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Combination of Q-switched and micropulsed 1064-nm Nd:YAG laser for global facial improvement

Combinação do laser Nd:YAG de 1.064 nm nos modos Q-switched e micropulsado para melhora facial global

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ABSTRACT

The 1064-nm Nd:YAG laser in Q-switched and micropulsed modes has been used in rejuvenation, pore reduction, skin texture improvement, and wrinkle reduction. The aim of this study is to evaluate the combination of 1064-nm Nd:YAG laser in micropulsed and Q-switched modes in the same session for global facial treatment. Thirty female patients underwent six treatment sessions every two weeks. Three blinded dermatologists evaluated the results through clinical photographs and Visia® or Focco® images obtained before and 30 days after the last treatment session. The parameters of interest were solar melanosis, telangiectasias, wrinkles, dilated pores, melasma and skin texture. Three patients had face biopsies before and 30 days after the end of treatment. Most patients showed improvement in all evaluated parameters, except for two patients who had worsening of melasma. An increase in collagen was observed in two of the three histological examinations performed after treatment. The combination of laser modes studied herein offers a safe treatment that can improve wrinkles, skin texture, and laxity with minimal downtime.

Keywords: Lasers; Skin Aging; Rejuvenation

RESUMO

O laser Nd:YAG de 1.064 nm nos modos Q-switched e micropulsado tem sido usado no rejuvenescimento, redução de poros e melhora de rugas e da textura da pele. O objetivo deste estudo é avaliar a associação do laser de Nd:YAG de 1.064 nm nos modos micropulsado e Q-switched em uma mesma sessão para tratamento facial global. Trinta pacientes do sexo feminino foram submetidas a seis sessões de tratamento a cada 15 dias. Três dermatologistas cegos avaliaram os resultados com base em fotografias clínicas e imagens obtidas com os sistemas Visia® ou Focco®, tiradas antes e 30 dias após a última sessão de tratamento. Os parâmetros avaliados foram melanoses, telangiectasias, rugas, poros dilatados, melasma e textura da pele. Três pacientes realizaram biópsias de face antes e 30 dias após o término do tratamento. A maioria das pacientes apresentou melhora em todos os parâmetros avaliados, exceto duas pacientes que tiveram piora do melasma. Um aumento de colágeno foi observado em dois dos três exames histológicos realizados após o tratamento. A combinação de lasers estudada oferece um tratamento seguro e pode melhorar rugas, textura da pele e flacidez com mínimo tempo de recuperação.

Palavras-chave: *Lasers; Rejuvenescimento; Envelhecimento da Pele*

Original Article

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INTRODUCTION

The use of non-ablative lasers for facial rejuvenation has increased in recent years. The neodymium:yttrium-aluminum--garnet (Nd:YAG) laser, in both nanosecond (Q-switched) and millisecond (LongPulse®) modes and, more recently, in microsecond mode, has been used for this purpose.[1]

The 1064-nm Nd:YAG laser has been widely used in dermatology for removal of hair, tattoos, pigmented and vascular lesions and has also gained popularity in dermal remodeling for rejuvenation.[2,3] The micropulsed and Q-switched modes of Nd:YAG have potentially different effects due to differences in exposure time, pulse energy, and peak power. Pulse duration is related to the depth of dermal coagulation; in theory, the micropulsed mode would penetrate deeper into the dermis compared to the Q-switched mode, leading to greater skin remodeling.[2]

In the present study, 1064-nm Nd:YAG laser was applied in both micropulsed and Q-switched modes in the same session, seeking to combine the benefits of both techniques for global facial treatment while reducing downtime.

METHODS

Thirty patients were selected from three study centers. Patients had to be female, between 30 and 55 years old, and have solar melanosis, telangiectasias, wrinkles, and/or enlarged pores. Pregnant or lactating women, patients with collagen disorders, those treated with photosensitizing drugs or oral or topical isotretinoin, those who had undergone a facelift less than one year ago, and those who received chemical peels or laser treatments (ablative or non-ablative) in the last four months were excluded from the study.

Three patients were voluntarily selected to undergo a 3-mm punch biopsy at the angle of the mandible before (baseline) and 30 days after the end of treatment. Treatments were only performed once the patient demonstrated understanding and signed an informed consent form (ICF). This study was approved by the relevant Ethics Committee.

Digital photographic evaluation of the patients' faces was performed using the Visia® (Canfield Imaging Systems, USA) and Focco® (Focco Photographs, Fabinject, Taubaté, São Paulo, Brazil) systems before and 30 days after the last treatment session.

Patients underwent six treatment sessions, every two weeks, with two Etherea® platform handpieces (Vydence Medical, São Carlos, São Paulo, Brazil): LongPulse® (1064-nm Nd:-YAG, in Dynamics® mode) and Acroma-QS® (1064-nm Nd:-YAG, Q-switched mode) belonging to the investigators. Both were used in the same session, at every session. All laser applications were performed by dermatologists.

Prior to treatment, subjects had their skin cleansed and were fitted with safety goggles for eye protection. Laser shots were applied to orbital-adjacent skin, but never within the orbital rim. The LongPulse® mode was applied with a 6-mm spot, fluence ranging from 8 to 10mJ/cm^2, and pulse duration of 650μs, in a continuous motion until 2,000 shots had been completed on each hemiface and 1,000 shots on the forehead. The Acroma-QS® mode was applied with a 7-mm spot and fluence of 1200mJ/cm^2, for a total of 2 to 3 passes across the face. The endpoint was defined by the number of shots, but the applicator was attentive and could stop the treatment earlier if the patient developed significant erythema or had experienced side effects in the previous session. No cooling was performed, nor was topical anesthetic applied before the sessions; these were considered superfluous due to the excellent tolerability of the treatment among our patients.

Patients were instructed to apply daily UVA/B sunscreen with a sun protection factor (SPF) greater than or equal to 30, which should be continued throughout the treatment and follow-up period. At each visit, patients were asked whether they had any adverse events between visits.

At the end of treatment, patients completed a questionnaire evaluating the following factors: spots, erythema, wrinkles, dilated pores, and skin texture, and described any transient (up to 5 days after the procedure) and persistent (up to 30 days after the procedure) adverse effects which may have occurred.

Results were evaluated jointly by three experienced dermatologists using clinical photographs as well as Visia® and Focco® images. The parameters solar melanosis, telangiectasias, wrinkles, enlarged pores, melasma and skin texture were evaluated on a five-point scale, scored as follows: worsening, slight improvement (1-25%), moderate improvement (26-50%), good improvement (51-75%) excellent improvement (>76%). Collagen analysis of biopsy specimens was performed by a blinded pathologist.

RESULTS

The sample consisted of 30 female patients aged 33 to 52 years (mean 42.47 ± 4.96 years). Skin phototypes I to V were represented, with III and IV being most frequent. All patients had melanosis and dilated pores, and most had wrinkles (96.7%), telangiectasias (83.3%), and melasma (73.3%) (Table 1).

All patients completed the study and treatment was well tolerated. At each visit, patients were asked about adverse effects after the sessions or complications between them. Although most patients experienced mild discomfort during the sessions, this did not prevent treatment continuity. Three patients had complications: one developed erythematous papules after one session, treated with low-potency topical corticosteroids; one had worsening of acne; and another had two episodes of facial edema which resolved spontaneously in less than 24 hours. Lower laser energy (Dynamics LongPulse® mode, fluence 8mJ/cm^2; Acroma-QS®, 900mJ/cm^2) was used in this patient's subsequent sessions, progressively increasing in each session.

Most patients showed good or excellent improvement in all parameters of interest (Table 2). Except for two patients who had worsening of melasma, all other parameters, such as

Table 1. Sample profile (n=30)

	Patients (n=30)
Age (years)	42.47 ± 4.96
Maximum pain experienced	
None	10 (33.3%)
Mild (1-2)	4 (13.3%)
Moderate (3-7)	15 (50%)
Severe (8-10)	1 (3.3%)
Skin phototype	
I	2 (6.7%)
II	6 (20%)
III	9 (30%)
IV	10 (33.3%)
V	3 (10%)
Solar melanosis	30 (100%)
Telangiectasias	25 (83.3%)
Wrinkles	29 (96.7%)
Dilated pores	30 (100%)
Melasma	22 (73.3%)
Complications	5 (16.7%)

Data presented as mean ± standard deviation or absolute frequency (relative frequency).

enlarged pores, telangiectasias, wrinkles, and solar melanosis, improved (Figures 1 and 2).

Histological examinations performed before treatment revealed fine collagen fibers in the dermis. Of the three patients who underwent biopsy, two (43 and 47 years old respectively) had an increase in collagen thickness on histology 30 days after the end of treatment. The youngest of the three patients (33 years old) showed no change in biopsy findings compared to the pre-treatment baseline.

DISCUSSION

The aging process is characterized by a reduction in collagen synthesis and an increase in its degradation due to increasing levels of metalloproteinases, which leads to a reduction in dermal thickness. Collagen fibers become disorganized, more compact, and granular; elastic fibers decrease in number and diameter.[4] Clinically, cutaneous photoaging manifests as dyschromia, erythema, telangiectasias, wrinkles, changes in texture, and pore dilation.[2]

Several studies in the literature have documented the effects of 1064-nm Nd:YAG lasers in Q-switched and micropulsed modes on rejuvenation, pore reduction, skin texture improvement, and wrinkle reduction.[2,5,6,7]

The application of Nd:YAG laser at different pulse durations seems to be safe when used within the recommended parameters and can be useful to improve signs of photoaging with shorter recovery time and a lower risk of complications.[8]

Choi *et al* compared the effectiveness and safety of combination therapy using dual toning (low-fluence Q-switched and long-pulse Nd:YAG laser) in the treatment of melasma, and concluded that dual toning could represent a safe and effective treatment, as it is associated with minimal adverse events and improved treatment efficacy compared with Q-switched toning monotherapy.[8,9]

Laser treatment for photorejuvenation usually involves ablation of the superficial layers of the epidermis, with 10600-nm CO_2 and 2940-nm Er:YAG being the most traditional lasers used for this purpose. Although effective, potential risks include a recovery period of up to 2 weeks, persistent erythema, bleeding, pain, infection, crusting, unwanted changes in texture, and

Table 2: Post-treatment evaluation

	Solar melanosis (n = 30)	Telangiectasias (n = 25)	Wrinkles (n = 29)	Dilated pores (n = 30)	Melasma (n = 22)	Skin texture (n = 30)
Worsening	-	-	-	-	2 (9.1%)	-
Slight improvement (1-25%)	5 (16.7%)	1 (4%)	4 (13.8%)	2 (6.7%)	4 (18.2%)	3 (10%)
Moderate improvement (26-50%)	4 (13.3%)	8 (32%)	10 (34.5%)	7 (23.3%)	3 (13.6%)	2 (6.7%)
Good improvement (51-75%)	19 (63.3%)	14 (56%)	11 (37.9%)	17 (56.7%)	13 (59.1%)	17 (56.7%)
Excellent improvement (76-100%)	2 (6.7%)	2 (8%)	4 (13.8%)	4 (13.3%)	-	8 (26.6%)

Data presented as absolute frequency (relative frequency)

