and decreased vascular resistance distally, suggesting extrinsic compression of the artery horizontal labrum, but without signs of occlusion (Figure 2). Also, multiple

hypoechoic areas were observed in between, affecting the upper and lower lips throughout their extension, compatible with an important focal inflammatory process after using the filler. The patient was followed up and prescribed prednisone 40 mg and ciprofloxacin 500 mg daily. It was it was not necessary to apply hyaluronidase. Within 24 hours, there was a reduction in edema, with no signs of arterial occlusion.

#### DISCUSSION

The hyaluronic acid injection via a pneumatic microjet device is a system for administering substances into the skin through pneumatic pressure exerted by the equipment. As it is a needle-free device, it is believed to be safe.<sup>2</sup> However, as with any minimally invasive procedure, there are risks of complications, such as edema, ecchymosis, site infection, and arterial occlusion. Using a needle-free pneumatic injection pen, the application plan can be erratic, and the hyaluronic acid can penetrate the most diverse layers of the skin and lead to vascular compression, as in the case presented here. Furthermore, there are anatomical variations in the labial artery, which is a challenge for physicians <sup>3</sup> because both labial arteries are branches of the facial artery (FA). In the upper lip, the main one is the superior labial artery (SLA), and the septal (SA) and subalar (SAA) arteries are usually optional. It is important to emphasize that the superior labial artery is bilateral; nevertheless, it can present significant variations.<sup>4</sup> The lower lip, in its turn, is supplied by the inferior labial artery (ILA) and labiomental artery (LMA) - the last one has both horizontal and vertical branches.

Complications are classified as early (related to infiltration, such as edema, pain, ecchymosis, bleeding, inflammatory, and allergic reactions) or late (regarding infections, nodules, granuloma, and scars).<sup>5</sup> Vascular complications can arise due to the anatomical location, the injected volume, the use of narrow gau-



**FIGURE 1:** Edematous appearance, with ecchymosis on the lips



FIGURE 2: Compression external vascular of labial inferior artery

ge needles, previous scars, and the material composition.<sup>6</sup> The applied technique, the high volume of hyaluronic acid, and the previous reaction to hyaluronic acid may have exacerbated the reaction of the patient in this study. Based on current scientific evidence, if any complications occur in the procedure, it is recommended to stop it immediately, massage the area, use high doses of hyaluronidase as a way to undo it, and wait around an hour to reassess the need for a new infiltration.<sup>5</sup> In the case the patient evolves with greater edema and arterial occlusion, there would be a need for local injection of hyaluronidase to dissolve the product. Therefore, a good anamnesis, anatomical knowled-

ge, in addition to a professional trained to recognize complications and treat them, are essential to avoid a worse evolution of the case.

#### CONCLUSION

The application of hyaluronic acid using a pneumatic microjet device has risks. As the application is made via pressure, the product can penetrate the tissues erratically and lead to vascular occlusion and other complications. Thus, the search for a trained professional with well-studied filling techniques should always be recommended.  $\bullet$ 

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#### AUTHOR'S CONTRIBUTION:

Alexandra Brugnera Nunes de Mattos D ORCID 0000-0002-7284-7193 Approval of the final version of the manuscript; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases.

**Gabriela Martins Fim D** ORCID 0000-0003-2919-1253 Preparation and writing of the manuscript; critical revision of the manuscript.

**Gabriela Quadri Bortoli** ORCID 0000-0002-1691-518X Preparation and writing of the manuscript.

**Caroline Erthal** ORCID 0000-0002-3189-855X Critical revision of the manuscript.

**Márcio Guedes Brandão** ORCID 0000-0002-3114-693X Intellectual participation in propaedeutic and/or therapeutic conduct of studied cases.



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# Reconstruction of facial hemiatrophy using calcium hydroxylapatite filler: report of a safe and minimally invasive technique

Reconstrução de hemiatrofia facial com hidroxiapatita de cálcio: relato de uma técnica segura e minimamente invasiva

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#### ABSTRACT

**Introduction:** Progressive Facial Hemiatrophy, also known as Parry Romberg Syndrome, is a rare form of linear scleroderma. The management of facial atrophy sequelae is challenging.

**Objective:** This study aims to evaluate for the first time in literature the effectiveness of the calcium hydroxylapatite (CaHa) filler in the jawline reshaping of a patient with Parry Romberg Syndrome.

**Case report:** A 15-year-old woman with progressive atrophy of the right side of the face due to Parry Romberg Syndrome. After disease control, the patient's main complaint was facial asymmetry, mainly in the jawline region.

**Discussion:** CaHa is a biocompatible injectable filler that is gradually resorbed and replaced by fibrovascular stroma, mainly formed for new collagen, in a process that occurs without any immunological reaction. This safety profile makes CaHa a good choice for correcting stable scleroderma defects.

**Conclusion:** This report concludes that CaHa filler biocompatibility and suitability for the jawline correction are also applicable in reconstructive procedures for stable scleroderma, safely and minimally invasively, with optimal aesthetic results. The method must be programmed case-by-case, and a regular follow-up is also recommended.

Keywords: Scleroderma localized; Facial hemiatrophy; Dermal fillers

#### RESUMO

**Introdução:** a hemiatrofia facial progressiva, também conhecida como síndrome de Parry Romberg, é uma forma rara de esclerodermia, cujo manejo de sequelas é desafiador.

**Objetivo:** diante desse desafio, o objetivo deste estudo foi avaliar pela primeira vez na literatura a eficácia do preenchimento da hidroxiapatita de cálcio (CaHa) na reconstrução da mandíbula de um paciente com síndrome de Parry Romberg.

**Relato do caso:** paciente do sexo feminino, 15 anos, com atrofia progressiva do lado direito da face por síndrome de Parry Romberg. Após o controle da doença, a principal queixa da paciente era assimetria facial, principalmente na região mandibular.

**Discussão:** a CaHa é um preenchedor injetável biocompatível, que é gradualmente reabsorvido e substituído por estroma fibrovascular, formado principalmente por novo colágeno, em um processo que ocorre sem qualquer reação imunológica. Este perfil de segurança torna a CaHa uma boa escolha para a correção de sequelas de esclerodermia estável. **Conclusão:** este relato permite concluir que a biocompatibilidade do preenchimento de CaHa e a adequação para correção da mandíbula também são aplicáveis em procedimentos reconstrutivos para esclerodermia estável, de forma segura e minimamente invasiva, com ótimos resultados estéticos. O procedimento deve ser programado caso a caso, e um acompanhamento regular também é recomendado.

Palavras-chave: Esclerodermia localizada; Hemiatrofia facial; Preenchedores dérmicos

# **Case Report**

#### Authors:

Rossana Cantanhede Farias de Vasconcelos<sup>1</sup> Leonardo Navroski Durski<sup>1</sup> Artur Antonio Duarte<sup>1</sup>

<sup>1</sup> Universidade Santo Amaro, Dermatology, São Paulo (SP), Brazil.

#### **Correspondence:**

Leonardo Navroski Durski leonardo\_nd@hotmail.com

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Localized scleroderma belongs to the systemic sclerosis complex, a rare autoimmune disease. The extent of cutaneous involvement and extracutaneous manifestations characterize the specific subgroup. Two categories of scleroderma are known: systemic sclerosis, characterized by cutaneous sclerosis and visceral involvement, and localized scleroderma, classically confined to the skin and/or underlying tissues. A worldwide classification for localized scleroderma still does not exist; however, the most commonly used is the Mayo Clinic classification, which includes five groups: 1) plaque morphea, 2) generalized morphea, 3) bullous morphea, 4) linear scleroderma (including linear scleroderma "en coup de sabre" and progressive facial hemiatrophy or Parry Romberg syndrome), and 5) deep morphea.

Progressive facial hemiatrophy, also known as Parry Romberg syndrome, is a rare form of linear scleroderma that usually develops between the first and second decades of life with a slow and self-limiting progression. It is characterized by unilateral atrophy of the skin, subcutaneous tissue, muscles, and bone structures in the area of one or more branches of the trigeminal nerve. Treatment should be started before complications occur. Options are corticosteroids, methotrexate, cyclosporine, and interferon. However, the management of facial atrophy is challenging and must be decided on a case-by-case basis. Most patients benefit from fat grafting and reconstruction with flaps, but new techniques must be incorporated to improve the quality of life of these patients.<sup>1</sup>

The jaw contour plays an essential role in facial aesthetics. Many studies and techniques seek to improve this area, and calcium hydroxyapatite (CaHa), an injectable filler, appears as an ideal agent to restore the mandible due to its ability to provide immediate and prolonged improvement. In addition to its effectiveness, this agent draws attention to aesthetic and reconstructive procedures for its safety, proven in electron microscopy studies, which demonstrated collagen deposition around the CaHa microspheres with a minimal inflammatory response.<sup>2</sup>

This study aims to evaluate, for the first time in the literature, the effectiveness of CaHa filling in the remodeling of the mandible of a patient with Parry Romberg syndrome, considering the challenge of treating facial hemiatrophy and the availability of an effective and safe product.

#### **CASE REPORT**

A 15-year-old woman sought medical care due to progressive atrophy of the right side of the face. She had no history of febrile illness or trauma. Her medical history and family history were not significant. On examination, there was facial asymmetry, with atrophy of the skin and underlying tissues of the forehead and jawline, on the right side of the face. No neurological signs were present, and there were no other alterations in the systemic and skin examination.

The clinical diagnosis was Parry Romberg syndrome, with prompt initiation of corticosteroids and methotrexate. After less than two years, the patient had all medications discontinued and no sign of disease activity. After two more years of follow-up, at 19 years of age, the patient's main complaint was facial asymmetry, especially in the mandible and chin region (Figure 1).

A CaHa filler (CaHA; Radiesse, Merz Pharmaceuticals GmbH, Frankfurt, Germany) was chosen for the reconstruction procedure, considering the patient's biocompatibility and safety, and the author's experience. This filler comes in a 1.5 mL syringe, and a correction factor of 1:1 is used, with isotonic saline and 2% lidocaine as diluents. For areas where more projection was intended, such as the chin line, pre-jowl, and mandible,



**FIGURE 1:** Subdermal injection plan in atrophic skin



FIGURE 2: Before (left) and after (right) reconstruction of the lower third with calcium hydroxyapatite filling in a patient with Parry Romberg syndrome



#### FIGURE 3: Profile (left) and anterior view (right) at 90-day follow-up after lower third reconstruction with calcium hydroxyapatite fille

the amount of diluent was only 0.4 ml. A white marker delimited the treated area, and we injected it with a 22-gauge cannula positioned in the subdermal plane to correct the mandible. In the chin area, we addressed the submuscular and anteromuscular planes. The insertion points to treat the jawline were the pre-jowl sulcus and the mandibular; and for chin augmentation, the anterior submental area served as an insertion point. The total volume of filler used was 3.0 cc or two syringes. The distribution of the filler was performed according to the needs of each area, using a fan technique, with injections of 0.2 ml. The aesthetic result was immediate, and no adverse events occurred during or after the procedure, with a 90-day follow-up (Figure 2 and 3).

#### DISCUSSION

Parry Romberg syndrome is a rare disease, with an estimated prevalence of 1 in 700,000 people, affecting three times more women than men. The etiology is still unknown, but it is believed that there is autoimmune pathogenesis, possibly triggered by events such as trauma or viral infection, which activate lymphocytes and endothelial cells, followed by excessive collagen synthesis by fibroblasts. The initial treatment is based on immunosuppressants, in line with the autoimmune etiology. After stabilization, the remaining damage caused by cutaneous, fatty, and bone atrophy has a psychosocial impact on the patient and represents a therapeutic challenge for physicians.

In the last analysis of the literature, the most frequent procedure for correction of scleroderma defects was surgery (59%), with autologous fat grafting being the most used (50% of procedures), followed by flaps (24%). Looking for less invasive and painful alternatives, the literature provides reports of correction of facial defects in localized scleroderma with hyaluronic acid, polymethylmethacrylate, and poly-L-lactic acid.

A perfect agent for injection must be non-immunogenic, biocompatible, and stable at the implantation site. Thus, this case report aimed to describe for the first time in the literature the successful use of CaHa in the correction of sequelae of Parry Romberg syndrome.

CaHa is a biocompatible injectable filler composed of microspheres of 25-45 micrometers of CaHa suspended in a carboxymethylcellulose gel. CaHa microspheres have a smooth appearance and are identical in composition to the mineral substance of human bones and teeth. After implantation, the carrier gel is reabsorbed and gradually replaced by fibrovascular stroma, formed mainly by new and organized collagen, generating lasting volumization and improved quality, roughness, and skin pigmentation.

An experimental study using hematoxylin and eosin staining, special staining with picrosirius red (PSR), and immunohistochemistry (IHC) assessed the nature of the newly deposited collagen fibers. PSR and IHC staining confirmed the presence of type I collagen. On the other hand, type III collagen was found in much smaller amounts in the biopsy samples, consistent with its gradual replacement by type I collagen in the remodeling process.<sup>3</sup> In normal skin tissues, types I and III collagen are maintained in a relatively fixed ratio to each other, although there is an age-dependent increase in the ratio from type I collagen replaces gradually newly formed type III for optimal structural support and tensile strength.

Morphological evidence from a study using electron microscopy in tissues treated with CaHa filler suggests specific mechanisms involved in structural modifications, both in the filler microspheres and in the connective tissue cells. They demonstrate the absence of any immunological reaction and show that the filler used is very slowly modified over time by the action of connective tissue cells, without any phagocytosis activity.<sup>4</sup> This safety profile makes CaHa a good choice for the correction of stable scleroderma sequelae. Our report seeks to support its use and contribute to improving treatment options for these patients. In 2006, US Food and Drug Administration (FDA) approved injectable CaHa to correct signs of HIV-associated lipodystrophy and volumetric correction of soft tissue. In Europe, CaHa has approval for tissue augmentation, including treatment of nasolabial folds, marionette lines, and jaw contouring. The amount of filler injected varies depending on the location and extent of the restoration, but consensus recommendations guide both esthetic and reconstructive procedures. The consensus recommended a needle or cannula to correct the lower jawline. For cannulas the insertion points are at the mandibular angle or pre-jowl groove. The filler should be placed at the dermohypodermal junction or deep dermis using a fan technique.

In our experience, cannulas are safer, cause less trauma to atrophic skin, and allow a larger volume injection. The aesthetic result is immediate, and the adverse events are mild and transient, such as swelling and occasional bruising.

#### CONCLUSION

We conclude that the biocompatibility and technical adequacy of the CaHa filler, already known for the aesthetic correction of the mandible and chin, are also applicable in reconstructive procedures of stable scleroderma sequelae, in a safe and minimally invasive way, with excellent aesthetic results. The procedure should be scheduled on a case-by-case basis, and regular follow-up is also recommended.

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#### **AUTHORS' CONTRIBUTION:**

**Rossana Cantanhede Farias de Vasconcelos** D ORCID 0000-0002-6185-1840 Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Leonardo Navroski Durski 问 ORCID 0000-0002-1566-7372

Statistical analysis; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review; critical revision of the manuscript.

#### Artur Antonio Duarte D ORCID 0000-0003-0361-9776

Approval of the final version of the manuscript; study design and planning; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.



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# Harpoon nail: an unusual form of onychocryptosis

Unha em arpão: uma forma incomum de onicocriptose

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#### ABSTRACT

Onychocryptosis is a frequent nail disease, which most commonly affects the toes. It has some variants, including the little known "Harpoon Nail". The diagnosis is usually clinical, and the treatment is surgical, with different techniques described in the literature. We report the case of a 25-year-old man with a harpoon nail on the left hallux and the surgical method used for treatment with excellent results Keywords: Nail diseases; Nails ingrown; Hallux

#### RESUMO

A onicocriptose é uma doença ungueal frequente, que afeta mais comumente os pododáctilos e apresenta algumas variantes, dentre as quais a pouco conhecida "unha em arpão". O diagnóstico costuma ser clínico, e o tratamento cirúrgico emprega diferentes técnicas descritas na literatura. Relatamos o caso de um paciente masculino, 25 anos, com unha em arpão no hálux esquerdo, e a técnica cirúrgica utilizada para o tratamento com excelente resultado. **Palavras-chave:** Doenças da unha; Hallux; Unhas encravadas

## **Case report**

#### Authors:

Andréa Abê Pereira<sup>1,2</sup> Jéssica Lüders Bueno<sup>1,2</sup> Raquel Kupske<sup>1,2</sup> Leonardo Albarello<sup>2</sup> Renan Minotto<sup>2</sup>

- <sup>1</sup> Universidade Federal de Ciências da Saúde de Porto Alegre, Department of Dermatology, Porto Alegre (RS), Brazil.
- <sup>2</sup> Santa Casa de Misericórdia de Porto Alegre, Department of Dermatology, Porto Alegre (RS), Brazil.

#### **Correspondence:**

Andréa Abê Pereira andrea.abetm@gmail.com / E-mail alternativo: deiabah@yahoo.com. br

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The ingrown nail, also called onychocryptosis, results from a conflict between the nail plate and adjacent soft tissues, causing an inflammatory reaction that can lead to the appearance of granulation tissue and hypertrophy of nail folds.<sup>1</sup> It most commonly affects the hallux in its distal lateral portion.<sup>2,3</sup>

The literature describes some uncommon variants of onychocryptosis, such as the harpoon nail, where a sharp spike of the nail penetrates the periungual tissue forming a channel and emerging in the hyponychium. We report a case of this variant and its surgical treatment.

#### **CASE REPORT**

A 25-year-old man, student, sought medical care with a complaint of ingrown toenail of the left hallux for more than two years, accompanied by intermittent pain, more intense at the beginning of the condition. On physical examination, one of the lateral nail folds of the left hallux presented a marked increased volume, covering a good part of the nail plate and extending to the hyponychium. The end of the lateral nail fold had an erythematous papulo-nodular lesion covered by a small crust and surrounded by a keratotic collarette (Figure 1). In the contralateral fold, we identified a lesser degree of edema.

Due to the diagnosis of onychocryptosis in the two lateral nail folds and the formation of a harpoon nail in one of them, we referred the patient for surgery. We performed the resection of excess tissue from the lateral folds, which allowed the visualization of the sharp spike of the nail on the lateral portion of the nail plate (Figure 2). Then, we followed with the avulsion of a lateral nail strip and finished with chemical cauterization (phenol 88%) of the lateral segment of the nail matrix and the portion of the nail lateral folds (Figure 3). Healing occurred by secondary intention.

The patient evolved well in the postoperative period, with no signs of recurrence and a good aesthetic result after six months of progression (Figure 4).

#### DISCUSSION

Nail ingrown results from constant pressure from the nail plate on adjacent soft tissues,<sup>4</sup> leading to a local inflammatory process. It is a frequent condition, with a prevalence of 2.5–5%, more common in men in the third and fourth decades of life, but the literature has already described congenital cases and in the elderly.<sup>1</sup> It most frequently affects the distal lateral portion of the nails of the halluces.<sup>2,3</sup> It can present pain, erythema, ede-



**FIGURE 1:** Papulonodular, erythematous lesion covered by a small crust and surrounded by a keratotic collarette in the distal lateral portion of the left hallux



FIGURE 2: Sharp nail spike on the lateral portion of the nail plate of the left hallux



**FIGURE 3:** Immediate postoperative period, after avulsion of lateral bands of the nail plate of the left hallux and chemical cauterization (phenol 88%) of the lateral segment of the nail matrix and the bloody portion of the lateral nail folds



FIGURE 4: Result after six months of surgery

ma, secretion, and granulation tissue in the periungual tissues.<sup>2</sup> Several factors contribute to the onset and progression of the disease: incorrect nail cutting (too short or rounded), sharp curvature of the nail plate, wide and thick nail fold, hyperhidrosis, trauma, use of inappropriate footwear, tight socks, physical activities, and even obesity.<sup>1,3</sup>

Onychocryptosis can be classified according to different stages described by Heifetz, Mozena, and Martinez Nova, with some modifications among them. In general, in stage I, there is mild erythema and edema of the nail bed with pain on digital pressure, not exceeding the limits of the nail plate.<sup>3</sup> In stage II, pain, swelling, and erythema are more intense, and abscess formation may occur in the lateral nail fold, exceeding the nail plate limits (in phase IIa, the fold measures <3 mm; in phase IIb, the fold measures >3 mm). In stage III, there is chronic hypertrophy of the lateral nail fold and the presence of granulation tissue. In stage IV, there is a chronic deformity, affecting the nail plate, the lateral nail folds, and the distal nail fold.<sup>1,3</sup>

We report the case of an uncommon variant of onychocryptosis described for the first time by Richert, Caucanas, and Di Chiacchio (2014):<sup>4</sup> the harpoon nail. This name is due to its resemblance to a marine hunting instrument that has a sharp tip and a wide base, the harpoon.<sup>2</sup> It is a specific variant of distal lateral ingrowing. It occurs when the patient manipulates the side of the nail blade to relieve the pain of an ingrown nail in the nail fold but is unable to cut the most external and deepest part of the nail plate. Thus, the remaining lateral nail fragment grows and creates a nail spicule, which crosses the periungual tissue and forms a fistulous path, emerging in the hyponychium.<sup>2,4,5</sup> Its diagnosis is clinical<sup>1,5</sup> and can be aided by exams such as high-frequency ultrasound (HFUS), which will show the ingrowing in the lateral nail fold associated with the nail spicule.<sup>5</sup>

The harpoon nail treatment is surgical. If not performed, the condition may become chronic: the inflammation can disappear, and the canal containing the nail spicule can epithelialize.<sup>5</sup> The literature describes several surgical techniques, and the choice of any one of them depends on the stage and type of onychocryptosis and the surgeon's ability. The surgical approach that we used in this report was one of the most common techniques found in the literature. The procedure starts by opening the canal containing the nail spicule, removing the excess periungual tissue, then avulses the lateral nail band, and finishes by the chemical cauterization of the lateral spicule of the matrix with phenol 88%.<sup>2,4,6</sup> Alternatively, a wedge resection can be performed, containing the lateral nail fold with the nail spicule and its canal (Vandenbos procedure) or a Super U<sup>7</sup>, where all excess tissue is removed in a "U" shape.<sup>1</sup>

The harpoon nail is a little-known clinical variant of onychocryptosis that affects the individual's quality of life. Through an appropriate surgical approach, it is possible to achieve resolution of the condition with good aesthetic results and without recurrence •

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#### **AUTHORS' CONTRIBUTION:**

#### Andréa Abê Pereira D ORCID 0000-0001-7995-5050

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.

#### Jéssica Lüders Bueno D ORCID 0000-0002-3840-310X

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.

## Raquel Kupske D ORCID 0000-0003-3763-7366

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript

#### Leonardo Albarello D ORCID 0000-0002-8785-6885

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Renan Minotto D ORCID 0000-0002-1451-0461

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.



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# Role of Dermoscopy in Distinguishing *Tinea Nigra* from Acral Nevus

Papel da dermatoscopia na distinção entre tinea nigra e nevos melanocíticos acrais

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#### ABSTRACT

Dermoscopy is a practical, non-invasive tool that can be used to distinguish tinea nigra from other lesions that appear macroscopically similar, including acral nevus. Under dermoscopy, tinea nigra presents with a pattern of spiculated gray-brown pigment deposition, whereas acral nevus most often presents as brown pigment deposition in a parallel furrow pattern.

Keywords: Dermoscopy; Nevus; Tinea

#### RESUMO

A dermatoscopia é uma ferramenta prática e não invasiva que pode ser usada para distinguir a tinea nigra de outras lesões que parecem macroscopicamente semelhantes, incluindo o nevo melanocítico acral. Sob a dermatoscopia, a tinea nigra se apresenta com um padrão de deposição de pigmento marrom-acinzentado espiculado, enquanto o nevo melanocítico acral geralmente se apresenta como deposição de pigmento marrom em um padrão de sulco paralelo. **Palavras-chave:** Dermatoscopia; Nevo; Tinea

# **Case report**

Authors: Betty Nguyen<sup>1</sup> Antonella Tosti<sup>2</sup>

- <sup>1</sup> University of California Riverside School of Medicine, Riverside (CA), USA
- <sup>2</sup> University of Miami, Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, Miami (FL), USA

#### Correspondence:

Antonella Tosti atosti@med.miami.edu / E-mail alternativo: betty.nguyen@meds ch.ucr.edu

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Tinea nigra is an uncommon superficial mycosis of the stratum corneum caused by Hortaea werneckii, an ascomycetous yeast thought found primarily in soil, compost, and wood in (sub)tropical regions. It is characterized by the insidious onset of an asymptomatic brown-to-black macule with discrete borders. The lesions are usually unilateral and solitary, though multiple lesions can also be present. Tinea nigra preferentially affects the palmar surfaces of the hands and plantar surfaces of the feet, though they can occasionally extend to the fingers and toes. Spontaneous resolution of lesions is unlikely but has been reported.<sup>1</sup> Topical antifungal agents generally resolve tinea nigra within 2-4 weeks.<sup>2</sup>

#### **CASE PRESENTATIONS**

A 14-year-old man with no significant family or medical history presented to the clinic with a brown lesion on his left palm for "years." He reported no pain or discomfort. The patient was born in Cuba and moved to the United States when he was 8. He denied significant travel history. The physical exam showed a visible macular lesion with sharp borders on the left palm in the hypothenar region (Figure 1A) and a smaller adjacent macular lesion on the left 5th digit (Figure 1B). Dermoscopy of the hypothenar lesion revealed deposition of regular gray-brown spicules (Figure 2A). Also, dermoscopy of the adjacent 5th digit lesion showed brown pigment deposition predominantly in the linear furrows consistent with acral nevus (Figure 2B). Potassium



FIGURE 1: Macroscopic appearance of a well-demarcated macular lesion (A) on the hypothenar region of the left palm and an adjacent acral nevus (B) on the left 5th digit



**FIGURE 2:** Videoscopic image of macular lesion showing deposition of gray-brown spicules on the hypothenar region of the left palm consistent with *tinea nigra* (**A**) and an adjacent acral nevus with brown pigment deposition in the epidermal ridges in a parallel furrow pattern on the left 5th digit (**B**).

hydroxide (KOH) preparation from skin scrapings of the left palmar lesion showed branched brown hyphae with light brown septa. The subsequent polymerase chain reaction was positive for Hortaea werneckii. We observed mild acanthosis and hyperkeratosis on hematoxylin and eosin (H&E) stain (Figure 3A), and periodic acid-Schiff (PAS)-positive septate hyphae within the stratum corneum, consistent with *tinea nigra* (Figure 3B).

A 43-year-old man with no significant family or medical history presented to the clinic with a brown macular lesion on the sole of his left foot, as well as a smaller brown macular lesion on the sole of his right foot (Figure 4A-B). He reported no pain or discomfort. The physical exam was otherwise unremarkable. The patient was born in the United States and denied relevant travel history. Dermoscopy of the left foot lesion revealed a pattern of spiculated gray-brown pigment deposition suggestive of tinea nigra (Figure 5A), confirmed on biopsy. Also, dermoscopy of the smaller brown lesion on the right foot showed pigment deposited predominantly within the furrows suggestive of acral nevus (Figure 5B).