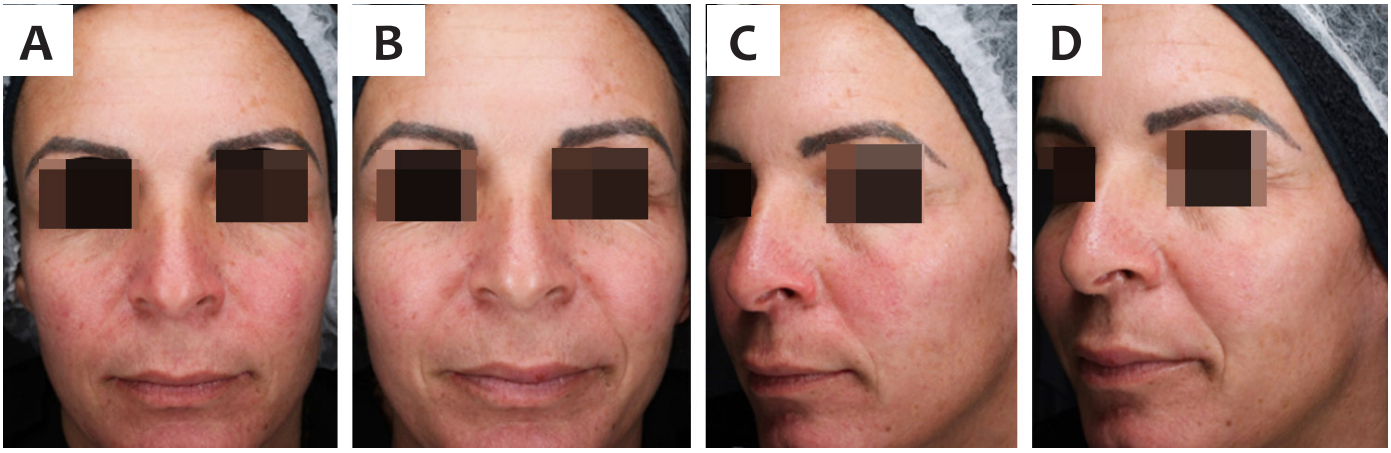

FIGURE 1: Clinical photographs obtained before treatment (**A** and **C**) and 30 days after the last session (**B** and **D**), showing improvement in all evaluated parameters (solar melanosis, telangiectasias, wrinkles, enlarged pores, melasma and skin texture)

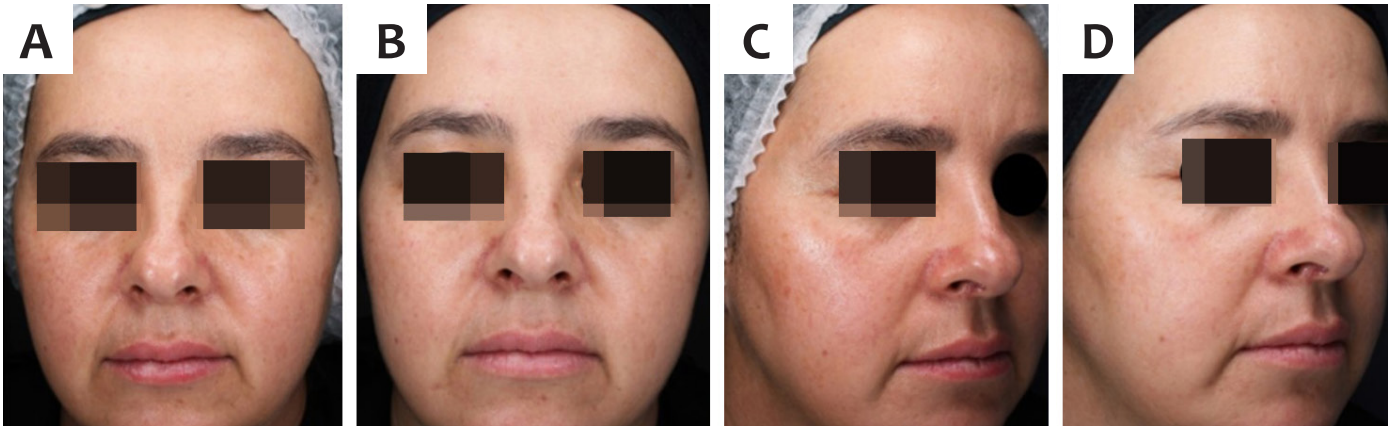

FIGURE 2: Clinical photographs obtained before treatment (**A** and **C**) and 30 days after the last session (**B** and **D**), showing improvement in all evaluated parameters (solar melanosis, telangiectasias, wrinkles, enlarged pores, melasma and skin texture)

scarring, with the greatest risk in patients with high skin phototype.[5] As patients increasingly seek procedures that do not take them away from their activities, lasers associated with shorter downtime are gaining ground.

The Q-switched Nd:YAG laser emits a nanosecond pulse-width beam that selectively destroys melanosomes without affecting surrounding tissue. The high energy peak instantly increases the temperature of the chromophore, leading to changes in pressure and vibration, which then effectively destroys it in the form of a shock wave (photoacoustic effect).[3,10] This laser is widely used for removal of hair, tattoos, and pigmented and vascular lesions.[3,6] Goldberg and Metzler first suggested the concept of laser toning in 1999, in which multiple passes with a low-fluence Q-switched Nd:YAG laser produced beneficial changes in photoaging skin, such as improved skin tone and texture, reduction of pores, sebaceous secretion, rhytids, and dyschromia.[5] Adverse events, including mottled hypopigmentation (MH) and rebound hyperpigmentation (RH), have been reported.[3,8]

The absorption of the 1064-nm wavelength of the laser by water is very low and the mechanism by which the Q-switched Nd:YAG laser can improve rhytids is not well established. It is believed to involve nonspecific dermal heating with subsequent collagen contraction.[5]

In 2001, in an anatomopathological study, Goldberg ***et al*** found mild fibrosis of the superficial papillary dermis with improvement in the organization of collagen fibers in four of six patients, suggesting that the Q-switched Nd:YAG laser would produce similar morphological changes, but to a lesser degree, than those observed with CO_2 and Er:YAG ablative laser resurfacing.[5] Berlin ***et al*** documented a slight decrease in elastosis, as well as increased vascularization and collagen deposition, in biopsies obtained 3 months after treatment with Q-switched Nd:YAG laser.[11]

Karabudak *et al* studied the use of Q-switched Nd:YAG laser in periorbital wrinkles in eight patients, finding an increase in collagen density in histopathological specimens from all patients. However, clinical improvement in rhytids was only observed in half of these individuals. The authors considered the treatment to be safe and effective in reducing periorbital wrinkles, especially in younger individuals.[12] Tian reported the use of low-fluence Q-switched Nd:YAG laser in the treatment of post-blepharoepicantoplasty scars. Although the exact mechanism of scar remodeling by this laser is unclear, it is postulated that microscopic damage occurs repeatedly rather than actual tissue destruction. Heating of the scar leads to disruption of disulfide bonds, with subsequent collagen breakdown and remodeling.[13]

Micropulsed Nd:YAG, with pulse widths in the microsecond domain, would also lead to rejuvenation while maintaining a short downtime when applied in multiple passes. In this case, the formation of controlled zones of mild photothermal damage is believed to induce neocollagenous wound healing mechanisms.[2,7] This laser can also be useful in reducing facial erythema, improving the appearance of keloid and hypertrophic scars, and enhancing skin texture.[1,4]

Schmults *et al*, in a study of nine patients, concluded that 1064-nm microsecond Nd:YAG lasers can produce new collagen formation in the papillary dermis, as demonstrated by a decrease in the overall diameter of collagen fibers, and suggest that these lasers can be also useful in reducing facial erythema and improving skin texture. Younger patients may form new collagen in greater amounts compared to older patients with photodamage.[1]

Roh *et al*, in a split-face controlled study with 20 patients, evaluated and compared the efficacy of the micropulsed and Q-switched modes of the 1064-nm Nd:YAG laser in the treatment of enlarged pores, finding that both had similar efficacy in reducing pore size and sebum level. They suggest that deposition of dermal collagen and remodeling of the perifollicular area could result in pore size reduction. The photothermal effect of the laser would result in a reduction of the sebaceous gland, which would account for the long-term maintenance of both reduced pore size and sebum level.[2] In a similar study, Chung *et al* showed that the combination of micropulsed Nd:YAG with Q-switched mode improved enlarged pores, and the result could be optimized with the use of carbon lotion.[7] In our study, all patients showed improvement in their enlarged pores; in 70% of patients, this improvement was greater than 50%.

Kang *et al* treated 30 female patients with melasma with the 1064-nm Nd:YAG laser in Q-switched mode, immediately followed by micropulsed mode. Patients received a total of 10 to 12 treatments repeated every 2 weeks. Overall, 67% had a fair to excellent degree of improvement and 7 (23%) had visible improvement, while little or no improvement was seen in 3 (10%) patients. There were no unexpected side effects. The dual toning technique using the 1064-nm Nd:YAG laser was safe, effective, and well tolerated.[14]

In the study, all patients had an improvement greater than 50% in wrinkles, telangiectasias, and solar melanosis, in addition to the aforementioned improvement in pores. Two patients (skin phototypes II and IV) had worsening of melasma, possibly secondary to micropulsed Nd:YAG, which causes greater thermal damage. The use of Nd:YAG laser in Q-switched mode for melasma is well established. The energy suggested by the company protocol for this treatment would be 600-900mJ/cm^2. In our study, however, we used an energy density of 1200mJ/cm^2 aiming at better photorejuvenation outcomes; this higher energy may have played a role in this complication. Nevertheless, it bears stressing that the other 20 patients with melasma included in the study showed improvement, which was scored as greater than 50% in 59.1% of these patients. Although clinical improvement was observed in all three patients who underwent before-and-after biopsies, collagen thickening was found in only two of them. As found by Goldberg *et al*, clinical improvement does not always correlate with histological findings.[2]

It is worth noting that the treatment protocol tested in the study was associated with a high level of patient satisfaction; a feeling that the skin was "fresher" was frequently reported by patients throughout the treatment. There were no serious adverse events.

CONCLUSIONS

The combined application of Nd:YAG laser in Q-switched and micropulsed modes provides a safe and effective treatment for sun-damaged skin. This technique can improve wrinkles, skin texture, and laxity with minimal downtime.

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Assessment of actual laser emission at 532nm in tattoo removal devices

Avaliação da emissão real de laser em 532nm nos equipamentos para remoção de pigmentos

Original Article

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ABSTRACT

Introduction: The use of potassium titanyl phosphate (KTP) crystals for second-harmonic generation of 532nm waves from a 1064nm source is presented as a more efficient method for removing residual tattoo pigments with lasers. It is crucial to measure the actual performance of the available technologies on the market, which has not been done to date.

Objective: To assess the performance of laser systems available on the Brazilian market by measuring the amount of energy from the fundamental wavelength (1064nm) that is effectively converted to 532nm.

Methods: The 532nm wavelength was measured on Etherea MX, Spectra XT, Inkie, Ladybug and Deltalight equipment using the metrological standard of the National Institute of Metrology of China, model NIM-1000 Results: The results were unsatisfactory for most of the analyzed systems.

Conclusions: The findings suggest potential photonic design flaws in the equipment and methodological deficiencies in the conformity assessment by product certification bodies, compromising the desired clinical outcomes.

Keywords: Lasers; Solid-State; Coloring Agents; Tattoo Removal; Lasers, Dye.

RESUMO

Introdução: *O uso da geração de segunda harmônica da banda em 1064nm pelos cristais de KTP, originando o feixe em 532nm, é apresentado como uma forma mais eficiente para a remoção de pigmentos residuais de tatuagem, sendo essencial mensurarmos a real entrega das tecnologias disponíveis no mercado, algo não disponível até a presente data.*

Objetivo: *Avaliar os dispositivos disponíveis no mercado brasileiro para mensurar o quanto do comprimento de onda fundamental, em termos de energia, é efetivamente convertido em 532nm.*

Métodos: *Realizado a mensuração do comprimento de onda de 532nm nos equipamentos Etherea MX, Spectra XT, Inkie, Ladybug e Deltalight através do padrão metrológico do National Institute of Metrology da China, modelo NIM-1000*

Resultados: *Notam-se resultados insatisfatórios para a maioria dos equipamentos analisados.*

Conclusões: *Os resultados indicam possível falha de design fotônico dos equipamentos e falha metodológica para avaliação de conformidade pelos organismos certificadores de produtos, comprometendo o resultado clínico almejado.*

Palavras-chave: *Lasers de Estado Sólido; Corantes; Remoção de Tatuagem; Lasers de Corante.*

INTRODUCTION

The practice of tattooing has been part of human culture since the beginning of civilization. The first descriptions of tattoos date back to 2000 B.C. on Egyptian mummies.[1] Over time, the methods of application and the use of various colored pigments have evolved, allowing for more complex tattoos.[2] Removal attempts are also ancient, with the first techniques dating back to 543 B.C., developed by the Greeks, who practiced abrasion followed by the application of inorganic salts.[1] Currently, quality-switched (Q-switched) lasers are most commonly used in permanent makeup and tattoo removal.[3] Q-switching refers to the mechanism used to control the temporal profile of the laser output, that is, it allows high-energy nanosecond pulses to be generated. These lasers gained popularity in the 1990s, when different studies demonstrated their effectiveness in reaching the pigments located in the dermis, such as tattoo ink.[4]

Three types of Q-switched lasers with pulse widths on the order of nanoseconds to microseconds are used for tattoo removal, but they vary in wavelengths: the ruby laser (694nm), the alexandrite laser (755nm), and the Nd:YAG laser (532nm in the second harmonic, 1064nm in the fundamental mode).[3] The Q-switched ruby and alexandrite lasers are used to remove black, blue, and green pigments. The Q-switched 532nm Nd:YAG laser is used for the removal of red pigments and the 1064nm Nd:YAG laser is used for removal of black and blue pigments.[5] Variations in the chemical composition and absorption spectrum of pigments make it a challenge to foresee the pigment reaction to a chosen laser wavelength.[6] Colors such as yellow and orange are known to be very resistant, and colors such as red and green have a highly variable response.[1] Reddish pigments are usually resistant to 532nm laser treatment due to the Purkinje effect, in which mesopic conditions give way to photopic effects. Under these conditions, the cones in the retina, which are responsible for the perception of color, are much more sensitive to light at wavelengths close to the absorption maximum of rhodopsin and that of the other opsins in the cones, meaning the average normal human eye is most sensitive at a wavelength of 555nm (green).[7] Thus, even a small amount of green light in a laser beam, such as the green light generated by the second harmonic of a 1064nm laser, can appear very bright to the naked eye when it hits a reflective target. This can create the false impression that that laser beam contains a much higher percentage of green light (532nm, in our example). The Q-switching technique, used in lasers for pigment removal, generates extremely short pulses (in nanoseconds) with high energy (in Joules). When absorbing this high energy, the target chromophore and the structures storing it are fragmented through a selective photothermolytic effect known as photodisruption.[8] Photodisruption is often accompanied by a photoacoustic effect, as rapid light absorption by the target chromophore results in a significant increase in temperature, leading to the formation of plasma and cavitation bubbles. This process is desirable in tattoo removal, as it enhances the breakdown of the pigment.[9] This means the interaction between the laser and the chromophore occurs in such a brief interval that the heat generated does not dissipate efficiently into adjacent tissues, significantly reducing damage to the area surrounding the tattoo.[9] Thus, the laser can specifically act on the target chromophore (pigment) and the cells that store it, preserving the other structures of the integument. Quantitatively, the region subjected to thermal damage by the laser can be determined by the laser pulse duration using the following formula, where D is the thermal penetration depth (cm), k is the thermal diffusivity constant, and t is the time (s).

$$D = (4kt)1/2 \quad (I)$$

Experimentally, the thermal diffusivity of biological tissues such as skin has been calculated to be approximately 2.9 ($\pm$0.5) x 10-4 cm^2 s^{-1}.[10]

To illustrate the impact of pulse duration on thermal penetration in tissue, consider a typical pulse from a laser hair removal device, which has a duration of 30ms. Under optimal conditions, when the laser pulse hits the target chromophore and is not absorbed by surrounding structures, it will increase the temperature until thermal equilibrium is reached at a depth of approximately 0.06mm (60μm, corresponding to the size of approximately 3 to 7 epithelial cells). In contrast, a typical Q-switched laser pulse, which has a duration of only 10ns, will generate a thermal penetration of only 0.034μm, smaller than the dimension of a single cell. However, due to the cavitation process resulting from photodisruption, the cells storing the pigments and other surrounding cells may be mechanically ruptured.[9] Although laser pulse energy and duration are crucial for the success of tattoo removal, another parameter determines which chromophores will be targeted: the wavelength. The preferred laser for pigment removal is the Q-switched Nd:YAG, which emits its most intense light at the 1064nm wavelength in the near-infrared spectrum, thanks to its quasi-three-level system. This wavelength can be absorbed by several pigments of different colors and compositions; however, some residual pigments, particularly red and orange, are resistant to removal with the 1064nm Q-switched Nd:YAG. Therefore, a nonlinear optical material is often used to generate the second harmonic, ie, to double the fundamental frequency of the incident laser. Antireflection-coated potassium titanyl phosphate (KTP) crystals are typically used for this purpose. Antireflection coating, in addition to generating a faint bluish reflection, also produces destructive interferences in the reflected beams, thereby preserving nearby optical structures. KTP allows the generation of a beam that maintains the same temporal profile and transverse electromagnetic mode as the incident beam, but with a wavelength shifted to 532nm in the green visible spectrum.[11] Structurally, most commercial lasers for tattoo removal use removable or adjustable lens sets containing KTP, placed extrinsically in relation to the resonant optical cavity. In this way, the 1064nm laser beam that would hit the operative field is now directly propagated through the KTP crystal to generate the second harmonic. Although some techni-

cal specifications of KTP crystals indicate a maximum conversion efficiency of over 80%,[12] in practice, a lower efficiency is observed in second harmonic generation due to several factors that will be discussed in this article, which can complicate or even prevent the removal of some residual pigments.

METHODS

This study assessed the following laser equipment (Table 1): Etherea MX® (Vydence, São Carlos, Brasil), Spectra XT® (Lutronic Goyang-si, South Korea), and Inkie® (Countourline Sete Lagoas, Brasil), all registered with the Brazilian National Health Surveillance Agency (ANVISA). Additionally, Ladybug® (WB Brasil), Delta Light® (Delta), and an unbranded model were included, which lacked ANVISA registration or were manufactured before ®completing registration at the time of testing. The objective was to evaluate the efficiency of second harmonic generation by these devices and their compliance with specific laser metrology requirements. These include the output energy reported on the human-machine interface (HMI) and the actual laser beam energy emitted, as per NBR/IEC 60.601-2.22 standards by the Brazilian National Institute of Metrology, Standardization and Industrial Quality (Instituto Nacional de Metrologia, Qualidade e Tecnologia, INMETRO) for ANVISA registration. The study also investigated whether low efficiency is a specific issue with certain models or a widespread phenomenon.

Measurements were conducted using a NIM-1000 metrology standard from the National Institute of Metrology (NIM) of China, capable of measuring short laser pulse energies from 400 to 2000nm, ranging from 20 to 2700mJ. A photovoltaic sensor with integrated attenuator, responsive to 1064nm at 1.34 x 10-1 J/V and 532nm at 2.02 x 10-1 J/V (manufactured in 2018), was employed. Results were cross-checked against an Molectron EM400 energy meter (USA) using Scintilum (Brazil) photovoltaic sensors with specific diffusers and attenuators for 532nm/1064nm, sensitive to 1064nm at 2.35 x 10-1 J/V and 532nm at 3.15 x 10-1 J/V. A Ranbond VLE-1000 laser energy meter (China, serial number 20220305E1), calibrated by the NIM of China on March 7, 2022, served as a reference. A calibration certificate was issued under code GXjg2022-00399 (Table 2).

Tests were conducted in a controlled laboratory environment with temperature and humidity monitoring. The mean and standard deviation of 10 consecutive pulses were recorded at 2 Hz frequency to measure average energy at 1064nm. Subsequently, another 10 consecutive pulses at the same frequency were performed using the second harmonic generated by each device, and the arithmetic mean and standard deviation values were recorded.

Table 1: Devices analyzed in the study

Device	Brand	Model	ANVISA registration N.	Serial N.
1	Vydence	Etherea MX	80058580021	008642-16
2	Countourline	Inkie	80832470003	895236
3	Countourline	Inkie	80832470003	569823
4	Lutronic	Spectra XT	10343650037	VX121A005
5	Lutronic	Spectra XT	10343650037	VX115C032
6	WB	Ladybug	Not registered	201900306
7	Delta	Delta Light	Not registered	X9B300021011 24
8	Not apparent	J-200	Not registered	AS102820J- 2005962

Source: Unpublished own data

Table 2: Calibration certificate results for the VLE-1000 laser energy meter

λ (nm)	Measurement range	Pulse width (ns)	Reference value	Measured value	Correction factor	Uncertainty (k=2)
1064	3.482J	10	1.140J	1.135J	1.00	Urel = 3%
1064	348.2mJ	10	197.6mJ	198.4mJ	1.00	Urel = 3%
532	351.8mJ	10	237.5mJ	235.3mJ	1.01	Urel = 3%
532	105.5mJ	10	50.19mJ	50.25mJ	1.00	Urel = 3%

Source: Unpublished data extracted from the GXjg2022-00399 calibration certificate issued by NIM on March 7, 2022.

Data on emission at 532nm were collected directly using the energy meters and sensors, employing special filters to assess the spectral composition of laser beams at 532nm, 1064nm, and combined 1064nm + 532nm wavelengths. The filters included were:

- BG38 (Tangsinuo, China): High transmittance in the visible spectrum, high absorbance in the near-infrared spectrum, 50mm in diameter, and 2mm thick.
- HB720 (Tangsinuo, China): Inverse spectrophotometric profile, 50mm in diameter, and 2mm thick.

The transmission spectra of the filters are shown in figures 1 and 2 and were confirmed via T% measurement using a Thermo Scientific Genesys 10S UV-Vis spectrophotometer in scan mode from 400 to 1100nm at 1nm increments.

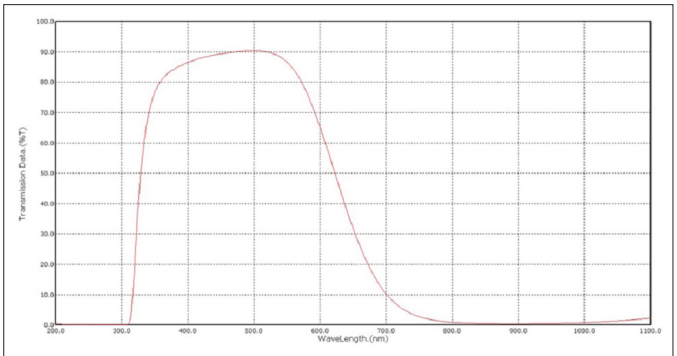
RESULTS

Measurements were conducted between October 3rd and 4th, 2022, at a mean ambient temperature of 22.0±0.5°C and relative humidity of 63.1±3%. The results for each device are summarized in table 3, obtained following the methodology previously outlined and considering a standard deviation (σ) < 0.037.

Most of the tested devices, including those registered with ANVISA, exhibited a conversion efficiency of less than 30% for generating 532nm, a parameter that does not appear to be assessed by INMETRO.