**FIGURE 3:** Hematoxylin and eosin (H&E) stain of left palmer macular lesion showing mild acanthosis and hyperkeratosis (40x) (**A**), and periodic acid-Schiff (PAS) stain showing PAS-positive septate hyphae within the stratum corneum (10x) (**B**), (40x) (**C**) consistent with tinea nigra.



FIGURE 4: Macroscopic appearance of two brown macular lesions on the sole of the left foot (A) and a similar smaller brown lesion on the sole of the right foot (B).



**FIGURE 5:** Dermoscopy of brown macular lesion on left foot showing a pattern of spiculated gray-brown pigment deposition consistent with tinea nigra **(A)** and smaller brown lesion on right foot showing pigment deposited preferentially within the furrows consistent with acral nevus **(B)** 

#### CONCLUSION

Given the macroscopic appearance and distribution of its lesions, tinea nigra can resemble many other conditions, including acral nevi<sup>3</sup> and acral lentiginous melanoma<sup>4</sup>. Prompt and accurate recognition of tinea nigra is required to minimize unneeded invasive diagnostic testing, such as surgical excision. Dermoscopy can provide a quick, non-invasive, and accurate diagnosis. The dermoscopic hallmark of tinea nigra is the presence of gray-brown or light brown spiculated pigments distributed throughout the skin without preference for ridges or furrows.<sup>5,6</sup> In contrast, dermoscopy of acral nevi most often reveals unevenly distributed brown pigment in a parallel furrow pattern.<sup>7</sup> One study of 50 cases found that the presumptive diagnosis of tinea nigra was made in 7/13 (53%) of cases when dermoscopy was used, as compared to 0/37 (0%) of cases that did not use this method (P<0.001).6 Recent case reports<sup>8-10</sup> have confirmed the similar diagnostic utility of dermoscopy in tinea nigra. Our two cases reiterate the importance of dermoscopy in the clinical evaluation of these lesions to ensure prompt diagnosis and treatment initiation while minimizing the need for invasive testing.

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#### AUTHORS' CONTRIBUTION:

#### Betty Nguyen (D ORCID 0000-0002-0402-3926

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### **Antonella Tosti** D ORCID 0000-0001-5516-4043

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.



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# Attagenus larva in the sinus cavity in a patient with complications after the use of hyaluronic acid filler

Larva de Attagenus na cavidade nasal em um paciente com complicações após o uso de preenchimento de ácido hialurônico

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#### ABSTRACT

A wide range of dermal fillers is now available for use in the beauty industry. We present a case of a 33-year-old woman with complications after hyaluronic acid injection by a non-medical practitioner. Two weeks after the injection, bilateral sinus pain, fever, and burning sensation occurred in the cheek area. She underwent a detailed diagnosis revealing *Attagenus* larva in the paranasal sinus. Despite treatment, the symptoms remained. Thus, hyaluronidase was administered in the infraorbital area, obtaining a full remission.

Keywords: Hyaluronic acid; Nasal cavity; Dermatology; Larva; Dermal fillers.

#### RESUMO

Uma ampla variedade de preenchimentos dérmicos está agora disponível para uso na indústria da beleza. Apresentamos o caso de uma mulher de 33 anos com complicações após injeção de ácido hialurônico por um não médico. Duas semanas após a injeção, dor nos seios da face bilateral, febre e sensação de queimação ocorreram na área da bochecha. Ela foi submetida a um diagnóstico detalhado revelando larva de Attagenus nos seios paranasais. Apesar do tratamento, os sintomas continuaram presentes, sendo administrada hialuronidase na região infraorbital com remissão completa. **Palavras-chave:** Ácido Hialurônico; Cavidade nasal; Dermatologia; Larva; Preenchedores dérmicos.

## **Case report**

#### Authors:

Zuzanna Swierczewska<sup>1</sup> Wioletta Baranska-Rybak<sup>1</sup>

Medical University of Gdansk, Department of Dermatology, Venereology and Allergology, Gdansk - Pomeranian Voivodeship, Poland

#### Correspondence:

Wioletta Baranska-Rybak Email: wioletta.baranska-rybak@ gumed.edu.pl

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СС ВҮ

Dermal fillers injection is one of the most common procedures in aesthetic medicine practice. According to Aesthetic Plastic Surgery Statistics from 2020, it is among the top two most popular non-surgical procedures, right after injection of neurotoxins.

Although facial filler treatments with hyaluronic acid (HA) are reasoned as minimally invasive, they are not free from complications. The most frequent non-vascular adverse events of hyaluronic acid administration include swelling, granulomas, and infections. However, ischemia, necrosis, and blindness are considered the most common vascular complications. Injections with hyaluronidase are indicated as the treatment of choice in dealing with complications after the use of HA fillers.<sup>1</sup>

We present a case of a patient with nasal infestation with *Attagenus* larva discovered during the diagnosis.

#### **CASE REPORT**

A 33-year-old woman was admitted in March 2021 due to exacerbation of persistent pain in the right infraorbital area starting four days before the hospitalization. At admission, the patient presented no concomitant edema, but a periodic burning sensation. Physical examination revealed soft skin with even consistency and no inflammation and no tissue resistance.

Detailed anamnesis revealed a history of rheumatoid arthritis, in remission for four years, as well as hypothyroidism. Also, the patient reported two episodes of acute urticaria of unknown etiology requiring ER intervention several years ago. Numerous cosmetic procedures were performed in the past.

In August 2020, a beautician performed a procedure to fill the cheeks and the tear trough with hyaluronic acid of unknown origin, 1 ml per side. Two weeks after the injection, the patient reported bilateral sinus pain, fever, and burning sensation in the cheek area. Therefore, amoxicillin with clavulanic acid was administered but without effect.

Due to lack of clinical improvement, a month later clindamycin 600 mg twice daily was included for a week. Also, nasal irrigation was performed by the ENT specialist, rinsing out the larva that was identified as *Attagenus* larva (Figure 1) in The Institute of Maritime and Tropical Medicine in Gdynia, Poland.

The patient was assessed with computed tomography (CT) scan twice over five months. The first CT scan revealed no visible foreign body in the sinus cavity, circular thickening of the mucous membranes in the maxillary sinuses suggestive of an inflammatory process, bilateral obstruction of the maxillary sinus ostia, and deviated nasal septum to the right side. The second CT scan showed only trace mucosal changes in the right maxillary sinus and no inflammation in the remaining paranasal sinuses.

During the appointment in March 2021, we implemented methylprednisolone 16 mg/day, azithromycin 500mg/day, and bilastine 20 mg twice daily. At the three-week follow-up visit, the patient admitted pain reduction; nonetheless, paresthesia was still inherent. Given these facts, hyaluronidase in the total dose of 30 IU was administered in the area of the right tear trough. Methylprednisolone was reduced to 12 mg daily.

Seven days after the hyaluronidase administration, we observed full remission of pain and paresthesia. Further reduction of methylprednisolone was applied, this time to 4 mg every seven days.

#### DISCUSSION

Due to the growing popularity of aesthetic medicine and its profitability, many other practitioners with minimal or no training and medical background have ventured into the aesthetic industry.<sup>2</sup> It is estimated that complications after treatments in aesthetic medicine occur relatively more often in patients treated by practitioners from outside the medical area.<sup>2,3,4</sup> Lack of appropriate professional qualification, incorrect injection technique, and absence of asepsis may lead to serious complications.

Regarding the facial aesthetic procedures, collecting a profound history of allergies, systemic diseases, current treatment, and previous procedures is mandatory.<sup>5</sup> Filler treatments are contraindicated in active autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and Hashimoto's disease. Our patient report is an example of how dermal filler treatments may be contraindicated, particularly due to a history of rheumatoid arthritis, and should undoubtedly be consulted with an experienced physician. Thus, we want to emphasize the necessity to perform aesthetic medicine treatments by trained doctors. Complementary measures by law enforcement and the communities themselves may help decrease the supply of illegal cosmetic procedures.<sup>3,4</sup>



FIGURE 1: Attagenus larva rinsed out of the nasal cavity

Direct trauma to the nerve, straight injection of filler into the nerve, or product compression can emerge into unintentional nerve injury, an uncommon complication of dermal filler procedures. Nerve injury is divided into reversible or permanent. The most frequent localization of paresthesia and anesthesia is the infraorbital nerve.<sup>6</sup> Presented patient's main symptoms, pain and paresthesia, must probably have resulted from compression of the infraorbital nerve caused by the dermal filler. Complete reduction of symptoms after the hyaluronidase administration supports this hypothesis.

Hyaluronidase is an enzyme that breaks down hyaluronic acid, and the Food and Drug Administration (FDA) has approved its off-label use in cosmetic medicine.<sup>1</sup> With the increasing popularity of hyaluronic acid fillers, hyaluronidase has become an essential tool for correcting complications and unsatisfactory outcomes following filler injection. For this reason, adequate knowledge of hyaluronidase is needed when conducting procedures involving hyaluronic acid filler. No major randomized trials are available on its use in aesthetic medicine, so the only information accessible is focused on a literature review and the authors' practical recommendations. Since different HA formulations exhibit different susceptibility to degradation after hyaluronidase administration, there are no defined recommendations for hyaluronidase dosage in overcorrection.

The authors have found only a few reports discussing the infestation on the nasal cavity.<sup>7,8</sup> Typically, it can occur in tropical and developing countries. Our patient was an accidental *Attagenus* larva host and probably became infested while on vacation in Masuria, Poland, in August 2020. To our knowledge, this is the first case report of infestation of the sinus cavity with *Attagenus* larva in humans. In conclusion, an infestation of the nasal cavity is a rare occurrence that often causes a mild selflimited illness. Nonetheless, it can pose a diagnostic challenge to physicians unaware of this condition. Furthermore, the lack of data on consensus treatment will make managing these cases more challenging.<sup>8</sup>

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#### **AUTHORS' CONTRIBUTION:**

**Zuzanna Swierczewska<sup>1</sup>** ORCID 0000-0003-3555-3070 Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review.

#### Wioletta Baranska-Rybak<sup>1</sup> D ORCID 0000-0002-4018-6706

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical revision of the manuscript.



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# Clinically ulcerated and granulomatous pilomatricoma in a cutaneous vaccination site: case report

Pilomatricoma granulomatoso e ulcerado em sítio cutâneo de vacinação: relato de caso

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#### ABSTRACT

Pilomatricoma is a benign skin tumor derived from the hair follicle. It has a varied etiology, and the traumatic one is often described as a triggering factor. The surgical treatment is curative and, therefore, the choice. We report a case of an atypical clinical presentation pilomatricoma – an ulcerated nodule topped by a central hematic crust, with peripheral telangiectasias probably triggered by the HPV vaccination. The ultrasound examination suggested the possibility of a chronic inflammatory granuloma, although the histopathological examination was definitive and confirmed the diagnosis of pilomatricoma. **Keywords:** Papillomavirus vaccines; Hair follicle; Ultrasonography, Doppler; Skin neoplasms

#### RESUMO

Pilomatricoma é um tumor cutâneo benigno derivado do folículo piloso que pode se desenvolver secundariamente a um trauma local. O tratamento cirúrgico é curativo e, portanto, é o de escolha. Relatamos o caso de um pilomatricoma de apresentação clínica atípica, como um nódulo ulcerado encimado por crosta hemática central, com telangiectasias periféricas desencadeado, muito provavelmente, pela aplicação da vacina de HPV. O exame ultrassonográfico sugeriu um possível granuloma inflamatório crônico, porém o exame histopatológico foi definitivo e confirmou o diagnóstico em questão. **Palavras-chave:** Vacinas contra papillomavirus; Folículo piloso; Ultrassonografia doppler; Neoplasias cutâneas

## **Case report**

#### Authors:

Rodrigo Scabora<sup>1</sup> João Gabriel Rodrigues Alberti<sup>1</sup> Carolina Scaff Haddad Bartos<sup>2</sup> Lucia Mioko Ito<sup>1</sup> Ayrton Roberto Pastore<sup>1</sup> Deborah Krutman Zveibil<sup>3</sup>

- <sup>1</sup> Health University Center of ABC, Department of Dermatology, Santo André (SP), Brazil.
- <sup>2</sup> Santa Casa de Misericórdia de São Paulo, Department of Dermatology, São Paulo (SP), Brazil.
- <sup>3</sup> Health University Center of the ABC, Department of Pathology, Santo André (SP), Brazil.

#### Correspondence:

Rodrigo Scabora Email: rodrigo.scb@hotmail.com / Alternative email: r.scb@hotmail. com

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Pilomatricoma represents about 1% of benign skin tumors and derives from the hair follicle matrix. They are solitary tumors, usually painless and well-delimited. Clinically, it is associated with many differential diagnoses, and complementary tests are necessary for diagnostic confirmation.<sup>1</sup> Ultrasonography (USG) of the skin and soft tissues can be helpful, but confirmation requires an anatomopathological examination. The pathogenesis is still poorly understood, but the appearance of the lesion is often associated with local trauma. Nonetheless, its association with vaccination, and the atypical, ulcerated, with extrusion of material through the center of the lesion, is infrequent, with rare cases reported.

#### **CASE REPORT**

An 11-year-old female patient, sought medical assistance due to a complaint of a wound in her right arm for more than a year. The lesion appeared one month after the HPV vaccination at the injection site. She reported that the lesion progressively evolved with an increase in diameter and sporadic drainage of purulent secretion and nonspecific material through its central portion. The patient received several treatments - topical (association of neomycin and bacitracin, ketoconazole, betamethasone, and collagenase) and systemic (azithromycin and cephalexin) - with no resolution. On clinical examination, she presented an erythematous nodule measuring 1.5 cm in diameter, with firm consistency, ulceration, and central serohematic crust, painless on superficial palpation but painful on deep palpation. The lesion had some peripheral telangiectasia and a small and discrete superficial bluish area, (Figure 1). The hypothesis of pyogenic granuloma was raised, and skin and soft tissue USG with Doppler were requested for further diagnostic investigation. The examination revealed the presence of a solid nodule, predominantly hypoechogenic, heterogeneous, and with regular contours, affecting the epidermis, dermis, and hypodermis (Figure 2). Color Doppler showed marked peripheral vascularization in the shape of a ring and inside the nodule. The diagnostic impression was of possible chronic granulomatous disease. We performed a ellipticall excision. The anatomopathological examination showed the presence of basaloid cells, ghost cells, and multinucleated giant cells, as well as epidermal ulceration with cell extrusion, compatible with the diagnosis of ulcerated pilomatricoma associated with a chronic granulomatous inflammatory process (Figure 3). The patient evolved with complete resolution of the condition after surgery.

#### DISCUSSION

Pilomatricoma, or calcifying epithelioma of Malherbe, is a rare benign tumor of the hair follicle matrix. It is usually located in the head and neck region and presents as a firm, solitary, well-defined, slow-growing dermal or subcutaneous mass.

Epidermal ulceration may accompany the clinical presentation of the lesion.<sup>2,3,4</sup> Different clinical forms of pilomatri-



**FIGURE 1:** Erythematous, firm nodule with serohematic crust and tiny central bluish macula

coma are described, such as anetodermic, proliferating, pigmented, familial, and perforating.<sup>2,4</sup> The latter presentation can be considered in the atypical case reported, both from the clinical and histological perspectives.

The tumor is frequent in the first and second decades of life, and its pathogenesis is uncertain. Mutations in the Wnt signaling pathway and genetic syndromes may be associated: the relationship with Turner syndrome and myotonic dystrophy is more common, but the association with Gardner syndrome,



**FIGURE 2:** Doppler US with solid and regular nodule and ring peripheral vascularization

MUTYH-associated polyposis (MAP), Rubinstein-Taybi syndrome, Sotos syndrome, and gliomatosis cerebri may also occur.<sup>2</sup> Previous events, such as vaccination, rarely induce the appearance of pilomatricoma. Long-term inflammation, delayed healing response, and the antigens used in the vaccine are possibly linked to the uncertain pathogenesis of this disease.<sup>3</sup>

Although described since 1880, these tumors are often underdiagnosed.<sup>2</sup> The variety of differential diagnoses includes dermoid or epidermoid cysts, calcified lymph nodes or hematomas, hemangiomas, and parotid gland tumors.<sup>3</sup> Combined with its low prevalence, which varies from 0.001% to 0.0031%, the suspected lesion can lead to diagnostic and therapeutic errors.<sup>2</sup> Studies indicate that preoperative diagnosis was correct in 30% to 50% of cases.<sup>7</sup>

The typical clinical presentation of pilomatricoma cor-

responds to a firm erythematous nodule with a smooth surface in a hairy region, sometimes accompanied by a tiny bluish surface area. Histologically, the presence of basaloid cells and "ghost cells" is observed, associated or not with a granulomatous response and local calcification, which varies according to the evolutionary stage of the tumor.<sup>2,3,5</sup> However, the presence of ulceration with the elimination of material through the lesion, combined with the histological presence of epidermal ulceration with extrusion of eosinophilic tumor cells, may configure a rare, atypical, and infrequent form of pilomatricoma, called perforating pilomatricoma, as considered in this case.<sup>4</sup>

Color Doppler ultrasound helps diagnose nodular skin lesions as it shows the tumor's position, depth, and degree of calcification. It is an accessible and non-invasive tool capable of increasing the diagnostic accuracy of several dermatoses, deter-



FIGURE 3: A - Basaloid proliferation, ghost cells, and multinucleated giant cells (Hematoxylin & eosin, 40x and 100x);
B - Ulceration with hemorrhage (Hematoxylin & eosin, 100x);
C - Cell extrusion (Hematoxylin & eosin, 100x);
D - Ulceration and pyogenic granuloma-like granulation tissue (Hematoxylin & Eosin, 100x)

mining the degree of local vascularization, and delimiting the tissue planes affected by the lesion. This exam allows for better surgical planning and preparation for the possibility of intraoperative hemorrhage. The sonographic findings regarding pilomatricoma correspond to ovoid, well-defined, hypoechoic masses with internal hyperechoic foci and peripheral hypoechoic edges. Completely echogenic masses with posterior acoustic shadowing in the subcutaneous tissue are observed.<sup>2,5,6</sup> The blood flow distribution pattern visualized on color doppler helped differentiate pilomatricoma from hemangiomas and other vascular malformations.<sup>2</sup>

To date, there are five published cases of post-vaccination pilomatricoma on MEDLINE (PubMed). However, there is no case published in this database of perforating pilomatricoma after the application of vaccines, nor even pilomatricoma occurring after HPV vaccination, which are unique and pioneering characteristics of this case report.

Given the low prevalence and similarity of pilomatricoma to other skin pathologies, clinical and histological examinations, associated with Doppler ultrasound, are extremely important in aiding diagnosis and therapeutic management, especially concerning surgical planning of a highly vascularized lesion. Pilomatricoma should be included as a differential diagnosis in chronic nodular lesions developed at sites of trauma, such as vaccination.

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#### **AUTHOR'S CONTRIBUTION:**

#### Rodrigo Scabora (D) ORCID 0000-0002-3153-3980

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### João Gabriel Rodrigues Alberti D ORCID 0000-0001-6495-8419

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Carolina Scaff Haddad Bartos D ORCID 0000-0001-7601-2946

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Lucia Mioko Ito D ORCID 0000-0001-9899-3036

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Ayrton Roberto Pastore D ORCID 0000-0002-6607-0488

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Deborah Krutman Zveibil D ORCID 0000-0002-3252-6192

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.



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# Q-Switched Laser for the treatment of mucocutaneous pigmentation on Peutz-Jeghers Syndrome

Laser Q-Switched para o tratamento da melanose labial na síndrome de Peutz-Jeghers

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#### ABSTRACT

Peutz-Jeghers syndrome (PJS) is a rare, autosomal dominant disease where there is a mutation in the tumor suppressor gene, with a greater predisposition to neoplasms, especially of the gastrointestinal tract. The first manifestations begin during childhood with the presence of mucocutaneous melanosis and, later, gastrointestinal hamartomatous polyps. We describe a case of a young woman whose initial PJS manifestation started during her childhood with cutaneous melanosis. Three sessions with the Q-switched 1064nm Nd:YAG and 532nm KTP lasers were performed to treat the melanosis with excellent results and without recurrence.

Keywords: Lasers; Lentigo; Peutz-Jeghers syndrome

#### RESUMO

A síndrome de Peutz-Jeghers (SPJ) é uma doença autossômica dominante, rara, em que há mutação no gene supressor tumoral, havendo maior predisposição para neoplasias, principalmente do trato gastrointestinal. As primeiras manifestações iniciam-se na infância com a presença de melanose mucocutânea e, posteriormente, surgem os pólipos hamartomatosos gastrointestinais. Apresentaremos o caso de uma paciente feminina, jovem, cujas manifestações iniciais da SPJ iniciaram-se na infância sob a forma de melanose cutânea. O tratamento dessas lesões foi realizado em três sessões com os lasers Nd:YAG Q-Switched 1064nm e KTP Q-Switched 532nm, evoluindo com excelente resposta terapêutica e sem recidiva.

Palavras-chave: Lasers; Lentigo; Síndrome de Peutz-Jeghers

# **Case report**

#### Authors:

Abdo Salomão Junior<sup>1</sup> Constança Pithon Pereira<sup>2</sup> Rodrigo Cesar Davanco<sup>3</sup> Daniella Grande Curi<sup>3</sup> Domingos Jordão Neto<sup>3</sup>

- <sup>1</sup> Life Medical Hospital, Guaxupé ( MG), Brazil.
- <sup>2</sup> Clínica Dermatológica Constança Pithon, Salvador (BA), Brazil.
- <sup>3</sup> Hospital Heliópolis, São Paulo (SP), Brazil.

#### Correspondence:

Rodrigo Cesar Davanco rodrigodavanco@gmail.com

**Financial support:** None. **Conflict of interest:** None.

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Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder clinically expressed by mucocutaneous melanosis and intestinal polyposis. It is a rare disease, with an estimated 1:8,000 to 1:200,000 births. The skin lesions are composed of multiple pigmented macules distributed in perioral, lip vermilion, buccal mucosa, palate, tongue, palms, soles, and perianal region. These lesions may fade after adolescence or adulthood. Several therapeutic modalities have been proposed to treat skin lesions but without effect. The exception is the Q-Switched laser, which is effective and presents no scarring or recurrence.

#### **CASE REPORT**

A 27-year-old woman sought medical care due to a complaint of spots on her lips. She mentioned that the spots appeared before the first year of life, and, at the age of two, they were diagnosed with Peutz-Jeghers syndrome. She had no other associated diseases and was using only oral contraceptives. No history with other family members. Control colonoscopy and upper digestive endoscopy were performed, requiring polypectomy during these procedures, and enterectomy in 2016.

We proposed therapy with the 1064nm Q-Switched Nd:YAG and Q-Switched KTP lasers 532nm (New Vektra, Solon Platform, LMG, Guaxupé, MG, Brazil). The first session was performed in June 2019 (Figure 1) and the others with intervals every 30 days (Figures 2 and 3). Table 1 describes the parameters.

The patient evolved well, without intercurrences, and did not experience a recurrence in the follow-up two years after the last session.

#### DISCUSSION

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disease associated with a mutation in the STK11 gene, located on chromosome 19p13.3, responsible for tumor suppression. <sup>123</sup> This mutation has been documented in 70-80% of patients, and up to 15% present partial or complete deletion.<sup>1</sup> Individuals with this syndrome are more predisposed to gastrointestinal neoplasms and, more rarely, breast, testicles, uterus, and ovaries cancer.<sup>3,4,5</sup>



**FIGURE 1:** Multiple hyperchromic macules on the upper and lower lips (first laser session and treatment start)

Table 1: Parameters for the treatment of lip melanosis				
Session	Filter (nm)	Spot (mm)	DP (ns)	Fluency (J/cm <sup>2</sup> )
1	1064 (dark lesions)	4	5	6
	532 (light lesions)	4	2	2
2	1064	2	5	19
	532	4	2	3
3	1064	2	5	19
	532	4	2	3

nm: nanometer; mm: millimeter; ns: nanoseconds



**FIGURE 2:** Attenuation in the staining of labial macules after the second laser session (30 days after the treatment start)



FIGURE 3: Significant reduction in the number of labial macules after the third laser session (60 days after the treatment start)

Clinically, it is characterized by hamartomatous polyps of the gastrointestinal tract, mainly in the jejunum, and mucocutaneous melanosis.1,5 Its onset is in childhood or early adolescence, while gastrointestinal changes appear in adolescence or adulthood.<sup>1</sup> The presence of multiple macules pigmented in the labial and perioral region suggests PJS, but is not pathognomonic, as they are also observed in Laugier-Hunziker syndrome (LHS).<sup>1,3</sup> Histologically, the analysis of mucocutaneous lentigines suggests an increase in melanin granules in the epidermis, without melanocyte proliferation,<sup>2,3</sup> and it is an excellent target for pulsed lasers that have melanin as a chromophore.<sup>2,3</sup>

The protocol for the management of intestinal polyps and the screening for neoplasms in PJS is already well established. Nevertheless, it is not for facial lentigos, which have there is no standard treatment.<sup>2,6</sup> Several therapeutic modalities are used, such as dermabrasion, cryosurgery, surgical excision, electrodissection, or carbon dioxide or argon laser ablation. However, they present incomplete removal of the lesion, scarring, or change in skin pigmentation.<sup>2,4,5</sup>

The most commonly used lasers to treat pigmented lesions have ultrashort or Q-switched pulses (QS Alexandrite; QS ruby laser; QS Dye laser, and QS Nd: YAG), damaging the endogenous chromophores without harming adjacent collagen.<sup>4,7,8</sup> Given the histology of skin lesions associated with PJS, these types of laser have been preferred as a therapeutic option, showing resolution of the lesions, absence of residual scars, and

preventing the recurrence of pigmented lesions.<sup>1</sup> For individuals with skin phototypes III and IV, QS Alexandrite and QS Nd:YAG are preferred over QS ruby, as this can cause residual hyperpigmentation.<sup>1</sup>

Few data are available in the literature regarding the use of QS Nd:YAG to treat lentiginous lesions in this syndrome. A retrospective study by Yiping Ge *et al.* demonstrated the effectiveness of this laser in the treatment of skin lesions associated with PJS, presenting excellent results with total remission with an average of 2.9 sessions and without recurrence after a follow-up of 12 to 97 months.<sup>1</sup> All patients were treated with the Q-switched Nd:YAG 532 nm laser, fluences of 1.8–2.2J/cm<sup>2</sup>, a spot of 3 mm, and pulse amplitude of 5–20 ns.<sup>1</sup>

We found similar results using two wavelengths in the same session to enhance the result: 1064 nm for dark brown lesions and 532 nm for light brown lesions.

We present this case report to demonstrate that the Nd-YAG laser is effective and safe in treating mucocutaneous lesions in PJS, constituting a good therapeutic option.

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#### AUTHORS' CONTRIBUTION:

Abdo Salomão Junior (D ORCID 0000-0002-5591-0293

Statistical analysis; approval of the final version of the manuscript; study design and planning; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.

#### Constança Pithon Pereira D ORCID 0000-0002-3751-8984

Statistical analysis; approval of the final version of the manuscript; study design and planning; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Rodrigo Cesar Davanco D ORCID 0000-0002-2254-8400

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Daniella Grande Curi D ORCID 0000-0002-3179-0485

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### **Domingos Jordão Neto D ORCID** 0000-0001-7752-6789

Approval of the final version of the manuscript; study design and planning; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.



# Surgical & Cosmetic Dermatology

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# Exclusive surgical treatment of a primary cutaneous marginal zone lymphoma: a case report

Tratamento cirúrgico exclusivo de linfoma B primário cutâneo da zona marginal: relato de caso

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.20221400120

#### ABSTRACT

Primary cutaneous B-cell lymphomas are non-Hodgkin lymphomas presenting only in the skin and represent 25% of all primary cutaneous lymphomas. Based on their clinical behavior, they are classified into indolent and intermediate forms. Treatment of indolent forms includes surgery, radiotherapy, and, in extensive disease, rituximab. We report a case of a 57-year-old woman with a single nodule in the left arm treated with surgical excision with 5-mm security margins, without relapse after 36 months. Surgery is a therapeutic option in these lymphomas without compromising disease-free survival.

Keywords: Lymphoma B-Cell; Lymphoma B-Cell marginal zone; Lymphoma non-Hodgkin; Surgical oncology

#### RESUMO

Os linfomas B primários cutâneos (LBPCs) são linfomas não Hodgkin, de acometimento exclusivamente cutâneo, e representam 25% dos linfomas primários cutâneos. São divididos, conforme comportamento clínico, em indolentes e intermediários. O tratamento das formas indolentes inclui a cirurgia, a radioterapia e, em casos extensos, o rituximabe. Relata-se o caso de mulher de 57 anos, com placa única no braço esquerdo, com diagnóstico de LBPC da zona marginal, tratado com excisão com margens de segurança de 5mm, sem recidiva após 36 meses de seguimento. A cirurgia é uma alternativa terapêutica com bom resultado clínico, sem impacto na sobrevida livre da doença.

**Palavras-chave:** Linfoma de células B; Linfoma de zona marginal tipo células B; Linfoma não-Hodgkin; Oncologia cirúrgica

## **Case report**

#### Authors:

Elisa Nunes Secamilli<sup>1</sup> Juliana Yumi Massuda-Serrano<sup>1</sup> Rafael Fantelli Stelini<sup>2</sup> Thais Helena Buffo<sup>1</sup> Paulo Eduardo Neves Ferreira Velho<sup>1</sup>

- <sup>1</sup> Universidade Estadual de Campinas, Dermatology, Campinas (SP), Brazil.
- <sup>2</sup> Universidade Estadual de Campinas, Department of Pathological Anatomy, Campinas (SP), Brazil.

#### Correspondence: Elisa Nunes Secamilli elisans42@gmail.com

Financial support: None. Conflict of interest: None.

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СС ВҮ

Primary cutaneous B-cell lymphomas (PCBCL) are B-cell non-Hodgkin lymphomas that affect the skin exclusively, with no evidence of systemic involvement in the initial evaluation. They represent approximately 25% of primary cutaneous lymphomas, with an incidence of four cases per million people, and they are more frequent in men and after 50 years of age.<sup>1</sup> They are divided into two main clinical groups through their morphological and immunophenotypic analysis: marginal zone and centrofollicular, considered to have indolent clinical behavior; and primary cutaneous large B-cell lymphoma, leg type, and primary cutaneous intravascular large B-cell lymphoma, regarded as presenting intermediate clinical behavior.<sup>2</sup>

There are no randomized trials to treat indolent primary cutaneous B-cell lymphomas (PCBCLs). The treatment is indicated based on case series and consensus from the World Health Organization (WHO) and the European Organization for Research and Treatment of Cancer (EORTC). Low-dose radiotherapy, surgery, or intralesional infiltration of corticosteroids or rituximab are the therapy of choice for localized disease. Clinical follow-up, multi-field radiotherapy, or rituximab may be indicated in patients with multiple lesions.<sup>1</sup> Surgical treatment still does not have well-established protocols, and it is not possible to know the ideal surgical security margin or whether or not the size of the margin influences the recurrence of lesions.

We report the case of a patient with PCBCL of the marginal zone, surgically treated with 5 mm security margins, without recurrence in 36 months of follow-up.

#### **CASE REPORT**

A 57-year-old white woman reported the appearance of an asymptomatic lesion in the left upper limb for three years. She denied fever, weight loss, or night sweats (Figures 1).



**FIGURE 1:** On the left, papules and swollen nodules grouped in a plaque, in the distal region of the left arm, with a diagnosis of primary cutaneous B-cell lymphoma of the marginal zone. On the right, after treatment, no recurrence after 36 months of follow-up

The examination showed clustered papules and lumpy nodules, forming a 1.5 cm x 1.2 cm plaque on the left arm. There was no peripheral lymphadenopathy or palpable visceromegaly. Clinical hypotheses included cutaneous lymphoma, sarcoidosis, pseudolymphoma, lupus tumidus, and tertiary syphilis. The histopathological study with immunohistochemical assay showed nodular and diffuse lymphocytic infiltration in the dermis, with 60% of this infiltrate composed of lymphocytes (CD20+, CD10- and BCL6-), frequent reactive T lymphocytes (CD3+), Ki67 proliferation index relatively low (10-20%), frequent plasma cells, and immunoglobulin light chain restric-



FIGURE 2: On the left, diffuse lymphocytic infiltration of the dermis, with irregular paler areas, and sparse small darker reactive follicles, sometimes with a germinal center (Hematoxylin & eosin, 40x). On the right, higher magnification, showing predominantly small to medium volume lymphocytes and frequent lymphoplasmocytoid cells (Hematoxylin & eosin, 400x).



**FIGURE 3:** Immunohistochemistry with markers CD20 (above left), CD3 (below left), *kappa* (above right) and *lambda* (below right), showing mixed lymphocytic infiltration, with populations of immunophenotype B or T, and restriction of immunoglobulin light chains with predominance of *kappa* expression.

tion (*kappa: lambda* index greater than 10:1), suggesting the diagnosis of marginal zone B-cell lymphoma (Figures 2 and 3).

After this result, we investigated systemic disease using computed tomography scans of the neck, chest, abdomen, and pelvis, which did not show extracutaneous manifestations. Laboratory tests, including blood count and LDH, were normal, and serology for HIV and syphilis were not reactive.

The diagnosis of PCBCL of the T1a marginal zone was made. We chose surgical excision with 5 mm security margins as the patient had a single lesion. The patient has been under outpatient follow-up for 36 months, with no local recurrence or appearance of new lesions.

#### DISCUSSION

Marginal zone PCBCL is an indolent cutaneous lymphoma with a five-year survival rate close to 100%. The reported case presents an excellent oncological and cosmetic result in a 57-year-old woman with high estimated survival.

Little is known about the possibility of recurrence with surgical treatment of indolent PCBCL. A study by Servitje *et al.*, 2013, including only patients with marginal zone PCBCL, showed no difference in the recurrence rate or disease-free survival between the groups treated with surgery, radiotherapy, or surgery + radiotherapy. There was a non-statistically significant increase in initial site recurrence in patients treated with surgery alone.<sup>3</sup>

Parbhakar and Cin retrospectively analyzed the database of their oncology center and identified 25 patients with indolent PCBCL: 16 treated with low-dose radiotherapy (30-40 Gy) and nine treated with surgical excision with a 5 mm security margin. Only one patient treated with radiotherapy had a recurrence and underwent surgical excision. The mean follow-up time was four years. The authors also report no local complications in patients treated with surgery; on the other hand, 14/16 of patients treated with radiotherapy had acute radiodermatitis, and 2/16 had a chronic ulcer at the irradiated site lasting up to a year and a half.<sup>4</sup>

Hamilton *et al.* retrospective analysis revealed that four of 12 patients treated with surgery experienced recurrence at the treated site. In this same series, only two of the 92 patients treated with radiotherapy had a recurrence in the irradiated field. However, there was no difference in disease-free survival at five years, which means that radiotherapy as a secondary treatment can be delayed until clinical recurrence of the lymphoma, without changing the patient's prognosis.<sup>5</sup>

In conclusion, surgical treatment is a valid option for radiotherapy in patients with primary cutaneous B-cell lymphomas of indolent clinical behavior with single or localized lesions. The rarity of the disease leads to scarcity of randomized clinical studies between the two therapeutic modalities, as well as the definition of the ideal surgical margins. Based on the previous studies, the authors used a 5 mm security margin. Long-term follow-up of these patients is recommended.

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#### AUTHORS' CONTRIBUTION:

Elisa Nunes Secamilli 问 ORCID 0000-0001-9036-4200

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review.

## Juliana Yumi Massuda-Serrano D ORCID 0000-0002-5221-2385

Approval of the final version of the manuscript; study design and planning; ; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

## Rafael Fantelli Stelini D ORCID 0000-0003-0618-1693

Study design and planning; preparation and writing of the manuscript; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Thais Helena Buffo D ORCID 0000-0002-6833-7596

Study design and planning; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

## Paulo Eduardo Neves Ferreira Velho D ORCID 0000-0002-7504-8370

Approval of the final version of the manuscript; study design and planning; active participation in research orientation; critical literature review; critical revision of the manuscript.



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# Neurothekeoma of the left upper eyelid: rare case report

Neurotecoma de pálpebra superior esquerda: raro relato de caso

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#### ABSTRACT

Neurothekeomas are rare, benign dermal tumors of presumed fibrohistiocytic lineage. They present multiple differential diagnoses, making their identification challenging at the dermatological and anatomopathological examination. We report the case of a 28-year-old man who presented a hardened papule growth on the left upper eyelid with histopathology and immunohistochemistry suggestive of neurothekeoma.

Keywords: Eyelid neoplasms; Neurothekeoma; Case reports

#### RESUMO

Neurotecomas são neoplasias raras, benignas, de presumida linhagem fibro-histiocítica. Ao exame dermatológico e ao anatomopatológico, apresentam múltiplos diagnósticos diferenciais, o que torna sua identificação desafiadora. Relatamos o caso de paciente do sexo masculino, de 28 anos de idade, que apresentou crescimento de pápula endurecida na pálpebra superior direita, com histopatológico e imuno-histoquímica sugestivos de neurotecoma. **Palavras-chave:** Neoplasias palpebrais; Neurotecoma; Relatos de casos

# **Case Report**

#### Authors:

Luisa Homem de Mello Maciel Campilongo<sup>1</sup> João Gabriel Rodrigues Alberti<sup>1</sup> Francisco Macedo Paschoal<sup>1</sup> Marisa Homem de Mello Maciel Campilongo<sup>1</sup> Fernanda Modolo de Paula Moura Campos<sup>2</sup>

- <sup>1</sup> Centro Universitário Faculdade de Medicina do ABC, Dermatology, Santo André (SP), Brazil.
- <sup>2</sup> Audioderma, Dermatology, Praia Grande (SP), Brazil.

#### Correspondence:

Luisa Homem de Mello Maciel Campilongo luisacampi98@gmail.com

Financial support: None. Conflict of interest: None.

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Neurothekeoma (NTs) are rare, benign, superficial soft tissue neoplasms of presumed fibrohistiocytic lineage. Generally, they affect women (F:M, 2:1) in the second and third decades and present as pink-erythematous, solitary, well-defined, slow-growing papules or nodules, asymptomatic, with a diameter smaller than 2 cm.<sup>1,2</sup>

Despite being described in 1969, NTs present uncertain pathogenesis and diverse histological patterns. The multiplicity of differential diagnoses, including the anatomopathological one, makes its identification challenging.<sup>1-3</sup>

#### CASE REPORT

A 28-year-old man, skin phototype V, observed the appearance and growth of a hardened papule on the left upper eyelid (Figure 1) six months ago. He denied pain, itching, or secretion and reported frequent manipulation and sun exposure. He had no relevant dermatological personal history. Regarding his family history, he mentioned "skin cancer" (sic) in his maternal grandmother. We opted for excision of the lesion and sent the material for anatomopathological examination.

The anatomopathological examination showed a dermal lesion composed of fusiform/oval cells arranged randomly with collagenized stroma, areas of collagen entrapment in the periphery, intermingled capillary proliferation, and rare mitotic figures (Figure 2).

The immunohistochemical study revealed expression for CD68 and MiTF and negativity for HMB-45, p16, BCL2, and protein S-100 (Figure 3). A low proliferative index (1%) was reported. Lesion findings fell within the spectrum of plexiform fibrohistiocytic tumor/ neurothekeoma. However, the immunoexpression of MiTF favored the diagnosis of neurothekeoma.



**FIGURE 1:** Clinical aspect of the growing left palpebral papule presented by the patient



FIGURE 2: Photomicrograph (Hematoxylin & Eosin, 200x) of epithelioid and fusiform cells with a certain degree of nuclear polymorphism and hyperchromasia, diffusely distributed among collagen fibers



FIGURE 3: Neurothekeoma. Immunohistochemical staining: CD68 and MiTF

At follow-up the patient had a recurrence with the same aspects as the previous lesion two months after excision.

#### DISCUSSION

Neurothekeoma is a rare, benign dermal neoplasm of uncertain pathogenesis and frequent diagnostic difficulty.<sup>1,2</sup> Until 2019, the literature described only 10 case reports of eyelid neurothekeoma.<sup>4</sup>

The differential diagnosis of NTs is diverse and includes benign, malignant, and inflammatory neoplasms. Histology is the gold standard for diagnosis and is characterized by the presence of a circumscribed and lobular dermal lesion. Nests of epithelioid cells or tumor cells predominate in a subtle spiral pattern. Abundant eosinophilic granular cytoplasm, with round or oval nuclei, is observed.<sup>1,3</sup>

NTs are classified according to the anatomopathological amount of the myxoid matrix. Their immunohistochemical profile is not specific. However, they are typically reactive to NK1-C3 and CD10 and negative to S-100, HMB-45, Melan-A, and CD56.<sup>3</sup>

Recent studies in histogenetics have evaluated the close relationship between NTs and plexiform fibrohistiocytic tumors. Even with common histogenesis, microphthalmia-associated transcription factor (MiTF) expression can be used as a reliable marker to differentiate between tumors.<sup>2,5</sup>

The chance of TN recurrence after surgical excision is approximately 3%,3 and its complications are restricted to an aesthetic scar.<sup>1</sup>

Given the unusual presentation of NTs and their clinical-histological similarities with benign and malignant tumors, head and neck surgeons, dermatologists and pathologists should be aware of the morphobiological spectrum of the neoplasm to perform an accurate diagnosis and appropriate treatment and follow-up of the patient.<sup>1</sup> •

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#### **AUTHORS' CONTRIBUTION:**

#### Luisa Homem de Mello Maciel Campilongo 🝺 ORCID 0000-0002-1555-807X

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review; critical revision of the manuscript.

## João Gabriel Rodrigues Alberti 🕩 ORCID 0000-0001-6495-8419

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

## Francisco Macedo Paschoal D ORCID 0000-0002-6264-1538

Approval of the final version of the manuscript; study design and planning; data collection, analysis, and interpretation; active participation in research orientation; critical literature review; critical revision of the manuscript.

## Marisa Homem de Mello Maciel Campilongo D ORCID 0000-0001-7584-3748

Approval of the final version of the manuscript; study design and planning; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

## Fernanda Modolo de Paula Moura Campos D ORCID 0000-0001-7471-4717

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.



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# NK/T cell lymphoma, nasal-type (rare, rapidly evolving, mutilating, and highly lethal lymphoid neoplasm): a case report

Linfoma de células NK/T tipo nasal (neoplasia linfoide rara, de rápida evolução, mutilante e de alta letalidade): relato de caso

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#### ABSTRACT

NK/T cell lymphoma is a rare, aggressive, non-Hodgkin tumor that is closely related to the Epstein-Barr virus. It has a poor prognosis and poor response to treatments. We report the case of a 91-year-old woman with a history of injury in the nasal region for three months. Histological study showed diffuse infiltration of the dermis by small and atypical lymphoid cells and positive immunohistochemistry for Ki-67, CD30, and CD3 (cytoplasmic). Due to the fast growth of the lesion and the high morbidity of the neoplasm, the patient was referred to the hospital for assistance but died before starting treatment. **Keywords:** Epstein-BarrVirus Infections; Lymphocytes; Medical oncology; Extranodal T-NK Cell Lymphoma; Lethal Midline Granuloma

#### RESUMO

O linfoma de células NK/T é um tumor não Hodgkin, raro, muito agressivo e intimamente relacionado ao vírus Epstein-Barr (EBV). Possui prognóstico ruim e resposta pobre aos tratamentos. Trata-se de uma paciente feminina, 91 anos, com história de lesão em região nasal há três meses. Estudo histológico evidenciou infiltração difusa da derme por células linfoides pequenas e atípicas e imuno-histoquímica positiva para Ki-67, CD30 e CD3 (citoplasmático). Devido ao rápido crescimento da lesão e à alta morbidade da neoplasia, a paciente foi encaminhada para internação para medidas de suporte, mas evoluiu para óbito antes do início do tratamento.

**Palavras-chave:** Înfecções por Vírus Epstein-Barr; Linfócitos; Oncologia; Linfoma Extranodal de Células T-NK; Granuloma Letal da Linha Média

## **Case report**

#### Authors:

Laura Nunes Lopes<sup>1</sup> Roberta Akeme de Oliveira Sato<sup>1</sup> Clóvis Antônio Lopes Pinto<sup>1</sup> Juliana Arêas de Souza Lima Beltrame Ferreira<sup>1</sup> Célia Antônia Xavier de Moraes Alves<sup>1</sup>

<sup>1</sup> Jundiaí School of Medicine, Internal Medicine (Dermatology), Jundiaí (SP), Brazil.

#### Correspondence:

Laura Nunes Lopes Email: launlopes@hotmail.com / Alternative email: launlopes@ gmail.com

Financial support: None. Conflict of interest: None.

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NK/T cell lymphoma is a non-Hodgkin tumor commonly described in Asia and Latin America. It is rare (about 1% of cutaneous T-cell lymphomas), very aggressive, and closely related to the Epstein-Barr virus<sup>1,2,3,4</sup> (the infection can happen before or simultaneously with the tumor genesis).<sup>2</sup> The precursor cell has lymphoid lineage, and in 95% of cases, it comes from the NK cell (cytolytic function).<sup>2</sup>

It constitutes the group of non-mycosis fungoid/non-Sézary syndrome cutaneous lymphomas (10% of cases),<sup>4</sup> with a rapid, mutilating, and highly lethal evolution (five-year survival rate <5%).<sup>1</sup>

The tumor is divided into non-nasal and nasal subtypes (former lethal midline granuloma<sup>2,3,4,5</sup>). It affects the nasal or nasopharyngeal region in 80% of cases.<sup>2,4</sup> However, it can also involve the aerodigestive tract,<sup>4</sup> testicles,<sup>5</sup> muscles, and the uterus, or evolve contiguously to the orbit, salivary glands, and paranasal sinuses. Many non-nasal cases probably had their subclinical onset in the nose (primary site).<sup>2</sup>

It has a poor prognosis and poor response to treatments.

#### CASE REPORT

A 91-year-old woman, white, hypertensive, presented a history of a nasal lesion for three months and weight loss (5 kg in 30 days). An erythematous and edematous lesion was found in the left nasal region, with local ulceration and an area of necrosis, at the initial dermatological examination. The diagnostic hypotheses of invasive squamous cell carcinoma (SCC), NK/T cell lymphoma, leishmaniasis, and mucormycosis were raised. The investigation was then started.

One week after the initial evaluation, the lesion worsened considerably in size and appearance, and antibiotic therapy was then introduced. Laboratory tests showed hypochromic and microcytic anemia, leukocytosis, thrombocytosis, and increased ESR and CRP (28 and 138, respectively). Cranial tomography revealed an area of dermal ulceration from the left nasal/malar region to the adjacent bone limits without signs of invasion, chronic osteomyelitis, or organized collections. An anatomopathological study (Figures 3 and 4) showed diffuse infiltration of the dermis by small and atypical lymphoid cells. Immunohistochemistry (Figures 5 and 6) was positive for Ki-67 (estimated at 80%), CD30, and CD3 (cytoplasmic), confirming the diagnosis of high-grade (CD30+) T lymphoma (CD3e+) or NK/T lymphoma nasal-type.

Due to the rapid evolution of the neoplasm (Figures 1 and 2) and the patient's clinical worsening (decrease in general condition, adynamia, difficulty swallowing), she was referred to the hospital for support measures and palliative care, under the supervision of the Dermatology, Clinical Oncohematology, and Head and Neck Surgery (HNC) teams. The patient died on the fifth day of hospitalization.



FIGURE 1: INITIAL EVALUATION (lesion with 4 cm in the largest diameter): ulcer with erythematous and infiltrated edges and background with hematic crust and necrotic material in the left nasal region. Perilesional erythema and edema. Involvement of a small portion of the nose on the left (nasal wall and ala)



**FIGURE 2:** EVALUATION AFTER ONE WEEK (lesion with 7 cm in the largest diameter): ulceration in the left nasal and malar regions, with infiltration of edges and bottom covered by fibrinonecrotic material. Perilesional edema and erythema. Involvement of the entire left nasal wall and ala and part of the nasal tip, causing disfigurement of the central portion of the face



FIGURE 3: Hematoxylin & Eosin, 100x - Pseudoepitheliomatous hyperplasia, hyperkeratosis, and corneal pseudocysts. Dense lymphocytic infiltrate in the dermis



FIGURE 5: Immunohistochemistry - positive cytoplasmic CD3



**FIGURE 4:** Hematoxylin & Eosin, 400x - Epidermotropism and microabscesses. Atypical lymphocytes with hyperchromatic nuclei. An intimate relationship with vessels



FIGURE 6: Immunohistochemistry - CD30 positive

#### DISCUSSION

Nasal-type NK/T lymphoma may present clinically with epistaxis, nasal tumor with perilesional edema, and hard palate perforation (causing communication between the nasal and oral cavities). Also, the patient may complain of nasal obstruction and/or secretion.<sup>4</sup> The case reported manifested similarly to the cases described in the literature, focusing on the extensive area of necrosis.

The anatomopathological study revealed infiltration of atypical lymphoid cells, neutrophils, and eosinophils, characterizing the so-called polymorphic reticulosis.<sup>2,5</sup> Another histo-

pathological characteristic of this tumor is its close relationship with blood vessels (wall invasion and vascular occlusion).<sup>2,3</sup>

Immunohistochemistry is generally positive for CD3 (surface: negative; cytoplasmic epsilon chain: positive), CD56, CD2, and cytotoxic molecules (granzyme B, perforin, and TIA1).<sup>2,3,5,6,7</sup> Positive Ki-67 indicates a high rate of cell proliferation.

The quantification of EBV-DNA in blood plasma (prognostic indicator) and *in situ* hybridization to assess tumor medullary bone invasion by detecting the virus genetic material can also be used.<sup>2,3,5</sup> Regarding imaging tests, in addition to computed tomography, Pet-scan (PET-CT)<sup>5,7,8</sup> and soft tissue magnetic resonance imaging (MRI) are considered, mainly to assess extension and complications. PET-CT is especially important in non-nasal cases as the absence of hypermetabolic areas (the tumor lymphoid cell has a high avidity for 18-fluorodeoxyglucose) in the nasal/ nasopharyngeal region excludes the possibility that the primary site is the face.<sup>2</sup> Regarding treatment,<sup>2,5,6,8,9</sup> combination of radiotherapy and chemotherapy is considered the gold standard. However, new protocols and therapies (targeted therapy, stem cell transplantation, immunotherapy targeting the EBV, among others) have been discussed.<sup>6,9</sup> In the case described, as in many others of this type of lymphoma, there was no time for treatment, only comfort measures. •

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#### **AUTHORS' CONTRIBUTION:**

#### Laura Nunes Lopes D ORCID 0000-0001-5268-0624

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Roberta Akeme de Oliveira Sato D ORCID 0000-0001-6449-8870

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Clóvis Antônio Lopes Pinto D ORCID 0000-0003-1711-0081

Author's contribution: Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Juliana Arêas de Souza Lima Beltrame Ferreira 🕩 ORCID 0000-0001-7338-3442

Author's contribution: Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Célia Antônia Xavier de Moraes Alves D ORCID 0000-0002-8421-8837

Author's contribution: Approval of the final version of the manuscript; study design and planning; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.



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# Rosettes in cutaneous angiosarcoma: a new dermoscopic clue

Rosetas em angiossarcoma cutâneo: uma nova pista dermatoscópica

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#### ABSTRACT

Cutaneous angiosarcoma is a rare cancer with a poor prognosis that affects mainly elderly men. It is related to chronic exposure to sunlight, chronic lymphedema, and procedures using radiation. We report a case of a 62-year-old man with a progressively growing violaceous tumor in the left temporal region. Dermoscopy showed erythematous areas of different shades, pseudo-follicular openings structures, and rosettes. The biopsy and the immunohistochemical study confirmed the diagnosis of cutaneous angio-sarcoma. The patient is currently undergoing chemotherapy treatment in the oncology service with significant improvement of the lesion.

Keywords: Dermoscopy; Hemangiosarcoma; Skin neoplasms

#### RESUMO

O angiossarcoma cutâneo é um câncer raro, de mau prognóstico, que acomete principalmente idosos do sexo masculino. Está relacionado à exposição solar crônica, linfedema crônico e procedimentos com uso de radiação. Relatamos o caso de um homem de 62 anos com presença de tumoração violácea de crescimento progressivo na região temporal esquerda. A dermatoscopia demonstrou áreas eritematosas de diferentes tons, estruturas semelhantes à pseudo-aberturas foliculares e rosetas. A biópsia e a análise imunohistoquímica confirmaram o diagnóstico de angiossarcoma cutâneo. O paciente atualmente está em tratamento quimioterápico no serviço de oncologia com melhora significativa da lesão. **Palavras-chave:** Dermoscopia; Hemangiossarcoma; Neoplasias cutâneas

# **Case report**

#### Authors:

Larissa Daniele Machado Góes<sup>1</sup> José Genival Alves de Macedo Júnior<sup>2</sup> Manoel Benjamim de Almeida Barbosa<sup>3</sup>

Tayenne da Silva Gomes<sup>4</sup> Lisandro Ferreira Lopes<sup>4</sup>

- Reference Center for Tropical Diseases of Amapá, Oncology Department, Macapá (AP), Brazil.
- <sup>2</sup> Federal University of Amapá, Medicine Department, Macapá (AP), Brazil.
- <sup>3</sup> Oncology Center of the State of Amapá, Oncology Department, Macapá (AP), Brazil.
- <sup>4</sup> Diagnóstika Surgical Pathology and Cytology, Pathology Service, São Paulo (SP), Brazil.