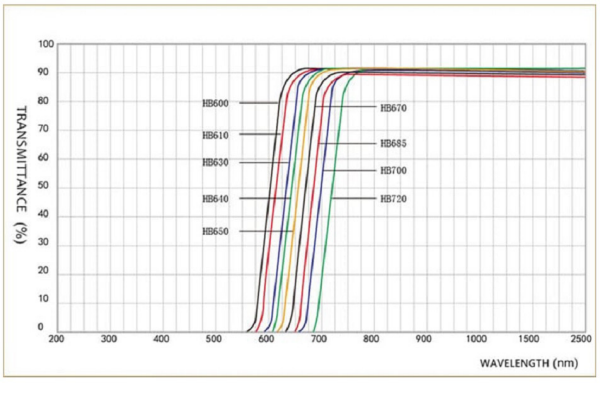
DISCUSSION

There is a common belief that the second harmonic generation of 532nm is high due to the photoacoustic effect in pigmented material. However, in practice, most laser emissions predominantly remain at the fundamental wavelength of 1064nm. In fact, KTP has a conversion efficiency far below the 50% or 80% stated in technical data sheets due to issues such as crystal quality or phase matching problems. This limitation is compounded by the photonic engineering of the laser equipment currently available on the market (with the exception of Lutronic's Spectra), in which KTP crystals are coupled to the laser output window, close to the patient's skin, without the use of additional elements to block the fundamental wavelength of the Q-switched Nd:YAG laser either by reflection (e.g., dichroic mirrors) or by absorption (e.g., traditional optical filters). As a result, the emitted beam typically contains both 1064nm and 532nm wavelengths rather than exclusively 532nm. This combined resultant beam induces a photoacoustic effect on the photographic paper used for laser cavity alignment and beam profile monitoring. Photovoltaic sensors confirm higher readings due to this combined beam, misleadingly suggesting efficient second harmonic generation. This sensory deception is corroborated by the Purkinje effect, where our retina is more sensitive to light in the center of the optical spectrum—precisely in the range of light emerging from the KTP crystal following irradiation by the Nd:YAG laser's most intense band emission (1064nm). Thus, even a small fraction of laser light at 532nm appears intensely bright compared with the fundamental wavelength of the laser, which is in the near-infrared (invisible). Consequently, during testing, laser operators are doubly deceived: first by seeing intense light emerging from the output window, corresponding to a minor conversion by often poorly positioned and low-quality KTP crystals; and second by a notable photoacoustic effect on some pigmented structures caused by unconverted 1064nm laser light also emanating from the KTP crystal without being converted or blocked by a filter.



*Fonte: Especificações técnicas do filtro QB21 ϕ50*1,0 mm comercializado pela Tangsinuo Store, disponível em https://pt.aliexpress.com/item/4000065793459.html e acessado em abril / 2022.*

FIGURE 1: T% spectrum of the Visible Bandpass Filter used in the tests



*Fonte: Especificações técnicas do filtro HB720 ϕ50*2,0 mm comercializado pela Tangsinuo Store, disponível em https://pt.aliexpress.com/item/4000438441353.html?gatewayAdapt=glo2bra e acessado em abril / 2022*

FIGURE 2: T% spectrum of the IR Pass Filter used in the tests (model HB720, represented by the green curve)

Table 3: Summary of measured values for each device (mean values)

Device	Adjusted energy (mJ)	Total energy (mJ)	Percent error between adjusted and total energy	Energy at 532nm with filter (mJ)	Conversion rate to 532nm
Etherea MX	600	537	10.5	92.4	17.21
	1200	1115	7.08	175.2	15.71
	1500	1410	6	213.4	15.13
Inkie (1)	112	123.3	10.09	20.01	16.23
	503	566.9	12.7	134.7	23.76
	792	813.5	2.65	187.1	23.00
	1200	1118	6.83	293.9	26.29
Inkie (2)	112	127.8	14.11	34.58	27.06
	503	549.4	9.22	118.7	21.61
	792	817.2	3.18	210.9	25.81
	1200	1210	0.83	328.4	27.14
Spectra XT (1)	52	36.84	29.15	36.63	99.43
	103	74.05	28.11	73.57	99.35
	206	148.1	28.11	147.1	99.32
	387	239.3	38.16	238.4	99.62
Spectra XT (2)	52	42.5	18.27	41.1	96.71
	103	94.3	8.45	93.0	98.62
	206	179.7	12.77	178.1	99.11
	387	325.1	15.99	323.9	99.63
Ladybug	100	238.2	138.20	9.3	3.90
	500	549.2	9.84	17.3	3.15
	1000	821.3	17.87	28.9	3.52
Delta Light	100	459.2	359.20	47.5	10.34
	500	620.3	24.06	63.3	10.20
	1500	1178	21.47	112.2	9.52
J-200	100	223.2	123.20	8.895	3.99
	220	221.2	0.55	7.446	3.37
	1000	793.4	20.66	23.57	2.97

Source: Unpublished own data. Measurements conducted at Scintilum facilities (www.scintilum.com.br).

Unfortunately, available photoelectric sensors for measuring pigment removal lasers (Q-switched Nd:YAG), such as those from Ophir,[13] Coherent,[14] and Gentec,[15] do not distinguish between wavelengths present in the measured beam. These sensors are crucial for product certification bodies (PCBs) tasked with approving equipment for metrological and health authorities. As a result, technical reports do not accurately reflect the 532nm laser dose delivered to patients according to screen settings but instead aggregate coaxial 532nm and 1064nm beams, leaving the 532nm component undetermined for metrological assessments.

The only exception noted in our tests is the Spectra XT by Lutronic, featuring a distinct photonic system where beam generation, amplification, and control—including second harmonic generation—occur within the equipment's main engine rather than the handpiece. The resultant beam is then guided through an articulated arm with mirrors to the treatment area.

The photonic system of the Spectra XT restricts user mechanical adjustments of optical components as they are pre-set. A higher complexity in second harmonic generation was also observed, with the use of a larger, high-quality pre-heated KTP crystal monitored by equipment software to prevent

532nm emission from a cold crystal and minimize risks of photochromic damage, such as gray tracking.[16] The system also includes dichroic filters for wavelength discrimination, making it the only equipment in the study capable of providing a monochromatic 532nm intensity relatively aligned with screen specifications, complying with the NBR/IEC 60.601-2.22 standard.

Some laser systems, such as Contourline's Inkie, incorporate a phase matching angle adjustment ring for crystal-based energy adjustments. However, user manuals often omit this requirement, and operational training does not consistently cover it.[17] Another difficulty in adjusting the position of the KTP crystal in relation to the phase matching angle is the lack of affordable energy meters to monitor maximum energy levels. As the KTP is removable in these devices, readjustment is necessary with each reinstallation and use.

Notably, the lack of spectral discrimination in coaxial beam components may intentionally obscure technical limitations related to KTP crystal quality, as most lower-cost components have poor second harmonic generation conversion rates. A similar discrepancy in pigment removal lasers is observed regarding deviations between screen-set low energy values and actual measured beam exit values, often exceeding 150% of the administered dose due to solid-state laser cavity instability at low energies. Consequently, laser source parameters are adjusted to ensure reliable operation even at minimum screen energy settings, often resulting in intentional firing at higher energies (e.g., 200mJ minimum for lasers with initial settings of 20 to 100mJ), compromising compliance with the NBR/IEC 60.601-2.22 standard, which mandates maximum deviations of 20% between selected and measured values.

FINAL CONSIDERATIONS

For medical professionals aiming to achieve optimal clinical outcomes in managing epidermal pigmented lesions or performing tattoo removal, selecting tools endorsed by industry expertise and approved by the competent bodies is of paramount importance. However, with the exception of the Lutronic Spectra XT, none of the 1064nm lasers analyzed in this study demonstrated sufficient conversion efficiency to 532nm. This inefficiency compromises the effective removal of residual red and/or orange pigments, as indicated values on screens do not align with actual measurements at the laser output window. Our analyses also highlight potential methodological flaws in laser measurements by PCBs concerning compliance with the NBR/IEC 60.601-2.22 standard for INMETRO and subsequent ANVISA approval of Class 3 laser equipment. Further studies with a larger sample size are needed to determine whether the observed trends are limited to the devices tested or are widespread. Future research should also investigate the risks associated with administering 1064nm and 532nm wavelengths simultaneously on the same treated area, given the misleading screen information suggesting that only 532nm is being administered at an energy level equivalent to 50% of the resultant beam. Additionally, evaluations of user manuals should be conducted to ensure regulatory compliance regarding the use of KTP crystals for generating the 532nm laser beam. ●

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Quality of life in individuals with auricular keloids

Qualidade de vida nos portadores de queloide auricular

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ABSTRACT

Background: Keloids are abnormal proliferations of scar tissue that do not regress spontaneously. Studies on the quality of life in patients with auricular keloids are rare. This condition is a frequent complaint, occurring in a highly visible area.

Objective: To assess the impact of auricular keloids on the quality of life of affected individuals, demonstrating that psychological and physical symptoms are common and significantly affect patients.

Methods: This is a cross-sectional, observational analytical study conducted in São Paulo. Patients with auricular keloids completed the QualiFibro questionnaire, a validated tool specific for assessing quality of life in individuals with auricular keloids.

Results: Seventeen patients with auricular keloids were analyzed. The questionnaire revealed that most participants experienced some degree of physical impairment (76% reported itching, and 58% reported pain in their keloids). All participants showed psychological distress to varying degrees.

Discussion: Patients often associate their keloids with feelings of shame and low self-esteem. We believe that raising awareness of the negative psychological impact of this condition can help dermatologists better understand these patients' concerns and provide empathetic support, aiming to make them feel more comfortable in their own skin.

Keywords: Keloid; Quality of Life; Ear Auricle.

RESUMO

Introdução: *queloides são proliferações anormais de tecido cicatricial que não regridem espontaneamente. São raras as investigações sobre a qualidade de vida em pacientes com queloide auricular. Trata-se de uma queixa frequente e localizada em um sítio de grande visibilidade.*

Objetivo: *avaliar o impacto dos queloides auriculares na qualidade de vida de seus portadores, a fim de demonstrar que sintomas psicológicos e físicos são frequentes e impactantes para os pacientes.*

Métodos: *trata-se de um estudo analítico observacional do tipo transversal conduzido em São Paulo. Pacientes com queloide auricular responderam ao questionário QualiFibro, validado e específico para o tema.*

Resultados: *foram analisados 17 pacientes com queloide auricular. O questionário evidenciou que a maioria dos participantes apresentou algum grau de prejuízo físico (76% dos pacientes reportaram prurido e 58% reportaram dor em seus queloides). Todos os participantes apresentaram prejuízo psicológico em graus variados.*

Conclusão: *os pacientes frequentemente relacionaram seus queloides a sentimentos de vergonha e baixa autoestima. Acreditamos que trazer visibilidade para a repercussão psicológica negativa desta patologia pode auxiliar o dermatologista a compreender melhor os anseios destes pacientes e acolhê-los empaticamente, com o objetivo de fazer com que eles se sintam mais confortáveis em sua própria pele.*