#### Correspondence:

Larissa Daniele Machado Góes Email: larissadaniele55@gmail.com

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Cutaneous angiosarcoma (CA) is a rare aggressive malignant vascular tumor with a poor prognosis, representing about 1.6% of soft tissue sarcomas.<sup>1</sup> According to its origin, it can be classified into cutaneous angiosarcoma associated with chronic lymphedema (Stewart-Treves syndrome), radiation-induced cutaneous angiosarcoma, and cutaneous angiosarcoma of the head and neck.<sup>2</sup> Cutaneous angiosarcoma can develop in various body regions, such as the breast, face, scalp, and limbs.<sup>3</sup> However, more than half of all cases occur in the head and neck, especially on the scalp.<sup>2</sup> The disease more frequently affects men over 60 years old, corresponding to about 85% of cases.<sup>4</sup>

Research indicates that the exacerbated expression of receptor tyrosine kinase and angiogenic growth factors are responsible for the deregulation of angiogenesis in cutaneous angiosarcoma.<sup>5</sup> As for the location, primary cutaneous angiosarcoma occurs preferentially in photo-exposed skin<sup>6</sup> while secondary cutaneous angiosarcoma usually occurs in areas that have previously undergone radiotherapy or with the presence of chronic lymphedema. Other studies associate cutaneous angiosarcoma with xeroderma pigmentosum, immunosuppression, and hemodialysis, due to its relationship with neovasculogenesis.<sup>6</sup>

Early lesions present as ill-defined violaceous to bluish areas with hardened borders. <sup>7</sup> At this stage, the disease must be differentiated from hematoma, rosacea, lupus erythematosus, and infections such as erysipelas and cellulitis. <sup>7</sup>

The evaluation of vascular structures of skin lesions is applied to various fields, from tumor, inflammatory, and scalp lesions to the evaluation of nail fold capillaries in connective tissue diseases. <sup>8</sup> However, the assessment of color variations of lesions has been neglected. <sup>9</sup> The dermoscopic findings of angiosarcoma are scarce, being described mainly in case reports. It presents varied shades of erythema, from pink-purple areas with a white or skin-colored central zone to a peripheral violaceous tone;<sup>9</sup> a reddish homogeneous area with white lines;<sup>10</sup> vapor-like regions with a white or skin-colored central area and a violaceous periphery;<sup>11</sup> a pink to violaceous erythema with white peri-follicular zones; a homogeneous violaceous to the black area covered by a whitish veil; or a diffuse violaceous erythema with follicular plugs.<sup>12</sup>

Rosette is a dermoscopic sign visible under polarized light, characterized by four white dots arranged like a 4-leaf clover.<sup>13</sup> These structures can be found in melanocytic and nonmelanocytic lesions, and are not pathognomonic of any dermatosis.<sup>14,13</sup> A series of 6,108 ex vivo dermatoscopies found rosettes in a variety of conditions such as scars (6.4%), dermatofibroma (6%), molluscum contagiosum (5.9%), squamous cell carcinoma (4.0%), basal cell carcinoma (1.7%), melanoma (1.4%), and nevi (0.7%).<sup>14</sup> A recent description in the Brazilian literature identified rosettes in T-cell pseudolymphoma.<sup>15</sup>

The therapeutic modalities used to treat cutaneous angiosarcoma are surgery, radiotherapy, and chemotherapy.<sup>2</sup> However, it tends to metastasize to regional lymph nodes and lungs, usually after repeated surgical excisions of the primary tumor. <sup>16</sup> The prognosis is poor, with a five-year survival rate of 10% to 35%.<sup>17</sup>

#### CASE REPORT

A 62-year-old man, without comorbidities, presented a progressively growing violaceous tumor on the left temporal region (Figure 1) for two weeks, accompanied by pain and local edema, with no previous history of trauma. Dermoscopy revealed the presence of erythematous areas of varying tones,



**FIGURE 1:** Figure 1: Violaceous tumor on the left temporal region

structures similar to pseudo-follicular openings and rosettes (Figure 2). The initial diagnostic hypotheses were cutaneous abscess, primary cutaneous T-cell lymphoma of the follicular center type, and angiosarcoma. Systemic antibiotic therapy was instituted, and after 14 days, there was a significant enlargement of the lesion (Figure 3), infiltration of the face and scalp, and areas of ulceration and bleeding.



FIGURE 2: Erythematous areas of varying tones, structures similar to pseudo-follicular openings, and rosettes

Skull CT scan showed extracranial formation in the left frontal pole without intracranial invasion. Chest, abdomen, and CT scans were normal. Serologies for HIV, hepatitis B, C, and syphilis were negative. Histopathological examination of the incisional biopsy of the lesion showed the presence of irregularly shaped anastomosing vascular channels lined by atypical cells and also spindle-shaped and epithelioid cells with ample eosinophilic cytoplasm, nuclei with coarse chromatin, evident nucleolus, and frequent mitotic figures (Figure 4). Immunohistochemistry was positive for ERG (Figure 5) and CD31 (Figure 6) and negative for HHV-8, confirming the diagnosis of angiosarcoma.



FIGURE 4: Histological sections demonstrate an infiltrative dermal neoplasm, formed by irregular anastomosed vascular channels lined with atypical endothelial cells. Cytomorphology is variable and may be polygonal, fusiform, epithelioid, or pleomorphic. Frequent mitotic figures are observed, many of them atypical



FIGURE 3: Friable violaceous tumor with central ulceration over an infiltrated area on the forehead



FIGURE 5: Positive immunohistochemistry for ERG



FIGURE 6: Positive Immunohistochemistry for CD31



FIGURE 7: After 5 cycles of neoadjuvant chemotherapy with ifosfamide, doxorubicin, and granulocyte growth factor

The patient was referred to the oncology service, where he is currently undergoing neoadjuvant intravenous chemotherapy with ifosfamide 1.8 g/m<sup>2</sup>, in 5 cycles, combined with doxorubicin 75 mg/m<sup>2</sup>, every three weeks, associated with granulocyte growth factor (G-CSF) 300 mcg/day, subcutaneously, with a daily dose divided into five applications. After treatment, we observed a substantial improvement in the lesion (Figure 7).

#### CONCLUSION

The description of rosettes in an angiosarcoma is, to the best of our knowledge, a new dermoscopic finding. We believe that sharing this information with the scientific community can broaden the range of differential diagnoses of dermatological diseases characterized by the presence of rosettes at dermoscopy, thus enabling early diagnosis and treatment of angiosarcoma.

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#### **AUTHORS' CONTRIBUTION:**

#### Larissa Daniele Machado Góes D ORCID 0000-0003-4140-3247

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### José Genival Alves de Macedo Júnior D ORCID 0000-0001-7887-3723

Approval of the final version of the manuscript; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; critical literature review.

#### Manoel Benjamin de Almeida Barbosa D ORCID 0000-0003-4283-4743

Approval of the final version of the manuscript; preparation and writing of the manuscript; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.

#### **Tayenne da Silva Gomes** (D ORCID 0000-0003-3379-6028

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review.

#### Lisandro Ferreira Lopes D ORCID 0000-0003-2873-4332

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.



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# A-T flap for cheek reconstruction

Retalho de avanço formato A-T para reconstrução malar

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#### ABSTRACT

The cheek is the largest anatomical unit of the face. In this area, surgical skin cancer treatment must aim for its complete eradication and the best aesthetic-functional result. A 69-year-old woman presented with a 3.5 cm tumor in the left cheek for three years. Biopsy showed moderately differentiated squamous cell carcinoma. We performed an A-T flap, where the surgical defect corresponded to the "A" and the junction of the inferior orbital, nasofacial, and nasolabial grooves, to the top of the "T". The patient evolved without recurrence and had an excellent aesthetic-functional aspect.

Keywords: Skin neoplasms; Carcinoma, Squamous cell; Zygoma; Surgical flaps; Reconstructive surgical procedures.

#### RESUMO

A região malar é a maior unidade anatômica da face. Nessa área, o tratamento cirúrgico do câncer de pele deve objetivar, além de sua erradicação completa, o melhor resultado estético-funcional possível. Paciente do sexo feminino, 69 anos, com tumoração de 3,5cm na região malar esquerda há três anos, teve evidenciado, por biópsia, carcinoma espinocelular moderadamente diferenciado. Realizaram-se exérese do tumor e reconstrução por meio do retalho A-T, em que o defeito cirúrgico correspondeu ao "A" e o encontro dos sulcos do rebordo orbital inferior, nasofacial e nasogeniano, ao teto do "T". A paciente evoluiu sem recidiva e com excelente aspecto estético-funcional.

**Palavras-chave:** Neoplasias cutâneas; Carcinoma de células escamosas; Zigoma; Retalhos cirúrgicos; Procedimentos cirúrgicos reconstrutivos.

### **Case report**

#### Authors:

Thais Florence Duarte Nogueira<sup>1</sup> Mariana Reis e Rocha Dultra<sup>1</sup> Mariana de Freitas Valente<sup>1</sup> Glaucio Farina<sup>1</sup>

Padre Bento de Guarulhos Hospital, Dermatology, Guarulhos (SP), Brazil.

Correspondence: Thais Florence Duarte Nogueira Email: thaisflorence@gmail.com

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Approximately two to three million people are diagnosed every year with non-melanoma skin cancer nowadays.<sup>1</sup> Also, there is a trend towards an increase in the condition incidence in recent decades due to the population aging.<sup>1,2</sup>

Among all skin malignant neoplasms, studies show that 70-80% are basal cell carcinoma (BCC) and 20% are squamous cell carcinoma (SCC).<sup>3</sup>

Regarding the topography of these skin cancers, the most affected areas of the human body are the face and neck since they are frequently exposed to ultraviolet radiation (UV), considered the most significant risk factor.<sup>3-5</sup> The malar region is one of the areas most affected by these face tumors.<sup>5</sup>

Current treatments for skin cancer and premalignant lesions include surgical excision, curettage and electrocautery, cryotherapy, and irradiation. However, surgical excision is considered the best method for treating cancer and preventing recurrence.<sup>2</sup>

When located in the malar region, even though the complete eradication of the tumor is the primary objective, it is also essential to achieve the best possible functional and cosmetic result.<sup>4</sup>

Regarding the functional aspect, the malar anatomical unit is connected to the surrounding facial structures: eye, nose, and lip.<sup>5</sup> The malar region defect site and possible sequelae – ectropion, effaced nasolabial fold, and mastication, phonation, and facial expression changes – should be assessed during surgical planning to avoid them.<sup>6</sup>

Concerning the cosmetic result, the malar region is complex since it is the largest facial anatomical unit and has a prominent position on the face.<sup>6,7</sup> As it has a flat and slightly convex contour, with few shadows or depressions, it is difficult to camouflage scars and irregularities. Also, it is a critical area for emotional expression. Thus, dynamic facial movement can further highlight the surgical sequelae. One should also pay attention to the symmetry, contour, skin color and texture in the surgical planning of this area.<sup>7</sup>

Cutaneous neoplasms and surgical scars on the face can be extremely visible and cause a significant psychosocial impact on the patient. Changes in facial appearance, regardless of magnitude, can result in anxiety, depression, and social isolation.<sup>8</sup>

To obtain a good surgical result and avoid undesirable consequences, reconstructing surgical defects after surgical excision of skin cancer in the malar region becomes challenging. The used surgical reconstruction methods are primary closure, skin graft, and local and free flaps. The choice of one of these methods is based on the tumor type, size and location, the recurrence possibility, the patient's age and health condition, and functional and cosmetic factors.<sup>2,9</sup>

Primary closure is generally an excellent reconstruction option when the surgical defect is small.<sup>9,10</sup> However, most surgical defects in the malar region present moderate size, thus they are not responsive to primary closure. Therefore, local flaps and skin grafts are widely used to correct these defects. Among these, local flaps present superior aesthetic results.<sup>10</sup>

In this case report, we used an A-T flap to reconstruct a malar defect after the excision of a squamous cell carcinoma (SCC), a technique rarely described in the literature for reconstructing defects in this site.

#### **CASE REPORT**

A 69-year-old white woman with osteoarthrosis presented to our Service with an exophytic tumor with serohematic crust, measuring 3.5 cm in its largest diameter, in the left malar region, three years ago. Anatomopathological examination showed moderately differentiated squamous cell carcinoma, ulcerated, and infiltrating into the hypodermis.

Thus, we planned the lesion excision. Both the patient's late search for the Health Service and the surgery delay occurred due to the pandemic caused by the Coronavirus-19. Before the surgical procedure, the safety margin of the lesion and the configuration of the A-T advancement flap design were performed (Figure 1).

After infiltration with perilesional local anesthesia and in the flap area, the tumor was excised with a 1 cm safety margin resulting in a surgical defect with a circular shape of 4.5 cm in diameter. The flap was dissected in a plane immediately superior to the superficial aponeurotic muscle, providing an easier, faster, and safer dissection due to less bleeding and a lower risk of neural injury. The flap was sutured with 5.0 mononylon, single stitches (Figure 2).

One week later, the patient presented edema and a slight left periorbital hematoma (Figure 3). However, she evolved with good integration of the flap and the receptor area, satisfactory and rapid surgical healing, and no suture dehiscence or signs of secondary infection. Secondary ectropion did not occur.

After one year, the patient has no signs of skin cancer recurrence and has an excellent aesthetic and functional appearance (Figure 4).

#### DISCUSSION

The malar region reconstruction planning must consider several factors: relaxed skin tension lines orientation, maximum distensibility lines, skin surface contour, subcutaneous anatomy, patient age, comorbidities, previous surgery or radiation, tumor size, depth, and location regarding other facial subunits.<sup>7</sup>

Appropriate margins for skin tumors depend on the type of cancer, tumor size and irregularity, and the time elapsed since its onset.<sup>2</sup> For SCC patients, surgical excision with a radial safety margin of 4 mm to 6 mm is recommended for low-risk primary cases. However, there is no consensus on the adequate safety margin for high-risk cases, and some references recommend a safety margin of 1 cm.<sup>11,12</sup> High-risk SCCs are those with a size >2 cm, ill-defined margins, subcutaneous extension, recurrence, immunosuppression, high-risk location, or previous irradiation.<sup>4, 10, 11</sup>



FIGURE 1: Exophytic tumor, with serohematic crust, measuring 3.5 cm in its largest diameter, in the left malar region



FIGURE 2: Immediate postoperative period of excision and reconstruction using the A-T flap

In this case, the patient had a high-risk SCC since the tumor measured 3.5 cm and was located in the malar region, a high-risk anatomical site. We chose a safety margin of 1 cm to minimize the risk of recurrence.

With a safety margin of 1 cm, a 4.5 cm circular surgical defect was established in the medial malar region.

The main objectives of the ideal closure of surgical defects on the face are skin closure under minimal tension, replacement of the tissue for one as similar as possible, main anatomical



FIGURE 3: Seventh postoperative day of the A-T flap. Edema and mild left periorbital hematoma are evident



**FIGURE 4:** One year after the A-T flap operation. There are no signs of skin cancer recurrence and an excellent aesthetic-functional aspect is noted

structures (eye, nose, lip) preservation, and scar location corresponding to the functional and aesthetic facial units. The objective is to provide the patient with a complete reconstruction with invisible scars.<sup>12</sup>

For the surgical planning of the surgical defect, it is essential to understand the anatomy of its location. The malar region can be divided into four anatomical subunits: medial, lateral, zygomatic, and buccal. The hair implantation line in the temporal region, the preauricular crease and the mandibular inferior border delimit the malar region laterally and inferiorly. The central facial subunits mark their boundaries through the lower eyelid, nasal dorsum and ala, nasolabial folds, lip, and labial commissure superiorly and medially. Closure or flap margins should be projected along these anatomical borders or parallel to relaxed skin tension lines to camouflage surgical scars.<sup>7</sup>

Another method is grafting. An advantage of this technique is that it enables the detection of a tumor recurrence more easily.<sup>8</sup> Moreover, the incompatibility of the graft color and texture with the skin adjacent to the defect can result in a "patch" appearance.<sup>68</sup> Healing of the graft can also produce retraction capable of causing deformities of the central facial subunits that surround the malar region.<sup>13</sup>

We chose a local flap to minimize damage to normal tissue and avoid complications such as dog ears or excessive tension.<sup>14</sup> Local flaps promote better results in terms of color, texture, and skin thickness compared to grafts.<sup>8</sup> The choice of local flap depends on the availability of skin tissue and the location of the surgical defect. In practice, choosing the best flap depends on the surgeon's preference.<sup>2</sup>

For moderate-sized defects in the medial malar region, the most described flaps in the literature iarea the advancement and rotation flaps. Nonetheless, many authors use the cervicofacial flap for large defects in this location.<sup>7</sup> There are few reports on using the A-T flap at that location.

We chose to perform the A–T flap, where the surgical defect corresponded to the "A" and the junction of the inferior orbital, nasofacial, and nasolabial grooves, to the top of the "T". The A–T flap is classified as a bilateral advancement flap according to its main movement toward the defect area.<sup>15</sup> It is an excellent method to solve a moderate and deep defect, where the adjacent tissue does not allow direct closure.

Regardless of the surgeon's skills, it is essential to emphasize that the surgery success rate depends on numerous patient factors, such as age, general health status, medications in use, smoking, skin characteristics (elasticity, actinic and sebaceous damage, thickness), previous scars, and individual healing capacity.<sup>12</sup>

The patient in the case evolved with excellent healing. The scar resulting from the top of the "T" was naturally hidden in the preexisting grooves (infraorbital, nasofacial, and nasolabial folds), and the "A" scar (bottom of the "T"), in the bisector of the grooves of the infraorbital and nasolabial folds (Figure 4).

The A-T flap may be a good option for resolving large defects secondary to the excision of skin tumors in the malar region. It has the advantages of being performed with local anesthetic and resolution in a single surgical time.

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#### **AUTHOR'S CONTRIBUTION:**

#### Thais Florence Duarte Nogueira DORCID 0000-0002-7343-0218

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Mariana Reis e Rocha Dultra D ORCID 0000-0003-0510-221X

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Mariana de Freitas Valente D ORCID 0000-0002-6798-7116

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Glaucio Farina (D) ORCID 0000-0002-2273-7033

Approval of the final version of the manuscript; study design and planning; active participation in research orientation; critical revision of the manuscript.



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# Treatment of delayed inflammatory response to hyaluronic acid soft tissue filler in a Pfizer-Boosted Moderna-Vaccinated individual with hyaluronidase

Tratamento da resposta inflamatória tardia ao preenchimento de tecidual com ácido hialurônico em indivíduo imunizado Moderna após reforço com vacina Pfizer com hialuronidase

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#### ABSTRACT

We present a case of delayed-type hypersensitivity to hyaluronic acid (HA)-based filler on the face following the Pfizer booster in a Moderna-vaccinated individual. It is the first known case of treatment of the delayed-type hypersensitivity reaction with hyaluronidase following Covid vaccination. Hyaluronidase is a viable option to treat this reaction, particularly for patients who may not benefit from systemic treatment options. With an anticipated fourth round of vaccine boosters on the horizon, there may be an increased incidence of cutaneous adverse events, including the reaction discussed.

Keywords: COVID-19; SARS-CoV-2; Inflammation; Dermal fillers; Hypersensitivity, Delayed; Hyaluronic acid

#### RESUMO

Apresentamos um caso de hipersensibilidade tardia ao preenchimento à base de ácido hialurônico na face após o reforço da vacina Pfizer em um indivíduo imunizado com Moderna. Este é o primeiro caso conhecido de tratamento da reação de hipersensibilidade tardia com hialuronidase após a vacinação anti-Covid. A hialuronidase é uma opção viável para tratar esta reação, particularmente para pacientes que podem não se favorecer com as opções de tratamento sistémico. Com uma quarta ronda de reforço de vacinas planejada no horizonte, pode haver um aumento da incidência de eventos adversos cutâneos, incluindo a reação discutida.

**Palavras-chave:** COVID-19; SARS-CoV-2; Inflamação; Preenchedores dérmicos; Hipersensibilidade tardia; Ácido hialurônico

# **Case Report**

#### Authors:

Sabine Obagi<sup>1</sup> Zaidal Obagi<sup>2</sup> Yasmeen Altawaty<sup>3</sup> Zein Obagi<sup>4</sup>

- <sup>1</sup> University of Arizona College of Medicine, Tucson (AZ), United States
- <sup>2</sup> University of Arizona College of Medicine, Division of Dermatology, Tucson (AZ), United States
- <sup>3</sup> Western University of Health Sciences, College of Pharmacy, Pomona (CA), United States
- <sup>4</sup> ZO Skin Health Institute, Beverly Hills (CA), United States

#### Correspondence:

Sabine Obagi Email: sobagi@bu.edu

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The Covid-19 pandemic has presented numerous challenges that the literature continues to explore. Throughout the pandemic, aesthetic procedures persisted, with aesthetic plastic surgery generating a total revenue of over \$9 billion in 2020.<sup>1</sup> With the advent of the Covid vaccines, literature regarding the safety, efficacy, and adverse events have become of great interest to clinicians and the public.

Dermal fillers, neurotoxin injections, peels, and subcutaneous augmentations represent an ever-growing portion of cosmetic and surgical dermatology, and a 36–58% annual increase in dermal fillers was observed over the past few years. In 2020, about 1.3 million of these procedures were performed.<sup>2</sup>

Another round of boosters is underway, and the US Food and Drug Administration (FDA) recently approved the fourth Covid shot. The rise in filler popularity represents a significant population at risk for developing adverse reactions due to Covid vaccinations.

To date, five case reports have been published regarding delayed hypersensitivity reactions to soft-tissue fillers following Moderna and Pfizer vaccination, all on hyaluronic acid (HA)-based fillers. Steroids, antihistamines, and ACE inhibitors have been documented as possible treatments for this reaction.<sup>3-7</sup>

We present a case of delayed hypersensitivity to HA-based filler on the face following the Pfizer booster in a Moderna-vaccinated individual. Oral inflammation was self-resolved, but persistent inflammation of the infraorbital and trochlear region only resolved after hyaluronidase administration. Hyaluronidase (HAse) injection is used off-label for dissolving HA-based fillers.<sup>8</sup> It is the first known case of treatment of the delayed hypersensitivity reaction to HA following Covid vaccination with hyaluronidase. Also, it is another option to treat this reaction, particularly for patients who may not benefit from systemic therapy.

#### CASE PRESENTATION

A 29-year-old woman with a history of dermal fillers and no known medical conditions or allergies presented to the clinic with swelling of the bilateral vermillion (Figure 1A) and the bilateral under-eye compartments (Figure 2A), occurring 36-48 hours post-Pfizer booster. The patient reported a milder reaction after her second Moderna vaccination in the same areas, which self-resolved. She denied any tongue swelling or trouble breathing.

Four months before this reaction, the patient received HA dermal fillers: Juvederm Ultra XC 0.2 mL to the top lip and 0.1 mL to the bottom lip. She also received 0.5 mL of Belotero injected into each under-eye region.

The patient denied any history of infection, trauma, rosacea, or granulomatous cheilitis and did not have any new fillers injected since receiving her first two Covid vaccinations. The swelling only occurred at the filler sites: no additional swelling was noted elsewhere.



**Figure 1: A** - 36-48 hours following the Pfizer booster. Note the enlarged and edematous upper and lower lips, which may be mistaken for angioedema. **B** - Lips two weeks following conservative management.

The patient was diagnosed with delayed hypersensitivity to the dermal fillers following Covid vaccination. She opted for monitoring and non-medical treatments. The patient applied ice intermittently to the affected areas at home. After 48-72 hours, her lip swelling had resolved, but the inflammation around her eyes persisted.

After four days, the patient continued to have persistent swelling around the eyes and returned to the clinic. Each infraorbital area that contained the previous filler received 50 units of hyaluronidase mixed with saline.

By the following day, the patient reported complete resolution of the swelling of the bilateral periorbital region and total satisfaction with the treatment. She had no further complications at her follow-up appointment two weeks later (Figures 1B and 2B).

#### DISCUSSION

The 2019 American Society of Plastic Surgeons Statistics Report showed that soft-tissue fillers represent the second most common minimally invasive cosmetic procedure following Botox. HA-based dermal fillers made up 79% of the 2.7 million fillers in 2019.<sup>9</sup> HA-based dermal fillers can last between 6 to



**FIGURE 2: A** - 36-48 hours following the Pfizer booster. Note the inflamed and edematous skin overlying the infraorbital and lacrimal duct region. **B** - The eye of the same patient two weeks following hyaluronidase dissolution of under eye filler.

18 months and are preferred for their safety profile as an injection of hyaluronidase, an enzyme that hydrolyzes the filler, can instantly reverse them.

Although well tolerated, the rise in filler treatments has led to an increase in adverse events reported, including delayed hypersensitivity reactions to HA-filler. To date, five case reports have described this reaction. Various treatments were tried in these cases, such as antihistamines, steroids, and ACE inhibitors, nearly all with eventual resolution. We found no documented case involving hyaluronidase as a mechanism of treatment.<sup>3-7</sup>

Hypersensitivity reactions are classified into acute and delayed. Acute hypersensitivity reactions onset within minutes to hours from injection time and are immunoglobulin-E mediated. They can result in an anaphylactic reaction or swelling and often present as urticaria or angioedema.<sup>10</sup> Mild forms of this reaction respond well to antihistamines and topical or oral steroids, while severe cases require systemic treatments.

The mechanism of action of delayed hypersensitivity involves cell-mediated responses with downstream signaling unlikely to respond to OTC antihistamines. The mechanism to sensitize dermal fillers following Covid vaccination is unclear but is likely to be multifactorial, involving cross-reactivity and possibly epitope spreading.

Munavalli et al. suggest the potential mechanism of the delayed inflammatory reaction to HA fillers in Covid-19-related cases, involving the binding and blockade of ACE2 receptors, which are targeted by the SARS-CoV-2 virus spike protein to gain entry into the cell.<sup>11</sup> Munavalli postulates that cross-reactivity between the spike protein and dermal ACE-2 receptors forms an antigenic response favoring a pro-inflammatory, loco-regional TH1 cascade, then promoting a CD8+T cell-mediated reaction and leading to incipient granulomas formed around residual HA particles. They support this with evidence of clinical response of dermal filler inflammation to oral ACE-inhibitors.<sup>11</sup>

We present a case using hyaluronidase to improve the delayed inflammatory response following the Pfizer Covid-19 booster. Hyaluronidase injection as an alternative method to improve the inflammatory response can be an amenable option for patients unable or unwilling to take systemic medication.

Pre-existing data support the treatment with hyaluronidase for hypersensitivity reactions to HA-based fillers from other etiologies. DeLorenzi et al. report that soft tissue injection of hyaluronidase alone, without any ancillary treatments, has provided excellent results to hypersensitivity reactions to fillers, superior to his previous protocol.<sup>12,13</sup>

Clinicians should recognize the benefit of hyaluronidase in certain medical conditions and may collaborate with pharmacists to achieve an appropriate dose and method of administration.

A medical professional must administer hyaluronidase. Also, patients must be adequately hydrated pre-treatment and monitored post-treatment for signs of thrombosis, anaphylaxis, and injection site reactions.<sup>14</sup> Hyaluronidase injections should be avoided in patients with allergies to bovine collagen and bee stings due to potential cross-reactions.<sup>8</sup>

On March 29, 2022, the US FDA authorized a second booster dose of the Pfizer or Moderna vaccine for older and some immunocompromised individuals. With an anticipated fourth round of vaccine boosters on the horizon, there may be an increased incidence of cutaneous adverse events, including the reaction discussed.

Future studies are needed to develop a comprehensive understanding and treatment protocol for Covid-19 vaccine-related HA-based filler complications, considering patients' comorbidities and medication safety. Patients should be wary of more severe reactions with subsequent vaccinations, as seen in our patient, who had a mild response after the second Covid vaccine and a serious reaction after the booster.

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#### **AUTHORS' CONTRIBUTION:**

#### Sabine Obagi D ORCID\_0000-0002-1294-547X

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

**Zaidal Obagi** ORCID\_0000-0001-5773-8039 Approval of the final version of the manuscript; study design and planning; active participation in research orientation.

Yasmeen Altawaty Data collection, analysis and interpretation.

Zein Obagi D ORCID 0000-0002-3350-8586 Study conception and planning.



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# Basaloid follicular hamartoma

Hamartoma folicular basaloide

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#### ABSTRACT

Basaloid follicular hamartoma (BFH) is a rare and benign adnexal tumor that resembles basal cell carcinoma (BCC) and may present with different clinical manifestations. A mutation in the PTCH gene, involved in Gorlin-Goltz syndrome, could be associated with the pathogenesis of this neoplasm. We describe the case of a 7-year-old girl with multiple papules on her face. **Keywords:** Hamartoma; Carcinoma, Basal cell; Genes, Tumor suppressor.

#### RESUMO

O hamartoma folicular basaloide (HFB) é um tumor anexial raro e benigno, que se assemelha ao carcinoma basocelular (CBC), e pode apresentar manifestações clínicas diversas. Uma mutação no gene PTCH, envolvido na síndrome de Gorlin-Goltz, poderia estar associada à patogênese dessa neoplasia. Descreve-se caso de menina, sete anos, apresentando múltiplas pápulas na face.

Palavras-chave: Hamartoma; Carcinoma basocelular; Genes supressores de tumor.



#### Authors:

Luana Amaral de Moura<sup>1</sup> Paulo Sergio Emerich Nogueira<sup>1</sup> Elton Almeida Lucas<sup>1</sup> Lucia Martins Diniz<sup>1</sup> Emilly Neves Souza<sup>1</sup>

<sup>1</sup> Federal University of Espírito Santo (UFES), Cassiano Antônio Moraes University Hospital, Department of Dermatology, Vitória (ES), Brazil.

Luana Amaral de Moura Email: luanamoura@gmail.com

**Correspondence:** 

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Basaloid follicular hamartoma (BFH) is a rare benign tumor of hair follicles whose histopathological features can mimic basal cell carcinoma (BCC).<sup>1,2</sup> It can be hereditary or acquired and localized or generalized. Generalized hereditary forms are usually associated with systemic manifestations, which vary according to the subtype.<sup>1,3</sup>

#### **CASE REPORT**

A seven-year-old girl, previously healthy, presented papules in the central region of the face for about a year without associated symptoms. There was no relevant family history. The examination revealed mildly hypochromic papules on the nasal dorsum and malar regions (Figure 1), with no other skin lesions. The diagnostic hypotheses were milia, sebaceous hyperplasia, and syringoma. We performed an incisional biopsy, whose histopathology showed basaloid cells forming anastomosed cords and palisade distribution, initially suggesting nodular basal cell carcinoma (Figure 2). We opted for an anatomopathological review and immunohistochemistry, which showed positive Bcl-2 in the outermost layer of tumor cells, positive CD-10 in the surrounding stromal cells, Ki-67 index (proliferative activity) of 20%, and CD- 34 negative (Figure 3). Thus, we established the diagnosis of basaloid follicular hamartoma. The patient initiated a thorough investigation to rule out associated syndromes.

#### DISCUSSION

Although the pathogenesis of BFH is unknown, it is believed that a mutation in the PTCH (protein patched homolog) gene, which encodes a receptor involved in the Sonic hedgehog–Patched–Gli (Shh-Ptch–Gli) signaling pathway, could contribute to the tumor formation. This abnormality would promote an inadequate regulatory function, with constant positive signaling, resulting in atypical and uncontrolled cell division and growth.<sup>3-5</sup> The clinical manifestations are varied, but most cases of BFH present with one or multiple papules of 1 mm to 2 mm of normochromic to brownish color on the face, scalp, neck, axilla, trunk, and pubic region.<sup>1,5</sup> In this case, the lesions were mildly hypopigmented, multiple, and bilateral.

So far, five clinical forms have been described: (1) Solitary or multiple papules, as in the report; (2) Linear or unilateral localized papule or plaque; (3) Localized plaque with alopecia; (4) Autosomal dominant, generalized familial type, without associated diseases; and (5) Generalized papules associated with myasthenia gravis, alopecia, systemic lupus erythematous, hypotrichosis, and cystic fibrosis.<sup>2,3,5</sup>

Recently, a retrospective study conducted at the University Hospital of Strasbourg, France, evaluating 17 cases of BFH diagnosed between 1998 and 2017, described a higher incidence of the solitary form, characteristically confused with basal cell carcinoma. It also reported that the unilateral linear form often follows Blaschko's lines, reflecting cutaneous mosaicism. This clinical variant may be related to the ipsilateral brain, bone, and dental abnormalities. It may also be associated with Happle--Tinschert syndrome.<sup>4</sup>

Despite the variability of BFH manifestations, the histopathological appearance is remarkably constant. There are cords and extensions of branched basaloid epithelial cells arranged vertically in the superficial and middle dermis, most in connection with the epidermis and hair follicles, as in the case reported. When the palisade organization is present, it is much less marked than the BCC. By definition, cell atypia and mitosis are absent or very rare. Follicular involvement is marked by the vertical arrangement that replaces the normal follicle, lesion with a basophilic periphery and eosinophilic center, and mucin-rich stroma.<sup>1,4</sup>

Immunohistochemistry is not specific but may aid in the diagnosis. In the stroma, there is positivity for CD-34 and CD-



FIGURE 1: Slightly hypochromic papules on the nasal dorsum and malar regions



FIGURE 2: At lower (A) and higher (B and C) magnifications, basaloid cells forming anastomosed cords and palisade distribution (Hematoxylin & eosin, 40x, 400x, 400x)

FIGURE 3: (A) Immunohistochemistry with positive Bcl-2 only in the outermost tumor cells. (B) Immunohistochemistry demonstrating CD-10 positivity in stromal cells

10 (which also stains matrix cells).Tumor cells present an immunoreaction for Bcl-2 restricted to a few cells on the periphery of the islands, as in the report. The Ki-67 index is low. PCNA is not very prominent, and PTCH mRNA is overexpressed in cells in direct contact with the dermis, while CD-10 of tumor cells is negative.<sup>2</sup> The primary differential diagnosis of localized BFH is basal cell carcinoma, especially the infundibulum cyst. Contrary to BFH, BCC immunohistochemistry shows negative CD-34 in the stroma, diffusely positive Bcl-2, prominent PCNA, diffusely overexpressed PTCH mRNA, and positive CD-10, with a high Ki-67 index.<sup>12</sup> In cases of multiple localized lesions, as in the present report, other hypotheses would be adnexal tumors, trichoepitheliomas, sebaceous hyperplasias, syringomas, and sebaceous nevi.

The malignancy potential of BFH is uncertain, although transformation to BCC has been documented. Of the ten transitional cases reported, eight were linear or unilateral localized variants.<sup>2</sup> It is believed that the rapid growth or change in the clinical appearance of the lesions could alert about BCC development.<sup>2-4</sup> Prophylactic excision is not recommended, especially in multiple presentations.<sup>4</sup>

There is still no established algorithm for the BFH treatment. The literature describes options, such as surgical excision, cryotherapy, CO2 laser, photodynamic therapy, and imiquimod. We chose expectant management with regular clinical follow--up, considering the age of the reported patient and the existence of multiple lesions on the face. Vismodegib, an inhibitor of the hedgehog signaling pathway, may help to treat severe conditions in the future. The use of 5-aminolevulinic acid (5-ALA) associated with photodynamic therapy is safe, being a possible therapy for children with multiple lesions.<sup>1-5</sup>

The prognosis of basaloid follicular hamartoma is excellent, with a notable exception for cases associated with the development of BCC or systemic disorders.<sup>3</sup>

#### CONCLUSION

Basaloid follicular hamartoma is a rare benign neoplasm easily confused, clinically and histopathologically, with BCC. We present the case of a seven-year-old girl with multiple papules in the malar region and on the nasal dorsum, whose initial anatomopathological examination suggested BCC. It is crucial to consider the BFH in the presence of multiple nonspecific lesions in the pediatric age group in healthy children. In this case, revisions of the histopathological study and immunohistochemistry were essential for the diagnosis.

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#### **AUTHORS' CONTRIBUTION:**

**Luana Amaral de Moura** D ORCID 0000-0002-3697-0186 Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Paulo Sergio Emerich Nogueira D ORCID 0000-0003-1528-1100

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

### Elton Almeida Lucas D ORCID 0000-0002-6524-2030

Statistical analysis; approval of the final version of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.

#### Lucia Martins Diniz D ORCID 0000-0001-8107-8878

Statistical analysis; approval of the final version of the manuscript; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; critical literature review; critical revision of the manuscript.

#### Emilly Neves Souza D ORCID 0000-0003-1151-8537

Statistical analysis; approval of the final version of the manuscript study design and planning; preparation and writing of the manuscript; active participation in research orientation; critical literature review; critical revision of the manuscript.



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# Upper eyelid transposition flap for the reconstruction of a lower eyelid defect: a case report

Retalho de transposição da pálpebra superior para reconstrução de defeito na pálpebra inferior: relato de caso

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.2022140156

#### ABSTRACT

Squamous cell carcinoma (SCC) is the second most common skin cancer. When it is located in the lower eyelid region, the reconstruction of the resulting defect can be challenging for the dermatological surgeon, due to the local cosmetic and functional peculiarity. We report the use of an upper eyelid transposition flap for lower eyelid reconstruction with satisfactory results, both in terms of aesthetics and the resulting functionality

Keywords: Carcinoma; squamous cell; Surgical flaps; Eyelids; Eyelid neoplasms

#### RESUMO

O carcinoma espinocelular (CEC) é o segundo câncer de pele mais comum. Quando localizado na região palpebral inferior, a reconstrução do defeito resultante pode se tornar um desafio para o cirurgião dermatológico devido à peculiaridade cosmética e funcional local. Relatamos a utilização de retalho de transposição da pálpebra superior para reconstrução palpebral inferior com resultado satisfatório, tanto pela estética, quanto pela funcionalidade resultante. Palavras

Palavras-chave: Carcinoma de células escamosas; Retalhos cirúrgicos; Pálpebras; Neoplasias palpebrais

# **Case Report**

Authors:

- Rogerio Nabor Kondo<sup>1</sup> Betina Samesima e Singh<sup>1</sup> Victória Prudêncio Ferreira<sup>1</sup> Milene Cripa Pizzato de Araújo<sup>1</sup>
- <sup>1</sup> State University of Londrina, Medical Clinic, Londrina (PR), Brazil

**Correspondence:** Rogerio Nabor Kondo Email: kondo.dermato@gmail.com

#### Financial support: None Conflict of interest: None

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Squamous cell carcinoma (SCC) is the second most common type of skin cancer.<sup>1</sup> Depending on its size and location, the complete excision of this type of tumor requires using a flap to close the resulting defect.<sup>1,2</sup> Reconstructions in the lower eyelid region become more challenging for the dermatological surgeon due to local characteristics such as aesthetic and functional aspects.<sup>3</sup>

The transposition flap (TF) is one of the possibilities for closing larger skin lesions. It uses part of the adjacent skin to fill a nearby defect with little skin laxity. The redirection of tension vectors must be carefully analyzed in advance not to generate local anatomical deformities.<sup>4</sup>

We report the case of a patient who received the modified RT technique for the reconstruction of a lower eyelid defect, using a triangular and longer flap segment instead of a rectangular, short, and slightly rounded at the distal end. This case report aims to exemplify and demonstrate a technique option to correct defects in the lower-lateral eyelid, with easy execution, in a single surgical procedure, and with satisfactory aesthetic results.

#### **METHODS**

We treated a patient with SCC in the lower-lateral eyelid region on the right. A 52-year-old man, white, presented a 16 mm ulcerated plaque in the right infraocular region/outer corner (infra-lateral eyelid on the right). The histopathological examination confirmed SCC. We performed the excision of the lesion with safety margins of 4 mm. The resulting defect was 24 mm in the longest axis, and RT of the upper eyelid region was chosen (Figures 1, 2, and 3).

#### **Technique Description:**

• Patient in horizontal supine position;

• Marking with methylene blue or surgical pen of the lesion with a 4 mm margin and flap incision sites. The marking of the flap starts at the outer corner of the orbital region, 2 mm below the eyebrow tail, extending medially for 30 mm (near the inner corner) and ending at 4 mm below the eyebrow, returning with the incision marking until meeting the upper portion of the defect. The distance from the inferior incision of the flap to the supraciliary edge must be kept above 8 mm. (Figure 1A, 2A, and 2B)

- Antisepsis with topical 10% polyvinyl-iodine;
- Placement of surgical drapes:



FIGURE 1: A - SCC margin and flap marking; B - Defect



FIGURE 2: A - Flap incision; B - Flap detachment; C - Flap movement

• Infiltrative anesthesia with 2% lidocaine with vaso-constrictor;

• Incision with blade 15 of the lesion and bloc excision of the level of subcutaneous depth;

• Hemostasis;

• Incision of the flap, starting at the outer corner of the orbital region, on the upper eyelid, below the eyebrow tail, extending medially to the inner corner and returning with an incision to meet the upper portion of the defect (Figure 2A);

• Detachment of the flap of the level of subcutaneous depth (Figure 2B);

• Transposition movement of the flap from the upper eyelid portion to the defect in the lower eyelid region (Figure 2C);

• Removal of the distal excess of the flap. Fixation of the RT over the defect and closure of the donor area with sutures with mononylon 6.0, single stitches. (Figures 3A and 3B);

• Local cleaning with saline solution;

• Occlusive dressing.

#### RESULTS

The patient evolved uneventfully in the first postoperative days (Figure 3C). There was good healing and accommodation, with

satisfactory aesthetic results in the late postoperative period. (Figures 4A and 4B)

#### DISCUSSION

The upper and lower eyelids are complex structures with specific functions, such as protecting the eyeball from trauma, shielding from excessive light and executing movements towards the tear drainage system, also determining the eye's beauty and expression. Therefore, reconstructions at these sites represent a major challenge for dermatological surgeons, especially when primary closure is not possible.<sup>3</sup>

Flaps can be used in lower eyelid reconstruction. The transposition flap (TF) has a linear configuration, unlike rotation flaps, which have a curvilinear configuration. A rectangular, rhomboidal, or triangular segment of skin and subcutaneous tissue is used, projecting laterally on an axis until reaching the defect that is next to or near it.<sup>4</sup>

William Horner first described TF from the upper to the lower eyelid in 1837. Then Denonvilliers, in 1854, used the technique to correct cicatricial ectropion of the lower eyelid. But it was Denonvilliers' student, Cazelles, who established the method by publishing several drawings in his doctoral thesis



FIGURE 3: A - Flap placement; B - Sutured flap; C - Five days after surgery



FIGURE 4: A - Six months postoperatively, frontal view; B - Six months postoperatively, lateral view



**FIGURE 5:** Original drawing by Horner/Cazelles

in 1860 (Figure 5). Currently, some authors erroneously call it Fricke's transposition since this technique uses a monopedicle skin flap from the temporal or frontal region and not from the upper eyelid, as in the case in question.<sup>5</sup>

The present authors suggest that the flap starts at the outer corner of the orbital region, 2 mm below the eyebrow tail, as Horner/Cazelles originally proposed (Figure 5). However, they indicate that it extends a little further, near the inner corner, at 4 mm below the eyebrow, then returning to meet the upper portion of the defect. We advise keeping a >8 mm distance from the inferior incision of the flap to the supraciliary edge to avoid lagophthalmos (Figure 2A). The resulting triangular-shaped segment facilitates the primary closure of the donor area (Figures 1A, 2A, and 2B).

With the modified Horner/Cazelles technique (Figures 2 and 5), the longer triangular segment and lower flap incision,

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with a distance greater than 8 mm from the supraciliary edge, will hide the upper eyelid scar will in the upper eyelid orbital sulcus, as the suture sites and final healing show (Figures 3C and 4A). With the stress lines distribution, the resulting force will be lateral to the defect and not caudal, preventing ectropion (Figures 4A and 4B).

Despite the knowledge and use of TF for lower eyelid defects by many dermatological surgeons, there are still few cases reported in the literature. The authors consider this procedure a good surgical option, as in our case.

#### CONCLUSION

TF may be a good option to resolve defects in the lower-lateral eyelid regions, considering that it solves the problem in a single surgical procedure with good cosmetics and functionality.

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#### **AUTHORS' CONTRIBUTION:**

Rogerio Nabor Kondo D ORCID\_0000-0003-1848-3314

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

Betina Samesima e Singh D ORCID 0000-0002-6055-0341

Approval of the final version of the manuscript; preparation and writing of the manuscript; critical literature review.

### Victória Prudêncio Ferreira ᅝ 🔍 😳 😳 😳

Approval of the final version of the manuscript; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review.

### Milene Cripa Pizzato de Araújo DORCID 0000-0001-8749-2586

Approval of the final version of the manuscript; preparation and writing of the manuscript; critical literature review.



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# Intravascular papillary endothelial hyperplasia (Masson's tumor) in hallux nail matrix: a case report

Hiperplasia endotelial papilar intravascular (tumor de Masson) na matriz ungueal do hálux: um relato de caso

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#### ABSTRACT

Intravascular endothelial hyperplasia, or Masson's tumor, is a benign vascular lesion with no well-defined pathogenesis. The response to vascular damage is believed to be one of the main reasons for its development. It is a typically painless injury, solitary, with slow evolution. This report aims to describe a case of Masson's tumor in an unusual place, the hallux nail matrix, and discuss its main characteristics. **Keywords:** Hyperplasia; Hallux; Endothelium, Vascular.

#### RESUMO

A hiperplasia endotelial intravascular ou tumor de Masson é uma lesão vascular benigna que não possui patogênese bem definida. Acredita-se que a resposta à lesão dos vasos sanguíneos seja um dos principais motivos para o seu desenvolvimento. É uma lesão tipicamente indolor, única e de evolução lenta. O objetivo deste relato é descrever um caso de tumor de Masson em uma região não habitual, na matriz ungueal do hálux, e discutir suas principais características. **Palavras-chave:** Hiperplasia; Hallux; Endotélio vascular.

### **Case Report**

#### Authors:

Marielle de Godoi Spader<sup>1</sup> Ana Paula Naspolini<sup>1</sup> Sérgio Emerson Sasso<sup>1</sup> Tassiana de Boit Milanez<sup>2</sup> Guilherme Suchard<sup>3</sup>

- <sup>1</sup> Extremo Sul Catarinense University, Department of Graduation in Medicine, Criciúma (SC), Brazil
- <sup>2</sup> Rocha Laboratory, Pathological Anatomy Unit, Criciúma (SC), Brazil.
- <sup>3</sup> Radiological Unit of Criciúma, Department of Ultrasonography, Criciúma (SC), Brazil.

#### Correspondence:

Marielle de Godoi Spader Email: mariellegspader@hotmail.com

#### Financial support: None Conflict of interest: None

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Intravascular papillary endothelial hyperplasia (IPEH) was primarily reported by Pierre Masson in 1923. It is characterized as a benign vascular lesion that causes reactive proliferation of endothelial cells.<sup>1,2</sup> Since then, it has been described as intravascular angiomatosis, vascular proliferation, Masson's pseudoangiosarcoma, or Masson's tumor. Initially described as a specific type of hemangioma, Folke Henschen later confirmed it as a reactive non-neoplastic endothelial proliferation.<sup>2</sup>

#### **CASE REPORT**

We report the case of a 50-year-old man who presented a painless nail alteration in the right hallux with two years of evolution. He declared having already performed previous therapy for onychomycosis with oral fluconazole 150 mg/week for six months in addition to treatment with podiatry and topical antifungal for another four months, without success.

The examination revealed the presence of a longitudinal onychodystrophy of 0.5 cm, with a purplish/hemorrhagic area in the proximal 3 mm, painless to palpation (Figures 1 and 2). The ultrasound study identified a poorly defined, echogenic, subungual nodular lesion with a thickening area with little vascularization on Doppler.

We performed an excisional biopsy of the lesion (Figure 3), whose histological section showed a proliferation of vessels in the dermis, revealing endothelium of mild cytology with papillary formations of intraluminal fibrous bundles and no atypia or atypical necrosis and/or mitosis figures. (Figure 4). The microscopic diagnosis was characteristic of papillary endothelial hyperplasia (intravascular angiomatosis) in a lesion of the nail matrix of the right hallux, and the injury extended focally to the deep margin of the fragment.

#### DISCUSSION

The pathophysiology of this condition is not yet fully understood, although the response to blood vessel injury or thrombosis seems to be the reason.<sup>1</sup> The preference for women has focused on the possible involvement of hormonal factors among the pathogenic cause. The production of angiogenic growth factors and hyperemia by lymphatic stasis are also investigated as possible causes.<sup>3</sup>

Histologically, IPEH can be classified into three types: primary, pure or intravascular, which corresponds to 56% of cases and is associated with venous dilation or, less frequently, with arterial dilation; secondary or mixed (40%), which occurs due to preexisting vascular abnormalities; and extravascular or tertiary (4%), which is observed in extravascular hematomas.<sup>2,4</sup> Histo-



FIGURE 1: Longitudinal onychodystrophy with bleeding area



Figure 2: Lesions seen under dermatoscope



FIGURE 3: Excisional biopsy of the lesion

logically, it presents endothelial papillary projection within the intravascular space associated with thrombi, without endothelial stacking, atypia, or necrosis.<sup>5</sup>

It usually appears on the skin or subcutaneously as a superficial papule or deep nodule with well-defined contours.<sup>2</sup> It is a rare tumor, comprising about 2% to 4% of skin and subcutaneous tissue vascular tumors.<sup>5</sup> Typically, they are painless, slowly evolving, and more common in women. They are frequent in the upper limbs, head, or neck, manifesting between 30 and 40 years of age. Most injuries are unique, but the literature already described associated lesions have already.<sup>2,4</sup>



FIGURE 4: Histological analysis: papillary endothelial hyperplasia (Hematoxylin & Eosin, 200X)

IPEH can be a lobulated, hypoechoic lesion with abundant vascularization on Doppler.<sup>6</sup> In the case reported, we observed a heterogeneous, echogenic nodular lesion with little vascularization on Doppler. It shows how the ultrasonographic findings related to this condition can differ.

IPEH must be differentiated from malignant causes such as angiosarcoma and malignant endovascular papilloma due to their clinical and pathological similarities. The differential diagnosis from angiosarcomas is essential, as these are rarely confined to the vascular lumen.<sup>3</sup>

Surgical excision is the therapy of choice, with a favorable prognosis. Recurrence is not common and is associated with the form the excision was performed.<sup>7</sup>  $\bullet$ 

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#### **AUTHORS' CONTRIBUTION:**

Marielle de Godoi Spader D ORCID\_0000-0001-8957-6679

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.

### Ana Paula Naspolini 问 ORCID\_0000-0002-7201-5709

Statistical analysis; approval of the final version of the manuscript; study design and planning; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.

Sérgio Emerson Sasso D ORCID 0000-0002-2743-5026

Approval of the final version of the manuscript; study design and planning; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases.

**Tassiana de Boit Milanez** ORCID\_0000-0002-7426-1567 Data collection, analysis, and interpretation.

**Guilherme Suchard ORCID** 0000-0003-0561-5445 Data collection, analysis, and interpretation.



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# Chondroid syringoma: unusual presentation of a rare tumor

Siringoma condroide: apresentação incomum de tumor raro

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#### ABSTRACT

Chondroid syringoma, also known as a cutaneous mixed tumor, is a rare benign neoplasm originating from the sweat glands, composed of epithelial structures immersed in a myxochondroid stroma. It usually presents as a solid, single tumor located on the face or neck with a chronic and asymptomatic course. We report the case of a 75-year-old woman with a slightly elevated lesion on the forehead, whose diagnosis was defined by histopathological analysis.

Keywords: Adenoma, pleomorphic; Eccrine glands; Neoplasms.

#### RESUMO

O siringoma condroide, também conhecido como tumor misto cutâneo, é uma neoplasia benigna rara, originada das glândulas sudoríparas, composta por estruturas epiteliais imersas em um estroma mixocondroide. Geralmente, apresenta-se como tumor sólido, único, localizado na face ou pescoço, com evolução crônica e assintomática. Relata-se caso de mulher, 75 anos, com lesão discretamente elevada na fronte, cujo diagnóstico foi definido pela análise histopatológica. **Palavras-chave:** Adenoma Pleomorfo; Glândulas Écrinas; Neoplasias.

# **Case Report**

#### Authors:

- Luana Amaral de Moura<sup>1</sup> Lucia Martins Diniz<sup>1</sup> Robson Dettmann Jarske<sup>2</sup> Emilly Neves Souza<sup>1</sup> Marcela Scárdua Sabbagh de Azevedo<sup>1</sup>
- <sup>1</sup> Federal University of Espírito Santo, Cassiano Antônio Moraes University Hospital, Dermatology Service, Vitória (ES), Brazil.
- <sup>2</sup> Federal University of Espírito Santo, Cassiano Antônio Moraes University Hospital, Pathology Service, Vitória (ES), Brazil.

#### Correspondence:

Luana Amaral de Moura Email: luanamoura@gmail.com

Financial support: None Conflict of interest: None

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Chondroid syringoma is a rare benign adnexal tumor of the skin, composed of epithelial structures immersed in myxochondroid stroma.<sup>1</sup> It usually presents as a solid, single, asymptomatic tumor located on the face or neck, with chronic evolution, whose diagnosis is determined by histopathological analysis.<sup>2</sup> We report a case of a 75-year-old woman with a slightly elevated lesion on the forehead.

#### CASE REPORT

A 75-year-old woman with a history of photodamage and previous excision of three basal cell carcinomas (BCC) reported the appearance of an asymptomatic lesion on her forehead one year ago. On examination, she had an erythematous-atrophic plaque, with a higher and exulcerated medial portion located on the right forehead, close to the hairline (Figure 1). We considered BCC and performed an excisional biopsy with margins of 2 mm (Figure 2). Histopathological analysis showed a tumor characterized by the coexistence of eccrine glands (epithelial structures) and chondroid tissue (mesenchymal), without atypia, with infiltration up to the deep dermis and free resection limits (Figures 3, 4, and 5). Thus, we concluded the diagnosis of chondroid syringoma. The patient is being followed up and presents no clinical signs of recurrence six months after the excision.