Palavras-chave: *Queloide; Qualidade de Vida; Pavilhão Auricular.*

Original Article

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INTRODUCTION

The first description of a keloid related to surgical trauma was found in a papyrus dating back to 1700 BC. In 1806, Alibert coined the term "keloid," derived from the Greek word "khelé," meaning crab pincers, due to the lateral growth of the tissue toward unaffected skin.[1] Keloids are abnormal proliferations of scar tissue that form during the healing process in predisposed individuals and can cause symptoms such as pain, discomfort, itching, and even movement restriction. They appear as benign fibroproliferative tumors, with varying colors (ranging from erythematous to erythemato-brownish), elastic to firm consistency, smooth surface, and sometimes may present focal ulcerations. Keloid growth does not regress spontaneously and extends beyond the original scar margins, rarely invading subcutaneous tissue. Keloids should not be confused with hypertrophic scars, which are also raised but do not grow beyond the original boundaries and may regress over time. Keloids occur only in humans, typically appearing between the ages of 10 and 30, with no gender prevalence, and affect 5 to 15% of scars.[2] They are more common in individuals with darker skin types, affecting up to 16% of this population.[3] Keloids are more frequently found on the earlobes, anterior chest, anterior neck, shoulders, arms, and in wounds that are perpendicular to skin tension lines[4], with earlobes being the most affected site.[5] Although the exact pathophysiology of keloid formation remains unknown, it is believed that an imbalance between the anabolic and catabolic phases of the healing process leads to increased collagen production compared to its degradation.[6,7] The most important risk factor for keloid development is secondary intention healing, especially when healing takes longer than three weeks. Other risk factors include wounds with prolonged inflammation (due to foreign body reactions, infections, or burns), genetic predisposition, and individual susceptibility to form keloids.[8,9] Auricular keloids are mainly associated with earring use and thermal burns, affecting the helix, antihelix, and earlobes. There has been a recent increase in keloid incidence following piercings, particularly in the auricle of young individuals with darker skin types.[10,11] The incidence of auricular keloids is 2.5% for all ear piercings, and ear piercings after the age of 11 are associated with a higher incidence of keloid formation. Keloids may also arise after drainage of auricular hematomas, auricular trauma repair, or as secondary recurrences after the excision of pre-existing keloids.[12,13]

There are various treatment modalities, but none are consistently more effective than others, and recurrence rates are high. Combined treatments seem to be more effective, with lower recurrence rates compared to monotherapy.[14] Since there are no guidelines for keloid treatment, efforts are made to find therapies with the lowest recurrence rates, as these lesions can cause aesthetic and functional alterations, significantly impacting individuals' quality of life.[6, 7, 15] Auricular keloids are a frequent complaint in dermatology clinics, yet studies on the quality of life in individuals with auricular keloids are rare. The aim of the present study was to investigate the impact of auricular keloids on the quality of life of affected individuals, aiming to measure the severity and physical and psychological repercussions on these patients.

MATERIALS AND METHOD

An observational analytical cross-sectional study was conducted at Unidade de Cosmiatria e Cirurgia Oncológica (UNICCO), Universidade Federal de São Paulo, located in the city of São Paulo. The primary objective of the study was to assess the impact of auricular keloids on the quality of life of affected individuals using the QualiFibro questionnaire (Figure 1), validated for this purpose. The project was approved by the Teaching and Research Coordination of Hospital São Paulo (Protocol 242/2016) and the Human Research Ethics Committee (CEP-UNIFESP) (Protocol 0797/2016). All participants signed an Informed Consent Form to participate in the study. The study population was a non-probabilistic sample of individuals with auricular keloids treated at our clinic, of both sexes, aged 12 to 60 years, who signed the informed consent regarding the procedure to answer the questionnaire. Recruited patients underwent a medical consultation to analyze demographic and clinical parameters, followed by self-administration of the QualiFibro questionnaire. Exclusion criteria included patients with uncontrolled clinical, neurological, or psychiatric conditions or those who had difficulties understanding the study's objectives. Demographic parameters (sex, age, skin type, place of birth, and residence), keloid location, pain (on a scale from 0 to 10), itching (on a scale from 0 to 10), presence of ulceration, and size of the auricular keloid were collected. Next, patients were instructed to complete the QualiFibro questionnaire (Table 1), a validated tool by Bock et al.[16] and translated into Portuguese by Furtado *et al*.[17] for patients with fibroproliferative scars. QualiFibro is a specific, self-administered questionnaire consisting of 14 items that cover physical and psychological domains. The psychological domain includes items 3, 5, 7, 9, 10, 11, 12, 13, and 14, while the physical domain is assessed through items 1, 2, 4, 6, and 8. There is also a question regarding suicidal intent (item 15). Based on the answer selected, each item can receive one of the following scores: -5, -3, -1, +1, +3, or +5. The closer the score is to +5, the greater the impact of the keloid on the patient's life, indicating a poorer quality of life.

Specific quality of life assessment questionnaires can measure the severity and progression of physical and psychological repercussions in patients' lives, as well as the outcomes of therapeutic interventions. To calculate the final scores, an arithmetic mean of the obtained values was used, separating the questions related to physical aspects from those related to psychological aspects.

RESULTS

This study included 17 patients, consisting of 7 women and 10 men, aged between 15 and 57 years (with an average age

Table 1: Complete results of the questionnaire

	Completely false (-5)	False (-3)	Somewhat true (-1)	Almost true (1)	True (3)	Completely true (5)	Average score (-5 a +5)
1. Changes In weather greatly affect my scars (pain, tension)	6 (35%)	4 (23%)	2 (12%)	2 (12%)	2 (12%)	1 (6%)	-1.82
2. My scars limit my movements	11 (65%)	3 (17%)	2 (12%)	0 (0%)	1 (6%)	0 (0%)	-3.70
3. I can ignore how people look at me because of my scars	6 (35%)	0 (0%)	1 (6%)	3 (17%)	1 (6%)	1 (6%) -0.05	6 (35%)
4. Itching from my scars frequently bothers me	4 (23%)	0 (0%)	1 (6%)	2 (12%)	4 (23%)	4 (23%)	+0.41
5. Sometimes I feel ashamed to be sexually active due to my scars	6 (35%)	2 (12%)	1 (6%)	1 (6%)	2 (12%)	5 (30%)	-0.29
6. I find it hard to endure the itching in my scars	6 (35%)	5(30%)	0 (0%)	2 (12%)	2 (12%)	2 (12%)	-1.58
7. I avoid letting people close to me know that I have scars	4 (23%)	3 (17%)	0 (0%)	3 (17%)	0 (0%)	7 (41%)	+0.64
8. When my scars itch, I can't stop scratching them	6 (35%)	2 (12%)	3 (17%)	0 (0%)	2 (12%)	4 (23%)	-0.76
9. I don't feel physically attractive or sexually desirable when I think about my scars	3 (17%)	3(17%)	2 (12%)	1 (6%)	4 (23%)	4 (23%)	+0.41
10. I find it hard to accept my scars	1 (6%)	4 (23%)	2 (12%)	2 (12%)	3 (17%)	5 (30%)	+1.00
11. I avoid swimming pools or beaches because others might find my scars disgusting	9 (53%)	3 (17%)	2(12%)	1 (6%)	1 (6%)	1 (6%)	-2.76
12. I never feel embarrassed or ashamed because of my scars	6 (35%)	3 (17%)	1 (6%)	3 (17%)	2 (12%)	2 (12%)	+1.23
13. I have less self-confidence because of my scars	4 (23%)	2(12%)	1 (6%)	4 (23%)	3 (17%)	3 (17%)	+0.05
14. I don't feel comfortable when asked about my scars	0 (0%)	2 (12%)	4 (23%)	1 (6%)	6 (35%)	4 (23%)	+1.70
15. I have thought about committing suicide because of my scars	14 (82%)	2 (12%)	0 (0%)	0 (0%)	0 (0%)	1 (6%)	-4.17

of 25 years), all from São Paulo city. There was a predominance of higher skin types, with 88% of the patients having skin type III or above. The size of the keloids ranged from 0.5 to 5 cm on the longest axis, with an average size of 2.3 cm. The most affected area was the earlobe (82%), with a predominance of posterior location (65%) and left side (66%). None of the patients had ulcerated keloids. Regarding the pruritus scale for keloids, which ranged from 0 (no itching) to 10 (maximum itching), the average response was 4.58. Thirteen patients (76%) reported experiencing some degree of itching in their scars, with three of them indicating maximum itching. In terms of the pain scale, more than half (58%) of the patients reported feeling some degree of pain in their scars, with an average score of 3.52. In the analysis of the QualiFibro questionnaire responses, the physical domain had an average score of -1.49, with values ranging from -5 (least impact) to +4.6 (greatest impact), indicating a highly heterogeneous group. In the psychological domain, the average score was +0.20, with individual scores ranging from -4.55 to +4.55. Almost all patients denied having ever considered suicide; however, one patient reported having seriously considered suicide (score +5) due to their keloids.

DISCUSSION

This study highlighted the wide range of symptoms experienced by individuals with auricular keloids, particularly their impact on self-esteem and body image. Most patients scored significantly on the psychological impairment aspects of the QualiFibro questionnaire, demonstrating a link between auricular keloids and feelings of shame, difficulty with self-acceptance, low self-esteem, and even issues in their sexual lives. In terms of physical symptoms, most patients reported that their auricular keloids did not restrict their movements, which is expected given the anatomical location. However, itching was the most prominent physical complaint, affecting most cases. Patients with auricular keloids suffer similarly to those with other chronic skin conditions. The decline in their quality of life is often driven by stigmatization, which, in many cases, is more significant than the physical condition itself. In this study, we observed that most patients experienced more psychological than physical impairment. This is the first study to evaluate the quality of life using the QualiFibro questionnaire specifically applied to patients with auricular keloids. We believe that studying the quality of life in this population is crucial due to the potential impact of this condition on patients' work, academic lives, and interpersonal relationships. The limitations of this study include the small number of participants, allowing only descriptive analysis. A larger sample size would enable inferential data analysis. Moreover, this was a cross-sectional and observational study. Future research should focus on interventional and prospective studies, assessing the quality of life before and after reparative therapy. Treating auricular keloids remains challenging, often requiring combined treatment for better therapeutic outcomes.[18] We believe that effective treatment can substantially improve the quality of life of patients with auricular keloids, underscoring the need for further studies.

CONCLUSION

Despite the variability in symptoms, all patients associated their keloids with some degree of negative impact on their quality of life. Dermatologists should recognize the importance of providing empathetic support and attentive listening when managing this condition, as patients often present with distressing psychological and somatic symptoms, significantly affecting their quality of life. ●

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Efficacy of oral omega-3 polyunsaturated fatty acids to prevent post-inflammatory hyperpigmentation in high skin phototypes after non-ablative fractional 1340 nm laser

Eficácia de ácidos graxos poli-insaturados ômega-3 orais para prevenir a hiperpigmentação pós- inflamatória em fototipos altos após laser 1340nm fracionado não ablativo

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ABSTRACT

Introdução: os lasers fracionados não ablativos são tratamentos eficazes bem conhecidos para o rejuvenescimento da pele. No entanto, a alta incidência de hiperpigmentação pós-inflamatória aumenta os riscos de complicações, especialmente em fototipos mais altos. A suplementação de fosfolipídios de caviar tem sido utilizada com sucesso para reduzir o processo inflamatório, o que pode ser benéfico para o manejo da hiperpigmentação pós-inflamatória após laser.

Objetivo: comparar a incidência de hiperpigmentação pós-inflamatória em fototipos altos após a suplementação de fosfolipídios de caviar.

Métodos: 20 pacientes realizaram uma sessão de laser fracionado não ablativo (Nd:YAP 1340nm, Zye Vydence, Brasil), sendo que 10 deles utilizaram 200mg de fosfolipídio de caviar, via oral, diariamente, durante 15 dias, antes do tratamento, e 40 dias após. Imagens dos pacientes foram avaliadas antes e após 40 dias da aplicação do *laser*. A avaliação clínica baseou-se na presença ou não de hiperpigmentação pós-inflamatória. A análise estatística foi realizada por meio do teste Z.

Resultados: nenhum caso de hiperpigmentação pós-inflamatória foi observado no grupo experimental. No entanto, o grupo controle apresentou 30%.

Conclusões: assim, o fosfolipídio de caviar pode ser uma opção na prevenção da hiperpigmentação pós-inflamatória após lasers fracionados não ablativos visando ao não surgimento de efeitos colaterais.