#### DISCUSSION

Chondroid syringoma (CS), also known as a cutaneous mixed tumor, is a rare benign neoplasm originating from the sweat glands, which is part of the group of adnexal tumors.<sup>1,2</sup> It corresponds to about 0.098% of all primary skin neoplasms, and



FIGURE 1: A - Erythematous-atrophic plaque, with a higher and exulcerated medial portion, located on the right forehead, close to the hairline. **B** - Approximate image of the lesion



FIGURE 2: Excisional biopsy excisional biopsy with 2 mm margins. A - Pre-surgical marking of the lesion delimiting the margins. B - Immediate postoperative period



**FIGURE 3: A** - Histopathological examination showing proliferation of sweat glands amid the cartilaginous matrix. Absence of mitosis and cellular atypia (Hematoxylin & eosin, 40x). B) Detail of glandular proliferation (Hematoxylin & Eosin, 100x)



**FIGURE 4:** Mixed tumor consisting of proliferation of epithelial (glandular ducts) and mesenchymal (cartilaginous matrix) components (Hematoxylin & Eosin, 100x)

it's more frequent in men (2:1) between 20 and 60 years, which differs from the case reported.<sup>3</sup>

Typically, it manifests as a well-defined, firm, mobile, asymptomatic, slow-growing subcutaneous nodule measuring 0.5cm to 3cm.<sup>1,3,4</sup> The most common locations are the nose, upper lip, scalp, forehead, chin, and malar region.<sup>2</sup> A specific dermoscopic pattern has not yet been described.<sup>3,5</sup> The patient reported a slightly elevated plaque on the forehead, differing from the classic picture, although in the usual topography.

Differential diagnoses include epidermoid cyst, dermatofibroma, cylindroma, eccrine poroma, and basal cell carcinoma.<sup>1,3</sup>

The diagnosis is essentially histopathological due to the non-specificity of the skin lesion. Anatomopathology shows a well-defined tumor in the dermis and/or subcutaneous tissue with overlapping epithelial and mesenchymal components. The epithelial portion includes gland-like structures and cell nests



FIGURE 5: A - Cartilaginous matrix (Hematoxylin & eosin, 100x). B - Glandular ducts (Hematoxylin & Eosin, 400x)

that form ducts and tubules. The mesenchymal element is generally composed of chondromyxoid stroma but focal lipomatous and bone metaplasias have been described.<sup>1-3,5</sup>

CS is a benign tumor with a good prognosis. However, a de novo malignant variety has been described after incomplete resection and in tumors larger than 3 cm. Histological analysis reveals anomalous features, such as asymmetry, cytological atypia, necrosis, involvement of deep structures, and satellite tumor nodules in these cases.<sup>1-3</sup>

Surgical excision is the treatment of choice. The literature also describes the use of electrocoagulation, dermabrasion, and CO2 laser.<sup>1,3</sup> Clinical follow-up is indicated due to the possibility of local recurrence and malignancy. Wide excision is recommended in case of evidence of malignant transformation. Adjuvant radiotherapy may also be considered.<sup>2</sup>

#### CONCLUSION

The present report emphasizes the importance of considering chondroid syringoma as a differential diagnosis of nodular or flat lesions on the face and cervical region of adult and elderly patients, demonstrating a case of a rare tumor with a presentation that differs from the usual one.

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#### **AUTHORS' CONTRIBUTION:**

### Luana Amaral de Moura D ORCID\_0000-0002-3697-0186

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

### Lucia Martins Diniz DRCID 0000-0001-8107-8878

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.

#### Robson Dettmann Jarske D ORCID 0000-0003-0519-2032

Approval of the final version of the manuscript; study design and planning; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases.

### Emilly Neves Souza 问 ORCID\_0000-0003-1151-8537

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.

### Marcela Scárdua Sabbagh de Azevedo D ORCID 0000-0002-1664-3217

Approval of the final version of the manuscript; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.



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# Low-grade fibromyxoid sarcoma: important differential diagnosis in acral tumor lesions

Sarcoma fibromixoide de baixo grau: importante diagnóstico diferencial nas lesões tumorais acrais

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#### ABSTRACT

Low-grade fibromyxoid sarcoma (LGFS) is a rare, indolent spindle cell sarcoma with a risk of recurrence and metastasis. We report the case of a 34-year-old man with a tumor in his thumb that had recurred after excision eight years ago, with slow and progressive growth. The pathological examination was suggestive of SFBG, and we proceeded with the disarticulation of the phalanx. The patient remains in follow-up, with no evidence of metastases. Although rare, it is essential to recognize the diagnosis of an LGFS with its potential risk of recurrences and metastases, especially as a differential diagnosis of acral soft tissue tumors.

Keywords: Dermatology; Neoplasms; Sarcoma

#### RESUMO

O sarcoma fibromixoide de baixo grau (SFBG) é um sarcoma de células fusiformes raro, indolente, porém com risco de recorrência e metástase. Reportamos o caso de um homem de 34 anos, com tumor no polegar recidivado após exérese, há oito anos, com crescimento lento e progressivo. O exame anatomopatológico foi sugestivo de SFBG. Procedeu-se à desarticulação da falange. O paciente mantém seguimento, sem evidências de metástases. Apesar de raro, reconhecer o diagnóstico de um SFBG é importante, levando-se em conta seu risco potencial de recorrências e metástases, principalmente como diagnóstico diferencial de tumorações de partes moles acrais. **Palavras-chave:** Dermatologia; Neoplasias; Sarcoma

### **Case report**

#### Authors:

Flavia de Oliveira Valentim<sup>1</sup> Anna Carolina Miola<sup>1</sup> Hélio Amante Miot<sup>1</sup>

<sup>1</sup> Universidade Estadual Paulista, Dermatology, Botucatu (SP), Brazil.

#### Correspondence:

Anna Carolina Miola Email: anna.c.miola@unesp.br / Alternative email: anna\_fmrp@ yahoo.com.br

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Low-grade fibromyxoid sarcoma (LGFS) is a rare, slowgrowing spindle cell sarcoma that tends to affect young adults and is common in the trunk and proximal extremities.<sup>1</sup> Despite an indolent clinical course, LGFS can progress to local recurrence and metastasis, most commonly to the lungs.<sup>2</sup> We report a rare case of LGFS in the thumb and its treatment.

#### CASE REPORT

A 34-year-old male farmer with no comorbidities presented a slow-growing, painless, 5-cm-diameter tumor, which was excised at the beginning of the condition but had local recurrence after eight years. Dermatological examination revealed a hardened, adherent tumor with a multilobulated appearance and visible telangiectasias on the right thumb (Figures 1 and 2). The biopsy revealed spindle cell mesenchymal neoplasm with cytological atypia, but without relevant mitotic activity or necrosis, distributed in collagenous and myxoid areas in the dermis



**FIGURE 1:** Low-grade fibromyxoid sarcoma. Tumor in the right thumb measuring 5 cm x 3 cm



**FIGURE 2:** Low-grade fibromyxoid sarcoma. Tumor in the right thumb, with exposure of telangiectasia and multilobulated appearance

(Figure 3), suggesting the diagnosis of LGFS. Magnetic resonance imaging (MRI) detected a mass measuring approximately 5 cm x 3 cm, well delimited, lobulated, proximal to the long flexor tendon. We conducted a wide resection with disarticulation at the level of the metacarpophalangeal joint. Pathological examination confirmed the diagnosis of low-grade fibromyxoid sarcoma with free margins. The patient did not present metastases or recurrence after six months of follow-up.

#### DISCUSSION

Low-grade fibromyxoid sarcoma (LGFS) is a rare, slowgrowing spindle cell sarcoma that affects young adults.1 Despite its indolent clinical course, LGFS is a distinct variant of fibrosarcoma,<sup>1</sup> and it can progress to local recurrence and metastasis, particularly in the long term.<sup>2</sup> Most cases of LGFS have been shown to harbor a common t(7;16) (q34;p11) translocation, producing a gene called FUS/GREB3L2, which is characteristic of LGFS but with uncertain significance.<sup>3</sup> Clinically, it is a deep, painless, well-defined mass, more common in the trunk or lower limbs.

It has been reported in numerous anatomical sites, such as the head, neck, heart, and kidney.<sup>1,4,5</sup> However, the acral location is atypical. In a review, it was possible to find 24 cases of acral LGFS, two of them involving a phalanx or nail.<sup>6</sup>

Diagnostic confirmation requires an incisional biopsy, and anatomopathological examination shows alternating myxoid areas with fibrous sites and slightly pleomorphic cells, low or moderate cellularity, and absence of mitotic figures or necrosis. Fine needle aspiration, in turn, can make diagnosis challenging, as the findings overlap with other myxoid lesions.<sup>7,8</sup> Immunohistochemistry can be positive for vimentin and other markers, such as Bcl-2, EMA, and CD99, but without specificity.<sup>1</sup> Magnetic resonance imaging (MRI) can determine the



**FIGURE 3:** Area with fibrous and myxoid stroma with spindle cells (H &E;100xx increase)

surgical area and assess local infiltration and/or metastasis without pathognomonic findings.<sup>9</sup> The common differential diagnoses are desmoid fibromatosis, nodular fasciitis, perineurioma, neurofibroma, myxoma, and ossifying fibromyxoid tumor.<sup>1</sup>

Treatment consists of complete excision of the lesion, which can be challenging depending on the location. There is no need for adjuvant therapy. However, there is a risk of recurrence or metastasis,6 characteristics that justify long-term follow-up.

#### CONCLUSION

LGFS in acral sites is uncommon and may delay diagnosis and proper management. It is essential to recognize and include LGFS in the differential diagnosis of tumors involving acral areas due to its ability to progress to late recurrences and metastases.

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#### **AUTHORS' CONTRIBUTION:**

#### Flavia de Oliveira Valentim D ORCID 0000-0002-1600-3519

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical literature review.

#### Anna Carolina Miola D ORCID 0000-0001-8926-734X

Approval of the final version of the manuscript; preparation and writing of the manuscript; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Hélio Amante Miot D ORCID 0000-0002-2596-9294

Approval of the final version of the manuscript; study design and planning; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.


## Surgical & Cosmetic Dermatology

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## Usefulness of elastic compression bandage on fullthickness skin graft in lower limbs: a series of two cases

Utilidade do curativo compressivo elástico no enxerto de pele total nos membros inferiores: uma série de dois casos

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#### ABSTRACT

Reconstruction with grafting for defects resulting from the removal of squamous cell carcinoma in the lower limbs is a great challenge for the dermatological surgeon. A very thin skin for the receiving area, the inhomogeneity of the local vascularization and the transient venous insufficiency make it difficult to integration of the grafted skin in these regions. For the success of this type of procedure, some techniques can be used to repair these difficulties, such as an elastic compressive dressing that we use in the first postoperative days of a total skin graft on the foot and leg, with good results *Keywords:* Carcinoma squamous cell; Foot; Leg; Graft survival

#### RESUMO

A reconstrução com enxertia para defeitos resultantes de exérese de carcinoma espinocelular nos membros inferiores é um grande desafio para o cirurgião dermatológico, tendo em vista que uma pele muito fina para a área receptora, a não homogeneidade da vascularização local e a insuficiência venosa transitória dificultam a integração da pele enxertada nessas regiões. Para o sucesso desse tipo de procedimento, podem ser usadas algumas técnicas para reparar essas dificuldades, como um curativo compressivo elástico que utilizamos nos primeiros dias de pós-operatório de enxerto de pele total no pé e na perna, com bons resultados.

Palavras-chave: Carcinoma de células escamosas; Pé; Perna (Membro); Sobrevivência de enxerto

### **Case Report**

#### Autores:

- Rogerio Nabor Kondo<sup>1</sup> Suellen Tormina da Silva<sup>1</sup> Gabriela Bernardi Maia<sup>1</sup> Leticia Amstalde Bertoncini<sup>1</sup>
- <sup>1</sup> Universidade Estadual de Londrina, Department of Internal Medicine, Londrina (PR), Brazil

Correspondence: Rogerio Nabor Kondo Email: kondo.dermato@gmail.com

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#### INTRODUCTION

Squamous cell carcinoma (SCC) is the second most common type of skin cancer.<sup>1</sup> When located in the lower limbs, complete excision is usually performed, resulting in a defect that may require a flap or graft for closure. There is a greater preference for reconstructions in this region using a flap rather than a graft to maintain local vascularization.<sup>2</sup>

In addition to the grafted skin being too thin for the defect area of the lower limbs, the inhomogeneity of the vascularization of the receiving region<sup>2</sup> and the transient superficial arterial and venous insufficiency caused by the surgical excision of the site make it challenging to integrate the graft.<sup>3</sup>

To improve the chances of graft integration in the lower limbs, some technical options, such as negative pressure therapy (NPT), which consists of providing subatmospheric pressure to the wound bed, have been used.<sup>4</sup> NPT improves the exudate of venous insufficiency transient and promotes local angiogenesis.

This report aims to demonstrate the use of elastic bandage (EB) over Brown's dressing to improve comfort and protection for the patient. We report two patients where the autograft technique was used (in the foot and the leg), with good integration, aesthetic, and functional results.

#### METHOD

We treated two patients with SCC in the left foot and the right leg:

**Patient 1:** Woman, 78 years old, skin phototype III, from Londrina (PR), with erythematous plaque, 18 mm x 19 mm, on the left foot, compatible with SCC by histopathology. The lesion was excised with 5 mm safety margins, with free margins according to the anatomopathological examination. The resulting defect was 2.9 mm in the longest axis and a graft was chosen (Figures 1, 2, 3, and 4).

**Patient 2:** Man, 76 years old, skin phototype III, from Londrina (PR), with erythematous plaque, 29 mm x 15 mm, on the right leg, compatible with in situ SCC by histopathology. The lesion was excised with 5 mm safety margins, with

free margins according to the anatomopathological examination. The resulting defect was 39 mm in the longest axis and a graft was chosen (Figures 5, 6, 7 and 8).

Description of the Technique of patients 1 and 2 (Figures 1, 2, 3, 4, 5, 6, 7, and 8):

a) Patient in horizontal dorsal decubitus;

b) Marking of the lesion using methylene blue or surgical pen with 5 mm margin (Figures 1 and 5)

c) Antisepsis with topical 10% polyvinyl iodine

d) Placement of surgical drapes;

e) Infiltrative anesthesia with 2% lidocaine with vasoconstrictor;

f) Lesion incision using blade 15 and block excision;

g) Hemostasis;

h) Removal of the donor area (full-thickness graft). Patient 1, donor area from the left iliac fossa region. Patient 2, donor area from the inner arm;

i) Positioning the graft in the receiving area using 4.0 monofilament nylon and cardinal stitches with one of the longest points for fixation of the Brown's dressing. Between cardinal stitches, simple stitches with 4.0 mononylon (Figures 2, 3,6 and 7A) were performed;

j)Fixation of Brown's dressing (Figures 3A and 7A);

k) Wrapping with an elastic bandage, two layers Coban® 3M, 35-40 mmHG (Figure 3B, 7 B e 8A).

#### RESULTS

Patient 1:The patient evolved uneventfully in the immediate postoperative period. There was good healing and setting with satisfactory aesthetic results in the late postoperative period. (Figures 4A and 4B)

Patient 2: The patient evolved uneventfully in the postoperative period. There was good healing and attachment, with no epidermolysis or postoperative necrosis. (Figure 8B)

#### DISCUSSION

Elastic stockings and compressive dressings are therapies described in the treatment of ulcers due to venous or mixed



FIGURE 1: A - Squamous cell carcinoma in the left foot. B - Injury Detail



FIGURE 2: A - Resulting defect in left foot. B - Total skin graft sutured



FIGURE 3: A - Grafting of the left foot with a Brown dressing. B - Elastic band over the Brown bandage



FIGURE 4: A - Left foot grafting on the fifth postoperative day (Brown dressing removal). B - Grafting 6 months after surgery



**FIGURE 5: A** - Squamous cell carcinoma in situ in the right leg. **B** - Detail of the lesion



FIGURE 6: A- Resulting defect. B - Total skin grafting sutured

insufficiencies, and in addition to reducing edema, they improve local perfusion.<sup>5</sup> Surgical excision of the lower limbs causes a temporary superficial venous and arterial insufficiency,<sup>3</sup> which, by itself, leads to graft failure.

Devices that provide negative pressure therapy (NPT) can also facilitate graft take. The applied subatmospheric pressure

reduces edema and promotes local angiogenesis.<sup>4</sup> The problem with NPT is its high cost, making its use unfeasible.

We used a low-cost elastic bandage (EB) (Figure 7B). We kept the Brown's dressing on for five days and two more days after its removal, totaling seven days after surgery (time for local installation of a true circulation). Adequate limb compression



FIGURE 7: A - Right leg grafting with Brown dressing. B - Elastic bandage roll (Coban® 3M)



FIGURE 8: A - Elastic band over Brown's dressing involving the entire segment of the right leg. B - Seventh day after surgery

(according to the manufacturer information, 2-layer Coban® 3M provides 35-40mmHg compression for up to seven days) improved venous pumping as a reduction in local edema without impairing vascular neoformation (Figures 4A and 8B).

Patient 1 showed signs of improved venous insufficiency. There was a reduction in varicosities of the foot around the graft while she used EB (Figure 4A). Also, the bandage helped protect Brown's dressing from external trauma. (Figures 3A and 3B).

Before we implemented the EB technique, the success of lower limb graft survival was poor in our service. We made the graft intending to use it as a biological dressing in cases where the flap was not possible due to the lack of tissue mobility. Epidermolysis and necrosis were visualized when Brown's dressing was removed.

The patients reported in the present study who used EB over Brown's dressing had higher stability of the grafted area, with comfort and local protection. There was good integration and good aesthetic and functional results.

#### CONCLUSION

The use of EB can be a good option for successful lower limb grafts. •

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#### AUTHOR'S CONTRIBUTION:

#### Rogerio Nabor Kondo 问 ORCID 0000-0003-1848-3314

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Suellen Tormina da Silva D ORCID 0000-0002-4687-8332

Approval of the final version of the manuscript; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.

#### Gabriela Bernardi Maia 🕩 ORCID 0000-0002-3730-8207

Approval of the final version of the manuscript; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical revision of the manuscript.

#### Leticia Amstalde Bertoncini D ORCID 0000-0002-4687-8332

Approval of the final version of the manuscript; preparation and writing of the manuscript; data collection, analysis, and interpretation; critical revision of the manuscript.



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# Surgical approach to retronychia refractory to clinical treatments

Abordagem cirúrgica de retroníquia refratária a tratamentos clínicos

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#### ABSTRACT

Retronychia is an inflammatory onychopathy characterized by the disordered growth and stacking of nail plates, associated with an imbalance in the matrix production of plaques, which tend to overlap. This condition may be associated with trauma, evolving with an inflammatory reaction along the proximal nail fold and granulation tissue formation. We report the case of a patient with retronychia in the left hallux, submitted to surgical treatment after failure of therapeutic responses with previous clinical treatments. The surgical approach led to the avulsion of the overlapping nail plates and the excision of voluminous granulation tissues, achieving adequate postoperative evolution. **Keywords:** Nails; Nails; Nails ingrown

#### RESUMO

Retroníquia é uma onicopatia inflamatória caracterizada pelo crescimento desordenado e empilhamento de lâminas ungueais, associados ao desequilíbrio na produção matricial de placas, que costumam se sobrepor. Este quadro pode estar associado a trauma, evoluindo com reação inflamatória junto à dobra ungueal proximal e formação de tecido de granulação. Relatamos o caso de um paciente com retroníquia no hálux esquerdo, submetido a tratamento cirúrgico após falhas de respostas terapêuticas a tratamentos clínicos prévios. A abordagem cirúrgica levou à avulsão das lâminas ungueais sobrepostas e à exérese de volumosos tecidos de granulação, com adequada evolução no pós-operatório. **Palavras-chave:** Doenças da unha; Unhas; Unhas encravadas

## How do I do it?

#### Authors:

lago Gonçalves Ferreira<sup>1</sup>,<sup>2</sup> Livia Giacomet<sup>2</sup> Ana Cristina Dornelles<sup>1</sup> Renan Minotto<sup>1</sup>

- <sup>1</sup> Santa Casa de Misericórdia de Porto Alegre, Dermatology Service, Porto Alegre (RS), Brazil.
- <sup>2</sup> Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre (RS), Brazil.

#### Correspondence:

Renan Minotto Email: rminotto@gmail.com / Alternative email: iago\_ goncalves14@hotmail.com

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#### INTRODUCTION

Retronychia is an inflammatory onychopathy whose etiopathogenesis is still poorly understood. It is characterized by the disordered growth and overlapping of nail plates, associated with an imbalance in the matrix production of plaques and inflammation in the region of the proximal nail fold.<sup>1–3</sup> The term "retronychia" originates from the Latin "retro" ("backward") and Greek "onychia" ("nail"), being first described by De Berker and Renall in 1999 during the 8th Congress of the European Academy of Dermatology and Venereology.<sup>4,5</sup>

The primary triggering mechanism of retronychia is nail microtrauma, which causes the nail plate to lose its attachment to the matrix, leading to new matrix production of plaques and the growth of a new blade under the previous one. This rare condition mainly affects the hallux, and factors such as wearing tight, non-malleable shoes and activities associated with repetitive trauma (running, mountaineering, dancing, among others) can precipitate it.<sup>2,3,6-8</sup>

In refractory to clinical treatments, the surgical approach can be adopted for diagnostic and curative purposes, and it's performed through the avulsion of the overlapping nail plates and excision of the granulation tissue.<sup>3,6,9</sup> This study aimed to describe a surgery technique adopted in the case of retronychia in the hallux.

#### **METHODS**

We report the case of a 35-year-old man, without comorbidities, presenting pain, swelling, and redness in the proximal nail fold and left hallux cuticle, with evolution for about four months. He used antibiotics (cephalexin and amoxicillin) and anti-inflammatory drugs, in addition to topical use of clobetasol, including occlusive mode, fusidic acid, mupirocin, and gentamicin, without improvement. The signs and symptoms arose from the habit of supporting the distal ends of the hallux on the floor while working on the computer at the home office due to the covid-19 pandemic. He denied a similar previous condition and the use of tight shoes, even referring to using flip-flops, socks, or even being barefoot.

On examination, the nail apparatus of the left hallux showed erythema and an inflammatory aspect of the nail folds, edema and apparent hypertrophy of the hyponychium region, onycholysis, white-yellowish chromonychia, and granulation tissue emerging under the cuticle (Figures 1 and 2).

Ultrasonography showed significant thickening of the proximal nail fold and a hypoechoic halo around the nail matrix, associated with disruption of the proximal portion of the ventral nail plate, suggestive of a fragment. No bone remodeling was identified. The Doppler revealed an increase in flow near the proximal nail fold and matrix (Figure 3).

The surgical procedure started with the patient being placed in the supine position, supporting the affected limb, flexed, on padded support, with the sole on the surface of the operating bed. Then, the organization of the operating table, local



**FIGURE 1:** Dermatological examination of the left hallux shows voluminous granulation tissue at the proximal nail border – longitudinal and frontal planes



FIGURE 2: Dermoscopy of the nail plate of the left hallux, demonstrating voluminous granulation tissue under the proximal nail border

antisepsis, and placement of surgical drapes were conducted.

Local anesthesia was performed by anesthetic block (digital, distal, bilateral of the affected hallux) with lidocaine 2% without vasoconstrictor. Subsequently, hemostasis was performed using a number 2 Penrose drain, in a tourniquet, followed by the detachment of the first nail plate and retraction of the proximal nail fold with an electrocautery tip (Figure 4). The detachment of the nail plate evidenced voluminous granulation tissue, which was excised, then proceeding with the removal of the second and third nail plates, in sequence.

Then, the excision of granulation tissue and inflammatory debris was performed in-depth, with total cleaning of the cavity with saline solution. The proximal nail fold was repositioned with the placement of wide-lumen latex surgical drain, with the distal end advancing over the bed to drain postoperative secretions (Figures 5 and 6). We then proceeded to bilateral suture using 5-0 mononylon and applying a bulky containment



FIGURE 3: Doppler ultrasound of the left hallux, in lateral and frontal sections, showing overlapping nail plates below the proximal nail border and increased blood flow in the granulation tissue region



FIGURE 4: Sequence of the operative act: initial detachment of the first plate, folding of the proximal nail fold, exposure, and removal of granulation tissue under the fold, folded plate, and visualization of the second dystrophic plate under the first

dressing with mupirocin, gauze, and crepe bandage. The patient was instructed to perform daily dressings, in addition to the use of antibiotics, anti-inflammatories, and analgesics.

#### RESULTS

The patient had a good postoperative recovery, with clinical improvement (Figure 7). The anatomopathological examination showed chronic ulcerated inflammation with the formation of exuberant granulation tissue in the nail bed (Figure 8).

#### DISCUSSION

We present a case report of retronychia with extensive inflammatory reaction in a young patient, evolving with paronychia and pain in the left hallux. The diagnosis of retronychia is based on clinical manifestations, including paronychia, onychomadesis, chromonychia, reduction and nail growth interruption, and formation of new plaques in conglomerates, in addition to the granulation tissue production, emerging under the nail fold.<sup>1–3,6</sup> Also, other nail changes can be observed, such as xantonychia, onycholysis, and subungual hematoma.<sup>2,6</sup> Despite the characteristic clinical picture, cases of retronychia are often underdiagnosed, making ultrasound an essential diagnostic resource.<sup>2</sup>

In this regard, Fernández et al. established diagnostic ultrasound criteria for retronychia: the presence of a hypoechoic halo or band around the origin; distance between the nail plate origin and the distal phalanx base ( $\geq$ 5.1 mm in the hallux and/ or difference  $\geq$ 0.5 mm regarding the contralateral hallux); proximal nail fold thickness ( $\geq$ 2.2 mm for men or  $\geq$ 1.9 mm for women and/or  $\geq$ 0.3 mm concerning the contralateral hallux). Thus, the simultaneous presence of three criteria may indicate the diagnosis of unilateral retronychia, and, in bilateral cases, the presence of at least two criteria, one of which is the presence of a hypoechoic halo, may favor the diagnosis.<sup>10</sup>



**FIGURE 5:** Sequence of the operative act: detachment of the second plate and visualization of abundant granulation tissue in-depth, removal of the granulomatous material, removal of the third fragmented and dystrophic plate, removal of devitalized tissues on the bed, cleaning, and washing of the cavity, placement of a latex, proximal fold repositioning, suture



FIGURE 6: Nail blades excised during nail surgery for retronychia in the left hallux\*

\*Slides exposed in sequence, from the first to the last plate removed, from bottom to top In the case reported here, ultrasonography demonstrates the three diagnostic ultrasonographic criteria (increased distance between the nail plate origin and the distal phalanx base; increased proximal nail fold thickness, and a hypoechoic halo below the origin of the plaque). There is also a growth in blood flow in the dermis of the nail fold posterior to Doppler.

Regarding the retronychia treatment, in mild forms, a conservative approach can be adopted, considering that some of these types may spontaneously involute. Conservative therapy includes using adhesive tape and orthoses to fix the "loose" nail plate in the proximal region or applying topical corticosteroids to the proximal nail edge. Topical therapy can act by reducing inflammation and swelling in the proximal nail fold, as observed by Lencastre et al., where topical steroids, associated or not with occlusion, showed a complete or partial clinical response in 41.1% and 28.5% of cases of retronychia, respectively.<sup>11</sup> However, despite the clinical improvement, recurrences in these situations are frequent.

Thus, in advanced and/or recurrent cases, the surgical approach is more indicated, promoting the resolution of the condition from the avulsion of the overlapping nail plates and excision of the granulation tissue,<sup>1,3,6,7</sup> as performed in the reported case. The histopathological examination is not essential for diagnosis; however, it is recommended that the excised material is sent to pathological analysis to exclude the diagnosis of neoplasms of the proximal nail fold, as conducted in this case.

Concerning the postoperative complications, they involve onychocryptosis, micronychia, onychodystrophy, and periungual tissue hypertrophy.<sup>1,3,6,7</sup> Post-surgical recurrence is rare, but it can occur. Therefore, patients should be instructed on preventive measures to avoid triggering factors such as the use of properly sized shoes, correction of orthopedic disorders of the feet, and deviations in nail growth.<sup>3,6,9</sup>



**FIGURE 7:** Postoperative dermatological examination at 14 days and after 60 days, in sequence



**FIGURE 8:** Histopathological examination of the excised granulation tissue, showing neutrophilic infiltrate, extravasation of red blood cells, and fibrin deposits in the dermis: Hematoxylin & eosin staining 100x **A** and 400x **B** 

#### CONCLUSION

We described the surgical technique adopted in the case of exuberant retronychia without previous clinical response. We observed an abundant amount of granulation tissue intraoperatively, including under the plates, emphasizing the severity and peculiarity of the case, rarely reported in the literature. It's noteworthy that the technique described is one of the possible options for the surgical treatment of these cases.  $\bullet$ 

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#### **AUTHORS' CONTRIBUTION:**

#### Iago Gonçalves Ferreira D ORCID 0000-0002-4695-1982

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### **Livia Giacomet D ORCID** 0000-0001-8474-7002

Approval of the final version of the manuscript; preparation and writing of the manuscript; data collection, analysis, and interpretation critical literature review; critical revision of the manuscript.

#### Ana Cristina Dornelles D ORCID 0000-0001-8597-117X

Approval of the final version of the manuscript; study design and planning; intellectual participation in propaedeutic and/or therapeutic conduct of studied case; critical revision of the manuscript.

#### **Renan Minotto** (D ORCID 0000-0002-1451-0461

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical revision of the manuscript.





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# A.S.A.P. - The first algorithm to treat keloids and hypertrophic scars

A.S.A.P. - O primeiro algoritmo para tratar queloides e cicatrizes hipertróficas

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#### ABSTRACT

Keloids (K) and hypertrophic scars (HS) are highly prevalent, but their treatment is still challenging. Several treatments are beneficial to treat K/HS, but there is still no protocol or algorithm to address scars following an organized step-by-step and justifying each type of treatment in the scar phases. This study aims to present an algorithm to treat keloids/scars. It has been used for several years in our clinic and helps organize several therapies to treat scars. Combined, these sequences of treatments lead to progressive improvement in K and HS.

Keywords: Acne keloid; Hypertrophic scar; Keloid.

#### RESUMO

Queloides e cicatrizes hipertróficas são muito prevalentes, mas seu tratamento ainda é desafiador. Vários tratamentos se mostraram benéficos, mas ainda não há um protocolo ou algoritmo para abordar cicatrizes, que siga um passo-a-passo organizado e que justifique o uso de cada tipo de tratamento em uma fase da cicatriz. O objetivo deste estudo é apresentar uma proposta de algoritmo para tratar cicatrizes, usado em nosso serviço por alguns anos. Ele ajuda a organizar as diversas terapias empregadas no tratamento de cicatrizes. Combinadas, estas sequências de tratamentos levam a uma melhora progressiva em queloides e cicatrizes hipertróficas.

Palavras-chave: Acne queloide; Cicatriz; Cicatriz hipertrófica; Queloide.

### How do I do it?

#### Authors:

Gisele Viana Oliveira<sup>1</sup> Leandra D'Orsi Metsavaht<sup>2</sup>

- <sup>1</sup> Hospital Luxemburgo, Dermatology Outpatient Clinic– Cicatrizes, Belo Horizonte (MG), Brazil.
- <sup>2</sup> Leandra D'Orsi Metsavaht Dermatology, Rio de Janeiro (RJ), Brazil.

#### **Correspondence:**

Gisele Viana Oliveira Email: medderma@gmail.com / Alternative email: medderma@ gmail.com

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#### INTRODUCTION

Keloids (K) and hypertrophic scars (HS) are highly prevalent. However, their treatment is still significantly challenging.<sup>1</sup> Symptoms such as itch and pain, and aesthetic and psychological complaints negatively interfere with affected individuals' health-related quality of life (HRQL) and burden of keloid disease.<sup>1,2</sup> Surgery frequently leads to recurrence,<sup>1,2</sup> and the bad outcome can be interpreted as malpractice in litigation, which is always a concern among plastic surgeons and dermatologists.<sup>3</sup>

During a prospective randomized study to investigate the effectiveness of silicone dressings to treat scars due to an anti-scarring silicone effect, or occlusion, we employed silicone or hydrocolloid sheets on a group of K/HS, and we observed that both dressings were successful in decreasing K/ HS physical and subjective parameters. We also observed that the injection of triamcinolone in previously softened lesions was less painful, and the drug could diffuse throughout the whole lesion.<sup>4</sup> On our outpatient clinic focused on K/HS treatment, we later found out that after using this "softening" procedure for several weeks, fewer injections of steroids were sufficient to treat large lesions that previously would require more sessions.<sup>5</sup> We have later incorporated technologies such as Intense Pulsed Light (IPL), which made the injections even easier, motivating us to write a protocol to treat scars.<sup>5</sup> Also, the increased number of patients with atrophic scars after steroid injections on K/HS referred to our ambulatory became part of our incentive; we observed that following the guidelines of our protocol could avoid scar atrophy, which also leads to patient dissatisfaction.

The objective of this manuscript is to share a simple algorithm to treat K and HS. The A.S.A.P algorithm discusses the rationale to combine four sequential steps, leading to a progressive improvement in K/HS.

## Algorithm step 1. A – Assessment: analyze carefully before any treatments (<u>A.</u>S.A.P)

Patients that come to their first appointment to the keloids and scars outpatient clinic can be separated into four groups of scars:

1) K/HS, without previous treatments;

2) Post-burn or post-traumatic scars, referred to our facility after hospital discharge;

3) Recurrent keloids, after previous therapies; usually treated with surgery, cryotherapy, or steroid injections;

4) Atrophic scars, after the complete resolution of a previous K/HS, due to corticosteroid injections.

This last subset of patients is usually as dissatisfied as patients of the three other groups. Although previous K or HS improved after receiving multiple triamcinolone injections, or even occlusive steroids impregnated tapes for long periods, these scars evolved into depressed, achromic, teleangiectasic lesions. Steroid injections are popular among dermatologists and plastic surgeons due to the apparent ease of the technique and the possibility to be performed during the first appointment as an in-office procedure. Thus, they are usually chosen as the first approach to K/HS. While litigation and lawsuits involving cosmetic surgery are a growing concern, verifying the real need for drug administration or a medical procedure is an essential step to avoid iatrogenesis.<sup>3</sup>

The first algorithm phase ("A" – assessment) requires the physician to classify the scar to be treated, and analyze the best approach for each one of these lesions (Table 1). Steroids should not be used as a first method to treat hypertrophic scars, as natural subsequent atrophy might follow, and steroids could maximize the outcome. Keloids may need steroids injections at some point, but they may respond better to injections after softening by occlusive dressings – the next algorithm (Step "S" – Figure 1). Large lesions such as pedunculated earlobe keloids may be referred for surgery plus radiotherapy, or intralesional cryotherapy, with further follow-up and eventual referral to algorithm Steps 2, 3, and 4 to avoid keloid recurrence (Table 1). Retractile scars may also benefit from surgery in the beginning, although some may be treated with noninvasive methods<sup>5</sup> (Figure 2. A and B).

Histamine H1 blockers are anti-inflammatory and antiproliferative drugs that relieve pain and itching sensations on keloids and hypertrophic scars. They inhibit the deposition of collagen by a mechanism of TGF-beta suppression.<sup>6</sup> Oral antihistaminic drugs are given on this first treatment phase to relieve symptoms of very itchy scars. Therefore, Step A – "Analyze before any treatments" is the first algorithm stage (Figure 1, A, C, Figure 3, Table 1).

## Algorithm step 2. S - <u>S</u>often the scar before injections (A.<u>S</u>.A.P.)

Steroids and anti-neoplastic injections are worldwide accepted methods to treat K and HS. However, their use on keloids with substantial stiffness can be challenging, causing significant patient discomfort and pain. We have previously described that occlusive dressings can help soften the scars before the injections, decreasing pain and allowing lower steroid doses to diffuse better on the fibrotic tissue<sup>4</sup> (Figure 1, A, B,Video 1).

Occlusive silicone and hydrocolloid dressings lead to a comparable decrease in volume, symptoms, and erythema, finally softening the K/HS.<sup>4</sup> Scars treated with both dressings improve Vancouver Scar Scale parameters and reduce intra-scar pressure, facilitating intralesional triamcinolone (TA) injections.<sup>4</sup> Hydrocolloids are self-adhering and chosen to treat body regions that have greater mobility, such as eyelids and hands.<sup>5</sup> Silicone and non-silicone dressings are covered with microporous tape and can be changed each 7-15 days.<sup>4,5</sup> After 2-4 months, a significant improvement in pain/itching and scar pliability are observed, and injections are easily performed in . . . . . . . .

	TABLE 1: Clinical evaluation and management					
<b>PROTOCOL STEP 1.A -</b> Analyze the scar that will be treated   Requires scar classification						
	HYPERTROPHIC SCAR Respects de limits of the original scar Area not particularly prone to the formation of keloids May improve overtime	DO NOT use steroids (may cause atrophy)				
	<b>KELOID</b> It grows beyond the limits of the original scar Significant stiffness may difficult scar injections	Follow to next Protocol Step 2- S Softening the keloid will allow for easier injections				
	<b>PEDUNCULATED KELOIDS</b> It grows continuously It will not improve without treatment	Therapeutic approaches: Surgery plus radiotherapy and follow to Protocol Step 2 Protocol Steps 2-3 (some lesions may improve) Intralesional Cryotherapy followed by Protocol Step 2				

PROTOCOL STEP 2. S - Soften the scar or keloid to prepare them for future injections

SILICONE DRESSING	Comes in different forms and sizes Stripes, sheets	Must cover the whole K/HS It needs to be fixed on skin by microporous medical tape. After each 7 days, remove, rinse skin and silicone sheet. Can be reused for 1–4 months		
NON-SILICONE DRESSINGS		Must be replaced each 7 days		
PRESSURE GARMENTS	Can be manufactured to suit patient's needs	Earrings, elastic garments		
PROTOCOL STEP 3. A				
Approach the keloid or scar with lasers a	and injections			

Triamcinolone hexacetonide (TH)	Monthly injections	Very small volumes, 0,1-0,3 ml total dose		
5-FU	1:1 or 9:1 combinations with TH			
Bleomycine	1:1 combination with TH			
IPL	Applied immediately prior to the injections, may lead to transient edema that facilitates injections			

#### **PROTOCOL STEP 4. P**

It is easier to treat pigmentation and improve the quality of the skin/scar after hypertrophy has resolved

Retinoic acid, glycolic acid, hydroquinone - help prepare scar before peels and lasers

Peelings- Retinoic acid- several sessions

8-MOP-Topical, and sun exposure- Improve achromic scars

Microneedling- Improve achromic scars and the quality of the skin

Fractional and non-fractional laser- help organize scar collagen and improve the quality of the skin

Fat grafts- may help the resulting scar/skin quality and help decrease uneven scars

softer scars<sup>4,5</sup> (Video 1). Occlusive dressings and pressure garments may lead to a satisfactory outcome even without injections and technologies.

Pressure garments (PG) are a worldwide accepted method to treat K/HS<sup>6</sup> and they are also employed in this phase. Garments' correct use is mandatory to exert their effects; they should contact the whole scar for several hours/day, and promote blanching.7 PG helps dressings stay in place and protects the scar from sun exposure. We customize handcrafted garment devices using elastic and inelastic fabrics combined in different models to suit patients' needs.<sup>4</sup> Most HS become flat solely by the dressings and PG, as well as small K. An adverse event commonly observed in this phase is "miliaria", due to the long periods of occlusion. We advise patients to remove the dressings and garments for two days, rinsing the affected skin several times. It is important to mention that pain and itching significantly decrease during algorithm stage "S".4,5 Patients who present complete flattening do not need to go through the next algorithm step ("A"), but can follow to the last algorithm phase ("P") (Figure 3).

Algorithm step 2 "S" can be achieved after 1-4 months of occlusive (silicone and non-silicone) dressings and pressure garments.

## Algorithm step 3. A - Approach with injections and technologies (A.S.A.P.)

Once the K/HS is softened, it becomes prone to receive less painful injections with a better drug diffusion into the scar tissue<sup>4</sup> (Figure 1, B). Triamcinolone acetonide (TA) is the preferred intralesional drug to treat HS/K. However, it has been discontinued in Brazil, where triamcinolone hexacetonide (TH) is now used with satisfactory results.<sup>5</sup> The combination of TA with 5FU is more effective to treat scars than TA.<sup>5</sup> It can be used in different combinations with acceptable results.<sup>8</sup> Bleomycin seems to be more effective than 5-FU,<sup>9</sup> but it needs extra care during dilution to prevent inhalation, because it shows a higher incidence of hyperpigmentation, and its manipulation may require extra regulatory rules that may limit its use. Antineoplastic drugs are used in low doses, always combined with triamcinolone. The rationale is to be highly effective with the lowest possible volume. Pregnancy should always be ruled out.<sup>5</sup>

Intense Pulsed Light (IPL) is effective to treat HS/K, targeting scar vascular proliferation and pigmentation.<sup>10</sup> IPL is used immediately before the injections. Scars covered with dressings for several weeks become less pigmented, allowing a safer IPL session, except for higher skin phototypes<sup>11</sup> patients. The transient swelling that follows IPL application might enhance TH spreading throughout the scar.



FIGURE 1: This patient presented with keloidal acne lesions despite attempts of treatment with triamcinolone injections; he referred pain during the procedure and regrowth after a few months. B - 6 months after occlusive hydrocolloid dressings, with decrease in keloids height and symptoms; remaining keloids are now soft enough to receive injections. Algorithm: Step A - analysis showed him to have extensive keloids. Step S - he started with hydrocolloids to soften keloids before injections.



**FIGURE 2: Algorithm: Step A** - retractile scar. **Step S** - treated with occlusive dressings. **Step A** - scar was approached with IPL (1 session) and Step P- microneedling (2 sessions) was used to improve the quality of the scar. **C,D,E,F** - **burned pacient** showed progressive improvement with topical retinoids, hydroquinone, glycolic acid, followed by 6 sessions of retinoic acid peels. **Algorithm: Step A** - slightly hypertrophic and hyperpigmented facial scar, if approached with injected or topical steroids, could develop atrophy. She went straight to **Step P** in order to treat pigmentation and the quality of scar.



VIDEO 1. Keloids and scars must be softened to allow for and easier injection.

Algorithm Step 3 – "A"- can be achieved using triamcinolone injections, which may be associated with antineoplastic drugs Bleomycin and 5-FU, with IPL sessions immediately prior to the injections.

## Algorithm phase 4. P - Treat Pigmentation and the quality of the skin (A.S.A.P)

K/HS treated with occlusion, pressure garments, IPL, triamcinolone, and antineoplastic drugs become flat and pale. However, hyper/hypopigmentation frequently remains. The last stage of this algorithm ("P") focuses on improving the quality of the skin and the mixed scar pigmentation. Topical retinoids, the association of glycolic acid and hydroquinone, chemical peelings, and microneedling are then combined to achieve a more uniform scar color.<sup>12</sup> Topical tretinoin improves skin/scar by modulating keratinization and the differentiation of fibroblasts and keratinocytes. Retinoic acid (RA) peels are safely used in higher phototypes, leading to clinical improvement in the skin texture and appearance<sup>13</sup> after 5-10 serial sessions (Figure 2. Table 1).

The inkless tattoo microneedling has been described as an effective "needle dermabrasion" treatment for different scar types, with special benefits regarding achromic scars repigmentation<sup>14</sup> (Figure 2. A, B). Satisfactory results can be achieved after just one session in different types of scars<sup>14</sup> (Table 1).

Similar to other authors, we also treat the achromic scars using topical psoralen combined with daylight exposure.<sup>15</sup> A compounding 0,5%-1% (8-methoxypsoralen) cream was applied to the scar, exposed to sunlight starting 3 minutes/day, 3-4 times/week, and increasing 2 minutes/week up to 15 minutes (Table 1).

Autologous melanocytes transplantation<sup>16</sup> and fat graftings<sup>17</sup> may also be used on the last protocol phase to help achieve improved cosmetic results, as well as IPL, erbium, and  $CO_2$  fractional lasers. K is frequently observed in the skin of color and Brazilian patients culturally prone to sun exposure, leading to scar hyperpigmentation, although during the previous steps the skin usually loses its tanning (Table 1).

Nonablative fractional erbium (1540 wavelength),  $CO_2$ and ablative 2950 wavelength lasers contribute to a final retouch, allowing improvement of scar color and texture<sup>17,18,19</sup> (Table 1).

The A.S.A.P. algorithm has been extensively used in our clinic. It helps organize the several steps needed to improve those lesions (Figure 1, Figure 2), which may be used as a guide to treat virtually any HS/K after trauma, surgery, piercings, acne, and viral diseases that affect skin and burns (Figure 3).



**FIGURE 3:** The A.S.A.P algorithm can be used to treat virtually all hypertrophic and keloidal scars. **A** - analyze the type of scar (keloid, hypertrophic, atrophic) - Atrophic scars should be excised and replaced by a new scar. **K** and **HS** are treated on the second algorithm phase. HS could develop severe atrophy if treated prematurely with steroids. Keloids usually show significant stiffness that does not allow for easy injections. **S** - Soften scars before injections - using pressure garments, silicone, and hydrocolloid dressings, scars become pale, flatter, and soft - allowing for easier injections of triamcinolone combined with antineoplastic drugs. **A** - Approach with technologies and injections. IPL, when performed immediately before the injections, causes slight edema that also helps injected drugs to diffuse on the fibrous tissue. Triamcinolone may be combined with 5-FU, bleomycin, or calcium channel blockers in monthly sessions. Dressings and pressure garments may continue during this phase. Large keloids such as pedunculated earlobe keloids are treated with excision and radiation, with or without triamcinolone. Finally on the last algorithm phase- P- Treat pigmentation and the quality of the skin- fractional and nonfractional lasers, IPL, microneedling, peelings, and methoxypsoralen are combined to promote a more uniform scar.

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#### **AUTHORS' CONTRIBUTION:**

#### Gisele Viana Oliveira D ORCID 0000-0001-5101-7097

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

#### Leandra D'Orsi Metsavaht D ORCID 0000-0001-9009-9929

Approval of the final version of the manuscript; preparation and writing of the manuscript; study design and planning; data collection, analysis, and interpretation; critical literature review; critical revision of the manuscript.



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## FUE hair transplant: how I do it?

Transplante capilar com técnica FUE: como eu faço?

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#### ABSTRACT

Modern hair transplant is constantly evolving. We intend to demonstrate our techniques and methodologies, and especially to describe the dynamics of the entire surgical process of the FUE (Follicular Unit Extraction), technique, from the discussion of the surgical strategy with the patient and evaluation of the donor area to extraction and implantation. The dermatologist must understand the complexity of the procedure and the need for adequate training to achieve a good surgical result. Keywords: Alopecia; Hair; Hair follicle; Transplant donor site

#### RESUMO

O transplante capilar moderno está em constante evolução, e nossa intenção não é apenas demonstrar nossas técnicas e metodologias, mas, principalmente, descrever a dinâmica de todo o processo cirúrgico da técnica FUE (Follicular Unit Extraction), desde a discussão da estratégia cirúrgica com o paciente e a avaliação da área doadora até extração e implantação. É de extrema importância que o dermatologista compreenda a complexidade do procedimento e a necessidade de um treinamento adequado para que um bom resultado seja alcançado.

Palavras-chave: Alopecia; Cabelo; Folículo piloso

## How do I do it?

Authors: Luciana Takata Pontes<sup>1</sup> Antonio Ruston<sup>1</sup>

Restauração capilar, Ruston Clinic, São Paulo (SP), Brazil.

#### Correspondence:

Luciana Takata Pontes dra.luciana@ruston.com.br

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#### INTRODUCTION

A hair transplant is not a simple procedure. Regardless of the technique, there is a need for a trained team and an apt and experienced surgeon to achieve better results.

Initially, it was performed using large flaps. Then, the technique evolved to grafts with larger punches. Now we refined the method to follicular unit transplants. Follicular unit (FU) identification as a particular structure of hair follicles was essential to achieve the most natural result.<sup>1</sup>

In the Follicular Unit Transplant (FUT), a strip of the scalp is removed from the occipital donor region, reaching the temporal regions, and the FUs are separated under the microscope. In the Follicular Unit Extraction (FUE) method, FUs are taken individually from the entire safe donor area where there is no risk of miniaturization. Punch diameters ranging from 0.8 mm to 1.0 mm are used in most cases. These microincisions heal by secondary intention, with no need for sutures.<sup>1</sup>

Modern hair transplant is constantly evolving, and we intend not only to demonstrate our techniques and methodologies but also to describe the dynamics of the FUE technique surgical process, from the discussion of the surgical strategy with the patient and evaluation of the donor area to extraction and implantation.

#### **METHODS**

#### 1 - Surgical planning

In the preoperative room, photos are taken with the hair long, first dry, and then wet to better assess the rarefaction area. The surgical strategy is discussed with the patient (such as hairline height and priority areas), aligning expectations with what is possible in each case.<sup>2</sup> Then, the patient's hair is shaved between 0.5 mm and 1.0 mm and new photos are taken (Figure 1). In case of rarefaction, only at the entrances (Norwood-Hamilton 2) can one opt for a military-style shave (Figure 2).



FIGURE 2: Option for the military-style cut in the dense packing treatment of the entrances





FIGURE 1: Discussion of strategy and photographic documentation with long and shaved hair

#### 2 - Assessment of the donor area

Hair samples are taken from the occipital, parietal, and temporal regions to assess the donor area. A digital micrometer is used to evaluate the thickness of these hairs (Figure 3) and calculate the Coverage Value (CV). The software determines how many FUs can be extracted without visible rarefaction of the donor area.

The area is divided into five subunits, and photographic documentation is conducted using a dermatoscope attached to a tablet (Figure 4). Both the measurement in centimeters and the photographs are sent to the Coverage Value Software (Asmed



FIGURE 3: Data sent to Coverage Value: hair thickness, area in centimeters, and dermoscopic photos of safe donor area subunits

Hair Transplant, Istanbul). The approximate value of FUs/cm<sup>2</sup> and hairs/cm<sup>2</sup> in each subunit is calculated and a report is generated, providing information for management during extraction, such as the approximate value of FUs for future surgeries and regions where treatment be more aggressive without depletion of the donor area or cosmetic impairment (Figures 4 and 5).

#### 3 - Anesthesia

Anesthetic infiltration and regional block are performed with 2% lidocaine with vasoconstrictor extremely slowly and associated with a vibrating stimulus to minimize discomfort.<sup>3</sup> A tumescent solution is used both in the donor and recipient areas.

#### 4 - Extraction

The first step is to decide the punch depth. We started the extraction with a depth of 3.0 mm to 3.5 mm. If there is capping (the epidermis is removed but the follicle remains trapped), probably the punch is too superficial (Figure 6). If the graft undergoes transection and gets stuck inside the punch, possibly the punch is too deep.<sup>4</sup>

The next step is to decide the best punch diameter. The choice will depend on the characteristics of the graft, such as the degree of waviness, the level of opening, and how the follicles are distributed in each follicular unit. We performed a test extraction of approximately 50 grafts with each one to evaluate the hair/UF ratio and the transection rate.<sup>5</sup> For most patients, we used punches of 0.8 mm to 0.9 mm.

We started the procedure with the patient in the prone position to extract the occipital region. Then, we moved the patient laterally to extract the parietal and temporal regions.

We use the device Trivellini Mamba FUE (Trivellini Tech, Paraguay) as it can be used to determine, on a case-by-case basis, the rotation time followed by the punch oscillation time during skin perforation, decreasing the transection rates of the follicular bulbs.<sup>6,7</sup> After perforation, the grafts are extracted with two delicate forceps: one thinner and straighter to hold the epidermis and another serrated to remove the graft.<sup>8</sup>



**FIGURE 4:** Punch depth adjustment. If there is capping, it is because it is too superficial. If the graft gets stuck in the punch, it means it's too deep



FIGURE 5: Hair Counter Software: analysis of the occipital donor region

#### 5 - Quality control and cleaning of grafts

All grafts are reviewed under the microscope, separated into UFs of 1, 2, 3, or more hairs, and total and partial transection rates are calculated. The team cleans the grafts, removing excess epidermis, as there is less formation of crusts in the postoperative period, also allowing a higher final density since it is possible to place these grafts closer to each other.

#### 6 - Storage

The UFs are separated in flasks according to the area extracted and the amount of hairs (1, 2, 3, or more hairs). The first grafts removed are the first to be implanted, thus reducing the time out of the body as much as possible. They are stored in a specific refrigerator (4 °C) in saline. Air humidifiers are used throughout the procedure.