Palavras-chave: Lasers; Pele; Rejuvenescimento; Ácidos Graxos; Ômega-3.

RESUMO

Introduction: *Non-ablative fractional lasers are well-known effective treatments for skin rejuvenation. However, the high incidence of post-inflammatory hyperpigmentation increases the risk of complications, especially in higher skin phototypes. Caviar phospholipid supplementation has been used successfully to reduce the inflammatory process, which may be beneficial to manage post-inflammatory hyperpigmentation after laser.*

Objective: *To compare the incidence of post-inflammatory hyperpigmentation in high phototypes after caviar phospholipid supplementation.*

Methods: *20 patients underwent a non-ablative fractional laser session (Nd:YAP 1340nm, Zye Vydence, Brazil), and 10 of them used 200 mg of caviar phospholipid orally daily for 15 days before treatment and 40 days after. Patient images were evaluated before and after 40 days of laser application. Clinical assessment was based on the presence or absence of post-inflammatory hyperpigmentation. Statistical analysis was performed using the Z test.*

Results: *We observed no cases of post-inflammatory hyperpigmentation in the experimental group; however, the control group presented 30%.*

Conclusions: *Caviar phospholipid may be an option for preventing post-inflammatory hyperpigmentation after non-ablative fractional lasers, aiming to avoid adverse events.*

Keywords: *Lasers; Skin; Rejuvenation; Fatty Acids; Omega-3.*

Original Article

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INTRODUCTION

In dermatology, the term "high skin phototype" encompasses people with darker skin tones and comprises a wide range of racial and ethnic groups, including people of African, Asian, and Pacific Islander descent, Native Americans, Alaskans, Hispanics, Indians, Pakistanis, and of Middle Eastern origin, among others.[1] Skin color can be categorized using the Fitzpatrick skin phototype classification, which ranges from type I to type VI, with type VI being the darkest. This skin typing system was developed originally to characterize the skin's response to sunlight and UV radiation and correlate skin color to burning (in lighter skin types) or tanning (in darker skin types). Most patients with "high phototype" have been classically defined as skin types IV to VI.[2]

Lasers can be non-ablative fractional or ablative fractional. Ablative lasers use longer wavelengths and can disrupt the skin layers, while non-ablative lasers keep the stratum corneum intact. The non-ablative fractional laser (NAFL) is an innovative technology in aesthetic dermatology that aims to improve the skin appearance, especially regarding facial rejuvenation. Non-ablative lasers emit light within the infrared range (1000–1600 nm) of the electromagnetic spectrum. The most commonly used wavelengths are 1340 nm, 1410 nm, 1440 nm, 1540 nm, and 1550 nm.[3]

NAFL is indicated for photoaging, rhytides, melasma, sagging, stretch marks, scars, and dyschromia. The results are satisfactory, and recovery occurs within 1 to 5 days, depending on the energy and amount of skin affected by the treatment (thermal microzones). Also, adverse events are minimal, especially in lighter phototypes. However, it is essential to highlight that this procedure requires several sessions, especially when they are less aggressive, making the treatment costly.[3]

This laser acts by generating microscopic columns of thermal injury with dermal-epidermal coagulation without ablation of the epidermis. By delivering the energy more precisely and maintaining the integrity of the epidermis, it acts more gently, reducing the chances of complications and the recovery period compared to the ablative fractional laser.[3] NAFL is a safer treatment for different skin phototypes. However, it can generate local inflammation, culminating in post-inflammatory hyperpigmentation (PIH), especially in higher phototypes.

The risk of PIH following dermatological procedures is well known. It can affect any individual, regardless of age and sex, being more evident in higher skin phototypes and appearing as hyperpigmented spots on the skin.[4-6] Previous history of PIH, presence of PIH, and high skin phototype (Fitzpatrick IV-VI) are considered risk factors. PIH is a pigmentary disorder in which the skin develops reactive hypermelanosis due to different exogenous or endogenous factors induced by excess melanin in the epidermis and aberrant distribution of melanin pigment. Inflammatory and infectious conditions, such as lesions of different etiologies such as dermatophytosis, viral exanthema, allergic reactions, erythematous-scaly dermatoses, and cosmetic procedures, such as chemical peels, laser, and dermabrasion, can trigger PIH. The degree and depth of inflammation and skin color likely influence the severity of PIH. The condition has a chronic course with irregularly shaped lesions ranging from light brown to bluish-gray.[7] Prevention and treatment of underlying inflammatory diseases are crucial in PIH management. Topical depigmenting creams, including arbutin, hydroquinone, kojic acid, and azelaic acid, have also been tried with limited success.[7]

Overproduction or aberrant release of melanin in response to inflammatory stimuli and circumstances causes PIH. The oxidation of arachidonic acid produces eicosanoids, which are involved in cell signaling.[8] During the inflammatory response, prostaglandins, leukotrienes, cytokines, nitrogen, and reactive oxygen species stimulate melanocyte proliferation and increase melanogenesis.[8] In vitro studies have demonstrated that thromboxane B2, leukotriene C4, histamine, prostaglandin E2, and leukotriene D4 can activate melanocytes. Higher levels of immunoreactive tyrosinases are linked to the upregulation of these metabolites, resulting in greater melanin production and transfer of melanosomes to keratinocytes.[8]

Caviar phospholipids (CF) consist of a mixture of high levels of fatty acids, including polyunsaturated fatty acids (PUFAs), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), astaxanthin, and alpha-tocopherol which are beneficial for skin health.[9,10] Although some caviar-based cosmetic products have appeared on the market with the function of anti-aging the skin, the effects of caviar on the skin are still unclear.

PUFAs play a regulatory role, modulating the inflammatory response by producing eicosanoids, including series 3 prostaglandins, thromboxanes, and leukotrienes. Studies suggest that PUFAs play an essential role in skin homeostasis, modulating barrier function and inflammatory/immune reactions involved in various skin diseases.[11,12] PUFAs reduce skin inflammation by competing with arachidonic acid and stimulating the production of eicosanoids.[11,12] This study aimed to assess the influence of oral supplementation of 200 mg of CF on the incidence of PIH in black skin after a non-ablative laser.

METHODS

It is a prospective, randomized study conducted in two private and independent dermatological clinics (Clinics A and B). We selected 20 Caucasian volunteers aged 30 to 60 years with Fitzpatrick skin phototypes IV-VI. Exclusion criteria were phototypes below IV, pregnant women, lactating women, patients with unrealistic expectations regarding possible results, and patients using depigmenting agents or topical corticosteroids. All participants enrolled in this study signed an informed consent form.

Research Randomizer at https://www.randomizer.org generates the randomization. Patients in the experimental group (Group I) received 55 capsules, each containing 200 mg of CF orally, and were instructed to take one capsule a day at home after dinner. Individuals allocated to the control group (Group II) did not use the medication.

The dynamics of the study were as follows: each patient visited Clinic A three times (at T0, T15, and T55): at the beginning, an investigator1 distributed the treatment to patients allocated to the experimental group,2 classified the skin phototypes according to the Fitzpatrick scale and3 captured standardized images of the patients using the equipment Visia Canfield Imaging Systems Inc. Fifteen days later (T15), the patients returned to Clinic A and underwent a non-ablative fractional laser session (Nd: YAP 1340 nm, Zye Vydence, Brazil), with 2-3 passes over the entire face, except upper eyelids, following the parameters of 110 MJ, 10 ms, 100 MZT. Forty days after laser application (D55), patients returned to recapture facial images.

Patients were instructed to use a broad-spectrum sunscreen with SPF 50 and the capsules provided daily. In Clinic B, a dermatologist reviewed and evaluated each participant's paired images taken at baseline (T0) and day 55 (T55). Clinical assessment was based on post-inflammatory hyperpigmentation and was classified as 1: no or 2: yes. Statistical analysis was performed using the Z test to compare proportions with the R software.

RESULTS

No adverse events related to the supplement were reported. The main adverse event was PIH in 30% of the control group (Figure 1), with no cases observed in the experimental group (Figure 2). The Z test to compare proportions observed that the difference was statistically significant; therefore, we rejected the null hypothesis that the proportions of cases with PIH are statistically equal (p=0.027).

DISCUSSION

Changes related to skin hyperpigmentation, such as lentigo, melisma, and PIH, are frequent complaints in dermatological offices and impact significantly the patients' quality of life. Despite being very common, the literature lacks preventive treatments that could be indicated before risk situations, such as laser on skin with higher phototypes. Despite several treatments available, many can lead to a process irritative with subsequent worsening or even development of PIH. It is more evident in these phototypes, which makes treatment even more challenging for patients with phototypes between III-VI.[5,6,13] The risk of PIH can be a limiting factor in the choice of dermatological treatment in the skin with higher phototypes, sometimes restricting therapeutic options, as hyperpigmentation is one of the most common post-laser complications.

Resurfacing using an ablative fractional laser is considered the gold standard for skin rejuvenation, especially in the skin with intense photoaging, presenting surprising results. However, the prolonged recovery time and discomfort are limiting factors.[14] Furthermore, the risk of adverse events is greater in patients with higher phototypes.

The non-ablative fractional laser aims to generate thermal damage to the dermis through coagulation columns in the skin that stimulate collagen remodeling with minimal effects on the epidermis. It allows rapid tissue repair with few adverse events while keeping the skin intact without ablation. This laser works for skin rejuvenation in moderately aging skin, with excellent results, less discomfort, and a lower risk of complications.[3]

Although the non-ablative fractional laser is a therapy with excellent results in skin rejuvenation and is safer for patients with higher phototypes, as it is a procedure that generates irrita-

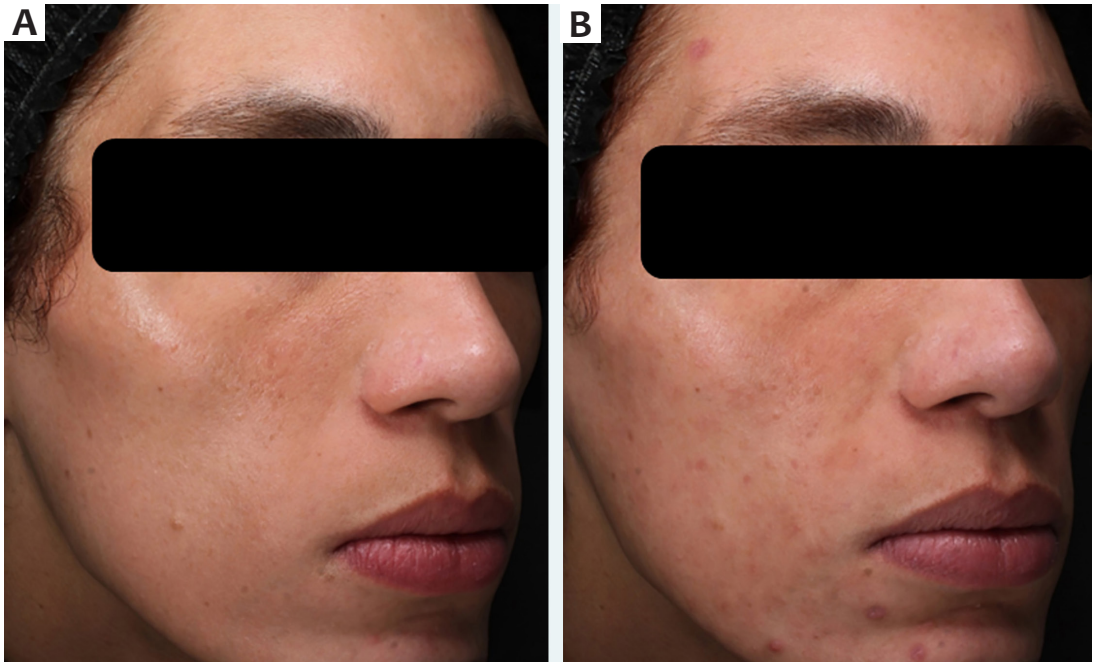

Figure 1: - A - Clinical images of the right side of the face before treatment (D1). **B -** 40 days after treatment (D55) - Control group

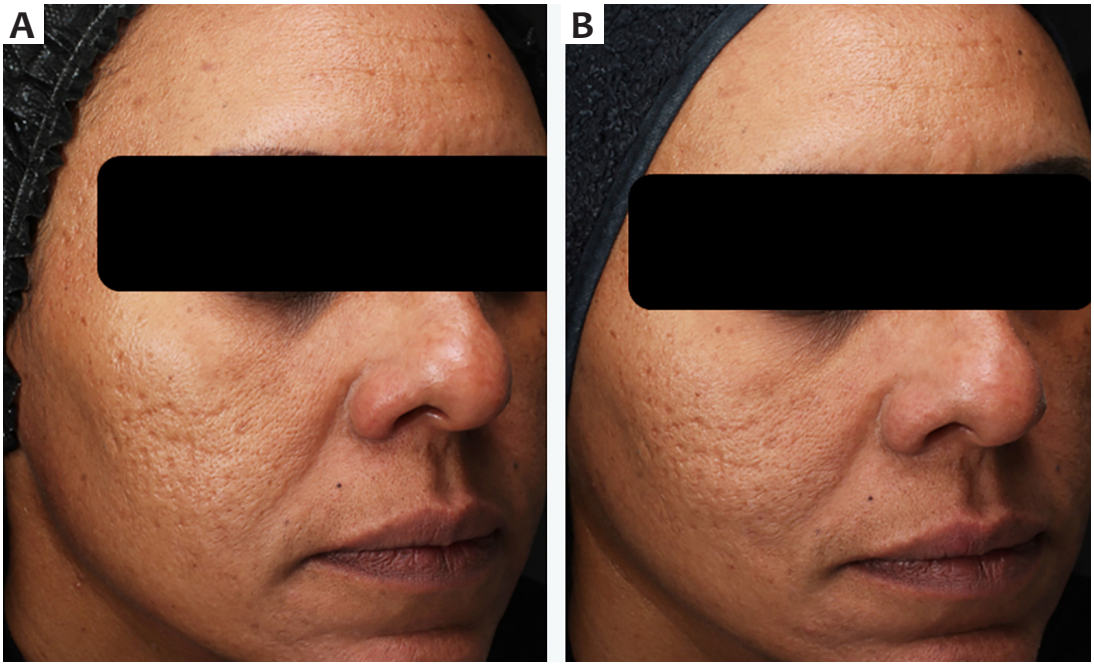

Figure 2: - A - Clinical images of the right side of the face before treatment (D1).
B - 40 days after treatment (D55) - Experimental group

tion and consequently an inflammatory process, it can cause PIH in predisposed skin.[15] Early treatment and even preventive care are essential to reduce long-term sequelae, such as hyperpigmentation and scars, which can be very difficult to treat or also reduce treatment adherence, as most treatments include several sessions. However, there are no studies on the use of a 1340 nm Nd:YAP (Neodymium:Yttrium Aluminum Perovskite) laser in higher skin phototypes and association with active ingredients in an attempt to minimize adverse events of hyperchromia. It is recommended to use refrigeration during treatment and photoprotectors, topical corticosteroids, and products with depigmenting action to reduce the risk of PIH. However, to date, little has been described about systemic prophylaxis for the occurrence of PIH after procedures.

Oral tranexamic acid has already been used for this purpose; however, without significant results.16 Furthermore, it is a medication that can have significant adverse events. Tranexamic acid started soon after the procedure would affect melanogenesis, blocking the interaction between melanocytes and keratinocytes and reducing inflammatory cytokines that stimulate melanocytes.[16] Several mechanisms are described. Nevertheless, the exact action of tranexamic acid on melanogenesis is still uncertain.

Previous studies have demonstrated the biological activities of marine fish oil. CF supplementation probably has the potential to reduce inflammatory processes, which may be beneficial to manage PIH. CF exerts a regulatory function by modulating physiological and pathological conditions on multiple mechanisms, such as the inflammatory response through the production of eicosanoids, which are inflammatory mediators of lipid origin, synthesized from omega-6 fatty acids, such as arachidonic acid (AA) or omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), including prostaglandins, thromboxanes, and leukotrienes. The literature corroborates the findings of this study by demonstrating the reduction of hyperpigmentation in the skin with the use of polyunsaturated fatty acids from fish oil.[17,18] It is worth highlighting that although CF apparently reduces the risk of PIH, combining sunscreen and established topical treatments is essential.

Fish oil can inhibit radiation-induced inflammation and hyperpigmentation (UVR) and improve skin barrier function. It also promotes skin protection against dry skin stimulation and accelerates the recovery of skin physiology. Omega 3 appears to have a photoprotective role in sun-exposed skin,[19] which may also be related to protection against PIH, as observed in this study.

Most studies that assess polyunsaturated fatty acid supplementation did not observe critical adverse events. The only adverse event described is mild gastrointestinal discomfort in a small number of patients,[20,21] that was not reported in our study. The safety of this supplement, combined with its anti-inflammatory and photoprotective properties, reinforces the promising characteristics for use in high phototypes who undergo procedures that generate irritation.

CONCLUSION

The study demonstrated that daily oral administration of 200 mg of CF can be an effective and well-tolerated treatment option for preventing PIH in the skin with a higher phototype after a non-ablative laser. The results of this study need to be confirmed in randomized, controlled studies with a larger sample size. ●

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Update on hair fiber assessment

Atualização na avaliação da fibra capilar

Review article

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ABSTRACT
Damage caused by chemical, physical, and thermal procedures can disrupt the natural morphological characteristics of the hair, causing the strands to become dry, dull, weak, and brittle. The objective of this article was to update dermatologists on the methods available for assessing hair shaft damage. The main laboratory (microscopy, tensile strength, structural assessment, physical and mechanical properties) and outpatient (diagnostic tests and patient history) diagnostic methods for evaluating the quality of the hair shaft are presented.
Keywords: Hair; Dermatology; Keratins.

RESUMO
Os danos causados por procedimentos químicos, físicos e térmicos podem atrapalhar as características morfológicas naturais do cabelo e levar a uma má condição, fazendo com que os fios fiquem secos, sem brilho, fracos e quebradiços. O objetivo deste artigo é atualizar o dermatologista quanto às formas de avaliação disponíveis para compreensão dos danos da haste capilar. Foram apresentadas as principais metodologias diagnósticas laboratoriais (microscopia, tração à ruptura, avaliação estrutural, propriedades físicas e mecânicas) e ambulatoriais (provas diagnósticas e anamnese) para avaliação da qualidade da haste capilar.
Palavras-chave: *Cabelo; Dermatologia; Queratinas.*

INTRODUCTION

The study of hair has been one of the most impacted by advances in diagnostic techniques in Dermatology over the last 20 years. A deeper understanding of alterations to the scalp and hair shaft has led to major developments in diagnosis and therapeutic approaches. New entities have been recognized and reclassified with dermoscopy and the new histological cross-sections applied to scalp.[1] Hair has multiple functions, mainly physical protection, thermal insulation, camouflage, sebum dispersion, and sensory perception. It affects quality of life, attractiveness, and self-esteem in contemporary human society.[2]

This review aims to update dermatologists on laboratory and outpatient diagnostic methodologies for the hair shaft. Evaluating the microscopic, dermoscopic, biochemical, and molecular characteristics of hair fibers allows for a better understanding of the biological processes related to the aging process, disorders of hair shaft keratinization, external damage from chemical treatments, and the ability to recover from aesthetic treatments.[3]

Hair structure

The hair fiber is extremely resistant and has three main morphological constituents: cuticle, cortex, and in some cases, medulla (Figure 1). Overlapping flat, scale-like structures surround the central core of the fiber, such as a thick, chemically resistant protective layer called cuticle. The cuticle prevents the cortex from external environmental damage.[4]

The protection of hair shaft against environmental and chemical damage begins with the adherence and organization of the cuticular cells. A thick, chemically resistant protective layer is responsible for the shine, resistance, and combability of hair shaft. The human cuticle has around six to eight layers and is made up especially of keratinized cells (80%), structural lipids, and proteins associated with keratin with a high Sulphur content.[5] The greater the alignment and integrity of the cuticles, the better the softness, shine, and frizz characteristics. Cuticle cells are classified into the epicuticle, which is more external and hydrophobic, followed by the exocuticle, which has the greatest mass (55%), and the endocuticle, which has the capacity to absorb water.[5,6]

The cortex accounts for most of the hair fiber's mass (75%) and plays a significant role in determining the fiber's intrinsic strength and mechanical resistance. The α-helix proteins in the cortex are held together by chemical bonds such as ionic bonds, hydrogen bonds, Van der Waal bonds, and disulfide bridges. In this region are the melanin granules which provide the color properties of the hair.[7] The cuticular membrane complex (CMC), responsible for cohesion between cortical and medullary cells, is rich in 18-methyl eicosanoic acid (18-MEA), providing hair with hydrophobicity and lubrication with reduced friction between the hair fibers.[8,9] A reduction in this lipid is related to hair fiber degradation and protein loss.

More internally, and not always present, is the medulla, a cellular vacuole located in the central part of the hair fiber. Several studies correlate the presence of the medulla with an increase in capillary diameter. Structurally, medullary cells are cortical cells together with melanosomes.[7,10]

Hair analysis

The hair fiber is produced by the hair follicle and any change in the follicle can have repercussions on its structure and quality.[11] In routine outpatient evaluation, hair shafts can undergo external and internal changes due to various factors (Table 1).

Hair fibers can be assessed by various clinical and laboratory methods. Clinical methods have a diagnostic purpose in the treatment of hair shaft alterations, allowing for outpatient dermatological evaluation. They allow the evaluation of hair shaft complaints due to internal and external factors. They are performed in the routine dermatological examination, which includes anamnesis, physical examination (pull test), dermoscopy, and the rapid protein loss test (also considered a laboratory test).[12]

Laboratory methods can identify damage and the response to cosmetic products in the hair fiber and can be conducted on both strands of hair and standardized strands. Cosmetic industry uses these methods as parameters for product development, as they allow physical and chemical characteristics of the hair shaft to be assessed and external damage caused by external agents to be graded.[13,14] They include various forms of micros-

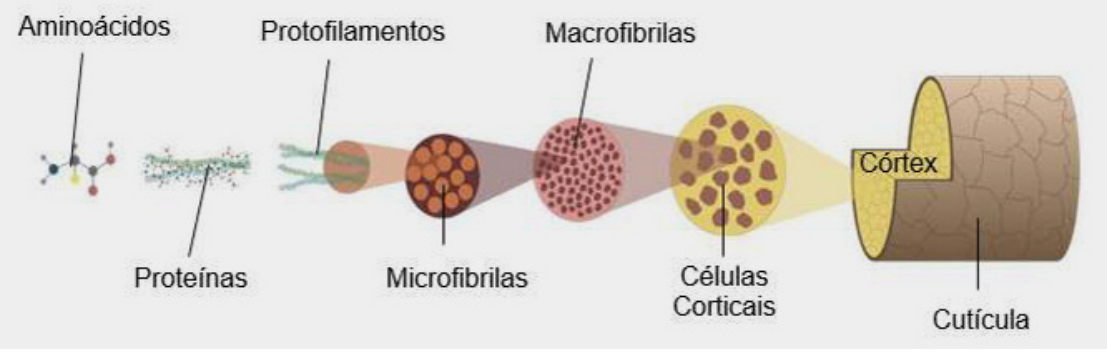

FIGURE 1: Follicle structure and its components

Table 1. External and internal factors inducing stem changes

External factors	Internal factors
• Weathering: ultraviolet radiation, salt and water immersion, exposure to cleaning products, exposure to pollution and smoking. • Thermal damage: hair dryer, hair straightener, curling irons and rotating brushes. • Physical damage: combing, special styling traction, rotating brushes. • Chemical damage: dyes, bleaches, perms, and straighteners.	• Inflammatory diseases of the scalp: psoriasis and seborrheic dermatitis. • Inflammatory diseases of the hair follicle: alopecia areata, lichen planus pilaris, and folliculitis decalvans. • Use of chemotherapy drugs, acitretin, valproate. • Systemic metabolic and deficiency diseases. • Smoking. • Nutritional deficiencies: trace elements, proteins, and nutrients.

copy, combined with optical coherence tomography, which visually assess the structure of the hair shaft. Spectroscopy techniques, assessment of protein loss, and tryptophan quantification evaluate the stem from a structural point of view. Color and gloss assessment, thermogravimetric analysis, measurement of mechanical strength (traction), combability and elasticity assess the physical properties of the stem.[4,14,15]

Outpatient methods

Clinically, the hair shaft can be assessed by exploring the macroscopic properties via clinical examination, from the root to the distal end. The longer the hair, the greater the exposure to external damage. A number of factors are involved in the development of hair shaft alterations. Correct diagnosis can be complex and requires a detailed clinical history, especially focused on routine hygiene care, chemical treatments, use of heat sources for drying, and daily environmental exposures. Epidemiological characteristics, such as age and sex, should be considered in this assessment.