#### 7 - Implantation: previous incisions

We prefer to make previous incisions in the recipient area with customized blades from 0.65 mm to 0.90 mm in width. We follow a specific order: 1) The irregular frontal line with two to three rows of one-hair UFs; 2) Transition zone with two-hair UFs); 3) Definition zone with UFs of three or more hairs; 4) Other regions of baldness or thinning.<sup>9,10</sup> It is important to measure the length of the grafts and reduce the depth of the incision

Calib	T	0,046 mm	Coverage Value	T	5,93				
	P	0,056 mm	(C x h/cm2)	P	9,91				
	0	0,051 mm		0	9,08				
Dens	÷.	CO CILLion	-	-	TOTAL	22424			
		69 FU/cm	2 nairs per area		10062 DUNOR	32434			
	P.	88,5 FU/cm	2 (A x n/cm2)	P	9912				
	U	84 FU/cm	2	0	12400		P	U	
h/cm2	T	129 h/cm2	FU per area	т	5382 DONOR FU	16218 Area	78 Area	56 Area	70
	P	177 h/cm2	(D x A)	P	4956	Density	69 Density	88,5 Density	84
	0	178 h/cm2		0	5880	Hair/FU	1.87 Hair/FU	2,00 Hair/FU	2,12
Area	T	78 cm2	TOTAL DONOR AREA		204	cv	5,93 CV	9,91 CV	9,08
	P	56 cm2	Hair per FU	T	1,87	EPCV	0,00 EPCV	0,00 EPCV	0,00
	0	70 cm2	((h/cm2)/D)	P	2,00				
				0	2,12				
			Average Hair/FU		tente.				
			(Ah/FU)		2,00				
			Average Caliber (AC)		0.051				
DONOR EVA	UATION								
Grafts that									
can be			Total grafts that can						
extracted	T	964	be extracted	5130	TOTAL %	31,63 %			
DxA-((Ax									
DDCV)/AC x	p	1001							
N/FU)	0	2174							
		44/7							
Dogor									

FIGURE 6: Coverage Value (CV) Statistics: Hair Counter Software results plus the average thickness of hair from the temporal, parietal, and occipital donor areas are used for the CV results. For no visualization of the scalp, the CV must be greater than 5.4. In this example, the CV in the temporal area is extremely low (5.94), warning of the risk of future cosmetic depletion. This patient has a total number of FUs of approximately 16,218. But, considering its measurements of safe donor area, follicle thickness, density and coefficient in each area, the CV software considers that only 31.63% of FUs can be extracted during its lifetime, that is, approximately 5,130 FUs



**FIGURE 7:** Pre-incisions with customized microblades throughout the recipient area. Use of KEEP for placement of grafts with less trauma to the bulbs, and result the day after the procedure, after washing performed in the clinic



FIGURE 8: Final result one year after the procedure, with 3,654 follicular units. Front resolution and middle and crown improvement. Associated clinical treatment was performed.

by 1 mm – it allows the epidermis to be just above the skin surface, decreasing post-operative folliculitis and uneven scarring.

#### 8 - Graft placement: use of KEEP

We have been using KEEP implants (Figure 7) for the last five years. This tool has a special tip that protects the graft during placement, avoiding traumatizing it. With a rotating movement, the graft is fitted inside the KEEP tip; then, the graft is gently slid into the previous incision with the aid of forceps. KEEP implanters come in different sizes to place UFs with a different number of hairs.

#### RESULTS

After the procedure is finished the entire surgical area is cleaned with saline solution. We didn't leave any bandages. The patient is referred to the resting room to receive all the instructions and postoperative medications. We assess the patient the next day for scalp washing and reorientation. We get the intermediate result in around six months and the final result in a year (Figure 8).

#### DISCUSSION

Despite being a superficial procedure, FUE hair transplant surgery requires the surgeon to be attentive to all stages of the procedure, considering the treatment of the receiving bald area and also the maximum preservation of the donor area for a better result for the patient.

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#### AUTHORS' CONTRIBUTION:

#### Luciana Takata Pontes D ORCID 0000-0002-9383-0569

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

Antonio Ruston D ORCID 0000-0003-0067-9255

Active participation in research orientation; critical literature review.



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## Dermoscopy of eruptive vellus hair cyst

Dermatoscopia do cisto veloso eruptivo

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#### ABSTRACT

Eruptive vellus hair cyst is a rare and benign dermatological condition in the development of vellus-type hair follicles. It affects mainly children and young adults, and is characterized by multiple asymptomatic papules, especially on the trunk. We report the case of a 33-year-old white man who presented multiple erythematous papules and pustules located on the trunk for about five years, refractory to topical treatments for acne. Dermoscopy revealed oval lesions with eccentric exulceration and rare protruding filiform structures. We established the diagnosis of eruptive vellus hair cyst based on the findings of dermoscopy and histopathological examination.

Keywords: Cysts; Acneiform eruptions; HIV

#### RESUMO

Cisto veloso eruptivo é condição dermatológica rara e benigna do desenvolvimento dos folículos pilosos do tipo vellus, que acomete principalmente crianças e adultos jovens, e se caracteriza por múltiplas pápulas assintomáticas, especialmente no tronco. Apresentamos o caso de um homem adulto, de 33 anos, branco, que apresentava múltiplas pápulas eritematosas e pústulas, localizadas no tronco há cerca de cinco anos, refratárias a tratamentos tópicos para acne. A dermatoscopia revelou lesões ovaladas, com exulceração excêntrica e raras estruturas filiformes acrômicas protrusas do seu interior. Estabeleceu-se o diagnóstico de cisto veloso eruptivo a partir dos achados da dermatoscopia e do exame histopatológico.

Palavras-chave: Cistos; Erupções acneiformes; HIV

## **Diagnostic imaging**

#### Authors:

Cesar Augusto Zago Ferreira<sup>1</sup> Bruno Augusto Alvares<sup>1</sup> Priscila Neri Lacerda<sup>1</sup> Helio Amante Miot<sup>1</sup>

Department of Infectious Diseases, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista Júlio de Mesquita Filho (UNESP), São Paulo, Brazil.

#### Correspondence:

Helio Amante Miot helio.a.miot@unesp.br / Alternative e-mail: heliomiot@fmb. unesp. br

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#### CASE REPORT

A 33-year-old man, white, unemployed, was referred to Dermatology due to isolated erythematous, non-pruritic lesions on the trunk for five years.

The examination showed multiple erythematous papules, between 1 mm and 2 mm in diameter, and pustules located mainly on the anterior and posterior trunk, with mild involvement of the upper and lower limbs, interspersed with areas of post-inflammatory hyperchromia (Figures 1 and 2). The patient denied a family history of similar lesions. He had HIV infection as comorbidity and was receiving antiretroviral therapy, with CD4 248 and undetectable viral load.

Dermoscopy revealed erythematous or hyperchromic oval macules, some showing eccentric exulceration, others revealing tiny filaments protruding from the center of the papule (Figures 3, 4, and 5).

Histopathology revealed small dermal cysts with keratinized epithelium and vellus hairs inside, surrounded by a foreign body giant cell reaction.

The patient began treatment with oral isotretinoin 20 mg/d. However, he was lost to follow-up during the covid-19 pandemic.



**FIGURE 1:** Eruptive vellus hair cyst. Multiple erythematous papules located on the trunk and abdomen



FIGURE 2: Eruptive vellus hair cyst. Detail of multiple erythematous papules, pustules, and hyperchromic macules

#### DISCUSSION

Eruptive vellus hair cyst (EVHC) is a rare benign condition associated with autosomal dominant inheritance, but it can also be acquired.<sup>1</sup> It has no preference for gender or race, affecting mainly young adults.<sup>2</sup> It was initially described in 1903, but only in 1977 Esterly considered it a clinical entity when he observed children with a clinical picture of multiple monomorphic, hyperchromic, asymptomatic papules on the trunk and limbs.<sup>1</sup>

The pathogenesis of the disease is unknown, and it is considered an abnormality of follicular development, with occlusion and dilation of the follicular unit and subsequent retention of the hair and keratinous material.<sup>3</sup> On the other hand, some studies associate the process with hamartomatous follicular growth and mutations in the gene encoding keratin 17.<sup>3</sup> It is also related to other conditions such as pachyonychia congenita, Lowe syndrome, and steatocystoma multiplex, which has already been described in association with EVHC.<sup>1</sup>

Multiple papules of 1–3 mm, regular or hyperchromic, with a smooth surface and increased consistency characterize the clinical picture. The lesions predominate in the thorax, upper and lower extremities, and are found rarely in the abdomen, neck, armpits, face, and groin.<sup>1,3</sup> Generally, the cysts are closed, and whitish material may be eliminated by manual pressure.

Characteristically, they are asymptomatic but may present associated pruritus or a change in sensitivity.<sup>1</sup>

Histologically, EVHCs are located in the middle or upper dermis, with wall-lining epithelium similar to the infundibular or follicular isthmic portion, and a variable number of layers of squamous epithelium (one to 12 layers), in addition to focal and discontinuous fine granular areas. The cystic cavity contains a variable amount of keratin and vellus hair. Usually, no sebaceous gland is present in the cyst wall, and there may be a granulomatous inflammatory process.<sup>3</sup>



**FIGURE 3:** Papular lesion, with eccentric exulceration and protrusion of filiform structures (vellus hairs)



**FIGURE 4:** Contact dermoscopy of eruptive vellus hair cyst. Oval erythematous lesion, with filiform structure protrusion



**FIGURE 5:** Contact dermoscopy of eruptive vellus hair cyst. Oval erythematous lesion with eccentric exulceration

Electron microscopy (EM) showed the presence of scarce basal lamina around the cyst wall. In epithelial cells, large vacuoles and a marginal band were observed; and, within the cyst wall, scattered melanocytes and Langerhans cells were found.<sup>1</sup>

EVHC dermoscopy is usually monotonous, but it can provide diagnostic elements in the most characteristic cases. Usually, it reveals circular or oval, erythematous, or hyperchromic lesions, presenting an eccentric hypochromic or yellowish structure, forming a pigmentary halo. In the most exuberant cases, it's possible to observe eccentric exulcerations and discrete, non-pigmented filiform structures protruding from the lesion, constituting groups of vellus-like hairs.<sup>4</sup>

Some studies assess EVHC using high-frequency ultrasonography and optical microscopy with 10% potassium hydroxide as an alternative to diagnosis by histopathological examination or dermoscopy.

Microscopic detection consists of making a small incision on the top of a previously anesthetized papular lesion, followed by a gentle pressure on the site, then capturing the cystic content using a sterile 18-gauge needle, with visualization of vellus hairs.<sup>6</sup>

Although optical microscopy in preparation with 10% potassium hydroxide appears to be a less painful alternative than biopsy for histopathological study, the technique may not be able to differentiate EVHC from steatocystoma multiplex since the latter may also present vellus hairs at the microscopic analysis.

On ultrasound, it is possible to observe ovoid hypoechoic nodules, located in the dermis, associated with strongly echogenic filiform areas in the middle of the cyst, corresponding to the vellus hair. Thus, dermoscopy and ultrasound are painless and non-invasive techniques to diagnose eruptive vellus hair cysts.5

The main differential diagnoses are steatocystoma multiplex, trichostasis spinulosa, folliculitis, and other cysts, such as infundibular and trichilemmal. Thus, dermoscopy and histopathological examination are crucial for diagnostic definition in many circumstances. Steatocystoma multiplex shows the expression of K10 and K17, in addition to a thin wall composed of squamous epithelium and empty cysts due to artificial loss in the fixation process, observed on histopathology. On the other hand, EVHC expresses only K171,<sup>3</sup> and, on histopathology, vellus hairs and laminated keratin. Therefore, some authors consider steatocystoma a variant of EVHC.

In cases where non-follicular blue homogeneous pigmentation is present, blue nevus and hemangioma should be considered among the differential diagnosis. Other clinical differentials include acneiform eruption, keratosis pilaris, syringoma, milium, and molluscum contagiosum.<sup>3</sup> The presence of light yellow homogeneous circular structures and the absence of vessels help to distinguish between molluscum contagiosum and comedonal acne.<sup>4</sup>

Most lesions persist if untreated, but spontaneous resolution may occur if vellus hairs penetrate the cyst wall, leading to the formation of a foreign body reaction. Also, inflammatory changes may occur with the appearance of whitish material, which can be eliminated spontaneously or by compressing the papule.<sup>2</sup> As a result, spontaneous remission occurs in 25% of cases due to its transepidermal elimination or inflammatory process destruction.<sup>5</sup>

EVHC treatment is challenging. There are reports of several therapies, such as tretinoin, tazarotene, calcipotriol, topical lactic acid, oral isotretinoin, exfoliation, dermabrasion, CO2 laser, Erbium:YAG laser, needle incision, curettage, and surgical excision. However, they have limited results,<sup>1,2</sup> leading to early recurrence, local atrophy, or hypertrophic scar formation. More exuberant cases, simulating acneiform reactions, present more exuberant dermoscopic findings, helping to define the diagnosis.

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#### **AUTHORS' CONTRIBUTIONS:**

**Cesar Augusto Zago Ferreira** OCCID 0000-0001-7299-1710 Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.

**Bruno Augusto Alvares** D ORCID 0000-0002-0061-2969 Approval of the final version of the manuscript; critical literature review.

**Priscila Neri Lacerda** D ORCID 0000-0001-8100-5978 Approval of the final version of the manuscript; critical literature review.

#### Helio Amante Miot 🕩 ORCID 0000-0002-2596-9294

Approval of the final version of the manuscript; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.



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# The accuracy of mobile teledermatoscopy in the assessment of pigmented skin lesions

Acurácia da teledermatoscopia móvel na avaliação de lesões cutâneas pigmentadas

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#### ABSTRACT

In this cross-sectional study, we compared the diagnosis made through teledermatoscopy with histopathological diagnosis. Conventional and dermoscopic photos of 31 pigmented lesions were taken and sent to an experienced dermatologist using the WhatsApp® Messenger application. A dermatopathologist excised and examined all lesions. The global accuracy of mobile teledermatoscopy was 90.32%. Regarding the ability of teledermatoscopy to define malignancy of the pigmented lesion, the specificity was 81.8% and the sensitivity was 100%. Our results provide additional evidence of the reliability of mobile teledermatoscopy with high sensitivity and accuracy.

Keywords: Dermoscopy; Teledermatology; Telemedicine

#### RESUMO

Neste estudo transversal, comparamos o diagnóstico feito por meio da teledermatoscopia ao diagnóstico histopatológico. Fotos convencionais e dermatoscópicas de 31 lesões pigmentadas foram enviadas a um dermatologista experiente por meio do aplicativo WhatsApp® Messenger. Todas as lesões foram excisadas e examinadas por um dermatopatologista. A acurácia global da teledermatoscopia móvel foi de 90,32%. Em relação à capacidade de a teledermatoscopia definir malignidade da lesão pigmentada, a especificidade foi de 81,8% e a sensibilidade de 100%. Nossos resultados fornecem evidências adicionais sobre a confiabilidade da teledermatoscopia móvel, com alta sensibilidade e precisão. **Palavras-chave:** Dermoscopia; Teledermatologia; Telemedicina

### Letters

#### Authors:

Norami de Moura Barros<sup>1</sup> Karin Milleni Araujo<sup>1</sup> Juan Piñeiro-Maceira<sup>1</sup> Carlos Baptista Barcaui<sup>1</sup>

Hospital Universitário Pedro Ernesto, Department of Dermatology, Rio de Janeiro (RJ), Brazil.

#### Correspondence:

Carlos Baptista Barcaui Email: cbbarcaui@gmail.com

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#### INTRODUCTION

Due to the peculiar characteristic of visual diagnosis, Dermatology is suitable for the development of new diagnostic tools such as teledermatology and, more recently, teledermatoscopy.<sup>1</sup>

In this context, mobile teledermatoscopy stands out, where clinical and dermoscopic images are captured and transmitted using mobile devices.<sup>2</sup> Despite the importance of the topic, there are technical, legal, ethical, regulatory, and cultural aspects that limit the routine use of teledermatology.<sup>3</sup>

Considering the continental dimensions of countries such as Brazil, India, and China, among others, and the difficulty of accessing specialized centers, mobile teledermatoscopy can positively impact the definition of conduct, reducing costs and diagnosis time and avoiding referrals and unnecessary displacements.<sup>4,5</sup>

However, studies in the literature comparing mobile teledermatoscopy to histopathological diagnosis (gold standard) are scarce.<sup>1,4,5</sup>

This study aims to assess the accuracy of the diagnosis of pigmented lesions using mobile teledermatoscopy. It is a cross-sectional study that consecutively selected patients at the Dermatology Service of Hospital Universitário Pedro Ernesto from September 2018 to June 2019.

#### MATERIAL AND METHODS

We included patients with pigmented lesions, melanocytic or not, with an indication for excision, after signing a consent form for the use of their data and images. Two images of each skin lesion were obtained with a cell phone camera (16 megapixels, resolution 4608 x 3456 pixels; Samsung Galaxy, model A8).

The clinical image was standardized at approximately 15 centimeters from the patient's skin. The image used the autofocus tool without flash or zoom.

The interface gel and a DermLite DL4 (3Gen, CA, USA) dermoscope attached to the cell phone (universal adapter; 3Gen) were used to capture the dermoscopic image; position 0 with polarized light. Thus, we defined the standard dermoscopic image.

The clinical and dermoscopic images were sent to a single dermatologist with experience in dermoscopy using the WhatsApp® Messenger application. Teledermatoscopic diagnoses were stored for further analysis. A dermatopathologist excised and examined all lesions, who had access to the clinical characteristics of the patients but no information related to the teledermatoscopic diagnosis.

We calculated the accuracy and sensitivity of mobile teledermatoscopy. The kappa coefficient was used to analyze the levels of agreement between teledermatoscopic and histopathological diagnoses. The Landis and Koc criterion was adopted to interpret the results: k=0.61-0.80 and  $k\ge 0.81$  were considered as substantial agreement and perfect agreement, respectively. The standard error was calculated to measure the accuracy of the kappa estimate: the smaller the standard error, the more accurate the estimate. The p-value for the kappa coefficient was also calculated to measure evidence against the null hypothesis (agreement between teledermatoscopic diagnosis and standard is due to chance). A value of  $p \le 0.05$  rejected the null hypothesis. SPSS 26.0 software (IBM, USA) was used.

#### RESULTS

We assessed 26 (57.7% women, aged  $66.1\pm16.1$  years) with a total of 31 lesions. In the evaluation of all pigmented lesions, the global accuracy of mobile teledermatoscopy was 90.32% (28 lesions). The agreement between mobile teledermatoscopy for pigmented skin lesions and histopathology was perfect (kappa = 0.850, standard error = 0.080, p<0.0001). There was diagnostic disagreement in three lesions (Figures 1-3).



**FIGURE 1:** Dermoscopy - Pigmentary network and exulceration suggesting a benign melanocytic lesion. Histopathology (Hematoxylin & Eosin, 100x) - Venous hemangioma and lentiginous hyperplasia of the epidermis



**FIGURE 2:** Dermoscopy - Blue-grey amorphous areas and black dots suggesting pigmented basal cell carcinoma. Histopathology (Hematoxylin & Eosin, 100x) - Epithelial neoplasm composed of interconnected masses of poroid cells, with melanin pigment in tumor cells, consistent with pigmented eccrine poroma



**FIGURE 3:** Dermoscopy - Reticulated pigmentation with black dots and rudimentary leaf structures, suggesting \ pigmented basal cell carcinoma. Histopathology (Hematoxylin & Eosin, 100x) - Hyperkeratosis with formation of discrete corneal tunnels, irregular acanthosis secondary to proliferation of hyperpigmented basaloid keratinocytes, and discrete papillomatosis consistent with seborrheic keratosis

Regarding the teledermatoscopy ability to define malignancy of the pigmented lesion, the specificity was 81.8%, and the sensitivity was 100%. Two lesions were misdiagnosed as malignant lesions during teledermatoscopy analysis. Subsequently, the histopathological analysis showed that they were two benign lesions (Figures 2 and 3), resulting in an accuracy of 93.5%. The agreement between teledermatoscopy and histopathology was also perfect (kappa = 0.853, standard error = 0.099, p<0.0001).

The sensitivity for melanoma diagnosis (four lesions on histopathology), basal cell carcinoma (16), and benign melanocytic lesions (five) was 100%. For the hemangioma diagnosis (three lesions on histopathology), seborrheic keratosis (two), and pigmented eccrine poroma (one), it was 66.7%, 50%, and 0%, respectively.

#### DISCUSSION

Previous investigations have demonstrated that teledermatoscopy is an effective, accurate, and reliable tool for assessing pigmented lesions.<sup>2,4,5</sup>

Also, earlier studies revealed that mobile teledermatoscopy had an 81-90% agreement with the face-to-face dermatological examination.<sup>4,5</sup>

Our results provide additional evidence of the reliability of mobile teledermatoscopy with high sensitivity and accuracy. The risk of a pigmented malignant lesion going unnoticed by mobile teledermatoscopic evaluation is low due to the high sensitivity of this detection (100%).

#### CONCLUSIONS

As dermoscopic and cellular devices are widely used by dermatologists,<sup>2</sup> we believe that mobile teledermatoscopy can be adopted as an additional tool to the diagnostic arsenal of dermatological practice.

Due to inconsistencies in the interobserver analyses,<sup>3</sup> future investigations should assess the influence of the examiner's experience on the accuracy of mobile teledermatoscopy.

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#### AUTHORS' CONTRIBUTION:

#### Norami de Moura Barros 问 ORCID 0000-0001-9765-602X

Statistical analysis; approval of the final version of the manuscript preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; critical literature review; critical revision of the manuscript.

#### Karin Milleni Araujo 问 ORCID 0000-0003-2421-3978

Statistical analysis; approval of the final version of the manuscript preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; critical literature review; critical revision of the manuscript.

#### Juan Piñeiro-Maceira D ORCID 0000-0002-8021-2374

Approval of the final version of the manuscript preparation and writing of the manuscript; data collection, analysis, and interpretation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases.

#### Carlos Baptista Barcaui D ORCID 0000-0002-3303-3656

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases.



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# Efficacy and safety of the 5% cysteamine cream left in overnight for facial melasma: a pilot study

Estudo piloto sobre a eficácia e segurança do uso da cisteamina 5% como terapia de contato por toda noite no tratamento do melasma facial

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**ABSTRACT** Not applicable, this is a letter. **Keywords:** Cisteamina; Transtornos da pigmentação; eventos adversos

#### RESUMO

Não se aplica, trata-se de uma carta **Palavras-chave:** Cisteamina; Transtornos da pigmentação; eventos adversos

### Letters

#### Authors:

Daniel Pinho Cassiano<sup>1</sup> Paula Basso Lima<sup>2</sup> Joana Alexandria Ferreira Dias<sup>2</sup> Ana Claudia Cavalcante Esposito<sup>2</sup> Hélio Amante Miot<sup>2</sup>

- <sup>1</sup> Federal University of São Paulo, Dermatology, São Paulo (SP), Brazil.
- <sup>2</sup> Federal University of São Paulo, Department of Dermatology and Radiotherapy, Botucatu (SP), Brazil.

#### Correspondence:

Daniel Pinho Cassiano Email: danielpcassiano@uol.com.br

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#### Dear Editor,

Melasma is a common, acquired chronic hyperpigmentation of the skin photoexposed areas. It mainly affects the face of women with intermediate phototypes during their childbearing age. As melasma affects visible areas and frequently relapses after treatment, it impairs the patient's quality of life.

The standard therapy of melasma relies on photoprotection based on broad-spectrum sunscreen associated with topical bleaching agents. Among the bleachers available on the market, L-cysteamine (mercaptoethylamine hydrochloride) is an aminothiol compound with antioxidant and depigmenting properties. It inhibits tyrosinase and peroxidase without the melanocytoxic effect of hydroquinone. The recommendation for cysteamine is as a rapid contact therapy, for up to three hours, due to its irritating potential.<sup>1-6</sup> Nevertheless, it has been suggested that leaving it in overnight was safe and well-tolerated to treat melasma, what was not yet been investigated.

We performed a prospective open intervention pilot study between October and December 2021, aiming to assess the safety profile and the efficacy gain of cysteamine left in overnight. Ten women with facial melasma, without treatment for at least one month, were oriented to apply 5% cysteamine cream (Clarité Cysteamin, Dermage, RJ, Brazil) on their face after the facial moisturizer, leaving it overnight for two months. The daily applications should be tailored according to individual tolerability. All the participants received the same sunscreen (SPF50, PPD19) to be applied during the day. Subjects were assessed at the inclusion and after 60 days of treatment. We evaluated the safety by the report of adverse events, such as facial erythema, scaling, and burning sensation (primary outcomes). Other parameters used were modified Melasma Area and Severity Index (mMASI), Melasma Quality of Life Scale (MELASQoL), and the difference in colorimetric luminosity (Dif\*L) between skin affected by melasma and the adjacent unaffected skin (<2 cm distance). The Global Aesthetic Improvement Scale (GAIS) was used to assess the difference (T0 versus T60) in the skin appearance through standardized photographs (Figure 1).

The age of the participants ranged between 40 and 58 years old, and their phototypes were intermediate (III-V). Most had a positive family history of melasma (70%) and reported the sun as a trigger (50%).

Only four patients (40%) tolerated cysteamine overnight for seven days a week. Albeit, the main obstacle to daily use was the discomfort generated by the sulfur odor. One patient reported worsening of migraine episodes due to the bad smell. Two other patients reported nausea also caused by the odor, and one did not tolerate overnight use on any day for the same reason. Three patients (30%) reported transient mild facial erythema, scaling, and burning at the beginning of the treatment, which faded over the eight weeks.

Five patients (50%) showed a consistent lightening of the melasma through the GAIS assessment (Table 1). Table 1 presents the other clinimetric parameters. The mMASI decreased by 13.5% (CI 95%: 4% to 27%) in eight weeks. There was



**Figure 1:** Patient with facial melasma treated with 5% cysteamine left-in overnight for 8 weeks

TABLE 1: Primary outcomes from ten participants with facial melasma treated with 5% cysteamine cream left in overnight					
Outcome	D0	D60	% Reduction (CI 95%)		
mMASI	7,6 (3.0)	6,7 (3.1)	-13.5% (-4.3% to -27.1%)		
MELASQol	46,8 (17.6)	41,3 (13.0)	-5.5 (-18.1% to 7.0%)		
Dif*L	5,1 (1.4)	4,6 (1.8)	-6.8% (-3.2 to 0.1%)		

mMASI: Modified Melasma Area and Severity Index; MELASQol: Melasma Quality of Life Scale; Dif\*L: difference between colorimetric luminosity (\*L)
no difference in colorimetric parameters between D0 and D60. Also, no improvement in the quality of life score at the end of the study was observed.

Topical 5% cysteamine left in overnight proved to be safe and well tolerated. However, in a similar study conducted in the same population, 5% cysteamine left in for three hours overnight, provided an mMASI reduction of 15–33% after two months.<sup>1</sup> As long as the overnight use did not exceed this value, the study suggests that overnight use may not add efficacy over short contact therapy. Interestingly, in this series, the frequency of use was limited by the sulfur odor and not by skin irritation.

In conclusion, 5% cysteamine cream left in overnight is a safe option to treat facial melasma for patients who prefer not to wash it out at bedtime. New cysteamine formulations aiming at minimizing the sulfur odor can increase adherence to the treatment and improve clinical outcomes. The efficacy gain of combining cysteamine with other tyrosinase inhibitors to treat melasma is warranted.

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#### **AUTHORS' CONTRIBUTION:**

### Daniel Pinho Cassiano D ORCID\_0000-0003-2615-0456

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

### Paula Basso Lima D ORCID 0000-0003-4659-2155

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

## Joana Alexandria Ferreira Dias D ORCID 0000-0001-9435-2303

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

# Ana Claudia Cavalcante Esposito D ORCID 0000-0001-9283-2354

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

# Hélio Amante Miot D ORCID 0000-0002-2596-9294

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

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