The anamnesis should address the onset, duration, and nature of the complaint; personal and family history, use of inappropriate cosmetics, medications (chemotherapy, retinoids, among others) and protein-restricted diets. During the examination, other hairy areas should be assessed, such as eyebrows and body hair, which can show alterations in systemic diseases and hair shaft abnormalities. Examination of the nails can help diagnose neuroectodermal dystrophies and inflammatory alopecia.[16]

Diagnostic tests

When excessive hair loss is identified by counting the hairs shed daily, the collected hairs can be analyzed under a microscope and classified according to diameter, indicating possible damage to the fiber.[11,17]

The tug test is a simple technique used to assess hair fragility. Some hair strands are held, and a traction force is applied to the end of the hair shaft with the other hand. Breakage of the hair shaft during the test indicates fragile hair and abnormalities in the hair shaft.[16,17]

Growth rates can be measured by scraping a small area of the scalp, which acts as a growth window. Expected growth is around 0.3 cm in a week, or an average of 1.0 cm per month. Growth rates vary between races: African hair has the slowest growth rate (0.9 cm/month), Caucasian hair grows at a rate of around 1.2 cm per month and Asian hair outperforms the other types, with a growth rate of 1.3 cm per month.[18]

The use of dermoscopy on the scalp has been incorporated into daily practice due to its practicality and potential to minimize the need for invasive examinations. It is useful in various diseases, from pediculosis and hair shaft anomalies to differentiating scarring and nonscarring alopecia. It can be performed using a traditional dermatoscope with polarized light, a videodermatoscope with polarized light or in association with computerized hair analysis.[18,19]

The traditional 10x dermatoscope is used in routine dermatology; however, the findings of this modality are limited in the study of the hair shaft. Dermoscopic examination of the hair shaft can be performed with or without gel application at magnifications of up to 300x. Trichoscopy without immersion has proven useful for analyzing distal characteristics such as fractures and other disorders of the hair shaft, such as trichorrhexis nodosa.[18,19]

Alterations to the hair shaft can be evidenced by the trichogram. This technique easily assesses the proportion of vellus and terminal hairs and capillary density, and is useful for monitoring and evaluating patients' therapeutic response.[18,19]

It is crucial to detect the first change in the protein in order to avoid more drastic changes in the hair's properties. Suggesting its protection would also ensure that the hair's physical properties, such as resistance and elasticity, are preserved against daily harmful exposure.[20]

A new methodology available is the rapid protein loss test, which uses a chromogenic reagent to quantify total protein. It is based on a conversion of ions that provide the result based on a colorimetric scale according to the amount of protein extracted from the patient's hair in just 25 minutes.[21,22] This test has been adopted as a valuable technique by dermatologists and

trichologists in the evaluation of the hair shaft, creating new possibilities for the doctor, allowing a solid and complete diagnosis of the hair shaft,[21,22] and directing to more specific and effective treatments.

All these clinical assessments can be complemented by laboratory evaluations, histopathological studies of the hair shafts and scalp biopsies for a general assessment of the patient's hair system.

Laboratory evaluation

Currently, several laboratory techniques can be used to assess the quality and condition of the hair fiber. Microscopy combined with optical coherence tomography allows the structure of the hair shaft to be studied visually. Spectroscopy and protein evaluation methods assess the shaft from a structural point of view. Studies of color, gloss, thermogravimetric analysis and measurement of mechanical strength (tensile strength), combability and elasticity allow a correlation to be established with the physical properties of the stem.[5,14,15]

Routine external damage to the shaft can affect its mechanical and structural properties by weakening the hair fiber.[5] Cumulative exposure to these factors leads to keratin denaturation, degradation of cortex components, rearrangement of disulfide bonds and reduced resistance due to loss of cortical protein, thus resulting in alterations in laboratory tests.[14]

Microscopic and tomography examinations are subjective but have advantages such as the use of hair strands and standardization of tests. Table 2 shows the characteristics and objectives of the microscopic tests available in laboratories to assess hair fibers and related damage.

Structural assessment

The structure of the hair shaft is mainly made up of proteins, providing resistance to the fiber. In the cortex, they make up 80% of the protein mass of the hair shaft. Spectroscopic and protein loss assessment methods allow structural correlation with the hair shaft.[5,15] Currently, several methods have been suggested for quantifying hair protein; however, no method is considered universal. Spectroscopic methods are based on the absorption and emission of electromagnetic radiation on molecules, which occurs due to the movement of electrons between their energy levels.[28] Spectrophotometric methods are described in table 3 and their main objective is to assess hair shaft damage due to chemical treatments and physical wear. The technique is used to investigate the mechanism that promotes a reduction in the tensile strength of human hair after the use of chemical treatments that modify the shape of the strand, such as wavy hair that has undergone treatments known as perming; the chronological alterations of the keratin in the fiber of virgin hair with the processes of aging; the influence of chemical treatments that promote reduction, heating and oxidation in the keratin of the hair; and the structure of the virgin white hair shaft (hair graying) that has been subjected to the permanent straightening process.[5,7,29] It can be applied in hair research when it is necessary to analy-

Table 2. Microscopic and tomography methods used in capillary assessment

Method	Visualization	End
Conventional microscopy	Surface magnification (20 to 70x). Associated with polarized light, it makes it easier to see structural alterations.[6]	Damage to the cuticle of the hair fiber. Allows assessment of fiber thickness and occasional observation of the medulla.[6]
Scanning electron microscopy (SEM)	Surface of the fiber by scanning it at 250 to 5,000x with focused electron beams.[13,23]	Topography and composition of the sample surface. Accumulation of particles in the fiber's outer layers and incorporation of cosmetic actives. Structural and morphological changes to the fiber.[23]
Transmission electron microscopy (TEM)	Transmission of electron beams in ultrafine samples. Interaction of the sample's constituents as it passes through it.[6,24]	Fine structures and morphological changes in hair fibers.[24]
Atomic force microscopy (AFM)	Surface scanning of the sample with atomic resolution.[25]	Fiber tension and particle deposition, structural and morphological changes in the fiber.[11,25]
Optical coherence tomography (OCT)	High resolution of internal structures per section.[8,26,27]	Internal microstructures of the rod and changes in the morphology and structure of the damaged fiber.[26,27]

Table 3. Spectrophotometric methods and their characteristics

Method	Characteristics of the technique	Objectives
Infrared (IR)	Absorption of infrared radiation (700 and 50,000 nm) of the electromagnetic spectrum.[28]	To evaluate physical properties and changes in hair fiber structure and morphology.[9]
Raman	High-resolution photonic technique with direct measurement of energy through the oscillation of photon emission.[28]	Chemical and morphological data of the fiber. To evaluate indirectly the tensile strength of the hair and the loss of protein from the shaft.[7,28,29]
Photoluminescence	Absorption of light by photoexcitation. Electrons in different structural states are excited in different ways.[29]	Photodegradation damage. Degradation of internal hair structures by solar radiation and the effects of photoprotective cosmetics.[30]
Diffuse reflectance	Energy reflectance and absorption and scattering coefficient of the sample.[12]	To evaluate shine and color of the hair fiber, virgin or altered by hair products. [5,15,31]

Table 4: Methods based on the loss of proteins and amino acids, their characteristics and limitations

Method	Characteristics of the technique	Limitations to the results
Lowry [14]	Reaction to reduce a protein previously treated with copper in an alkaline medium. Copper binds to the amino acids released by cavitation, forming a blue solution.	Interference from lipids, surfactants, ammonium sulphate and ethanol. Ammonium thioglycolate and thioglycolic acid, in an alkaline medium, alter the reaction.
Bradford [15]	Bond between high molecular weight protein and Coomassie dye, released by heating.	The quality of the dye can interfere with the reaction: absorptivity and degree of purity of the dye. Not recommended for low molecular weight proteins.
BCA [14]	The amino acids released from the hair are reduced by cavitation with the copper ion, forming a colorimetric reaction.	Reducing agents (residues in the hair) may generate inadequate results.
Quantifying tryptophan [31]	Alkaline digestion with degradation of the protein structure and release of the amino acid tryptophan.	Useful test for assessing wear and tear from ultraviolet radiation, but not very sensitive to other wear and tear.
Protein electrophoresis [33]	Protein fractions are isolated by migration in the gel according to electrical charge and molecular weight.	Despite its low cost, technical difficulties can lead to nonspecific results.

ze physical properties, such as moisturizing action, changes in the structure and morphology of the hair fiber promoted by treatments such as bleaching and hair pigmentation.[14-16] Another application of the technique is the study of the effects of solar radiation on the degradation of internal hair structures or the efficiency of using photoprotective hair cosmetics.[29,30]

Exposure of the hair fiber to physical or chemical aggression makes it susceptible to a large number of structural changes, including its protein composition. With the loss of cortical mass, aesthetic changes occur, such as porosity, frizz, and reduced resistance. Protein loss can be assessed by various quantitative tests of amino acids and proteins extracted from the hair.[15,32]

The success or failure of protein quantification depends on the quality of the analytical process used to characterize the samples. Table 4 shows the main methods for quantifying hair fiber proteins and amino acids (Figure 2).

Table 5: Physical and mechanical property analysis methods for hair fibers

Methods	Characteristics of the technique	Objectives
Thermal analysis	It evaluates the physical properties of the sample in a controlled program of temperature and time under specific conditions. Differentiations can be obtained using thermogravimetry, exploratory calorimetry, or thermomechanics.[34]	To identify the presence and quantify the benefits of thermal hair protectors.[35,36]
X-ray diffraction	It identifies crystalline structures present in the sample and can distinguish between various components.[34]	To identify structural changes occurring in fibers due to wear.[32]
Combability and friction	It assesses fiber resistance to friction.[25]	To define fiber quality and cuticle organization. To evaluate softness, shine, and frizz.[25]
Tensile strength	It quantifies the elastic and plastic properties of the fiber by means of an exerted tensile strength.[36]	To observe the strength of the hair fibers. To indicate the condition of the cuticular and cortical cells.[37,14,15]
Brightness	It observes the direction of the dissipated light.[5,38]	To identify the quality and organization of the cuticular cells.[38]

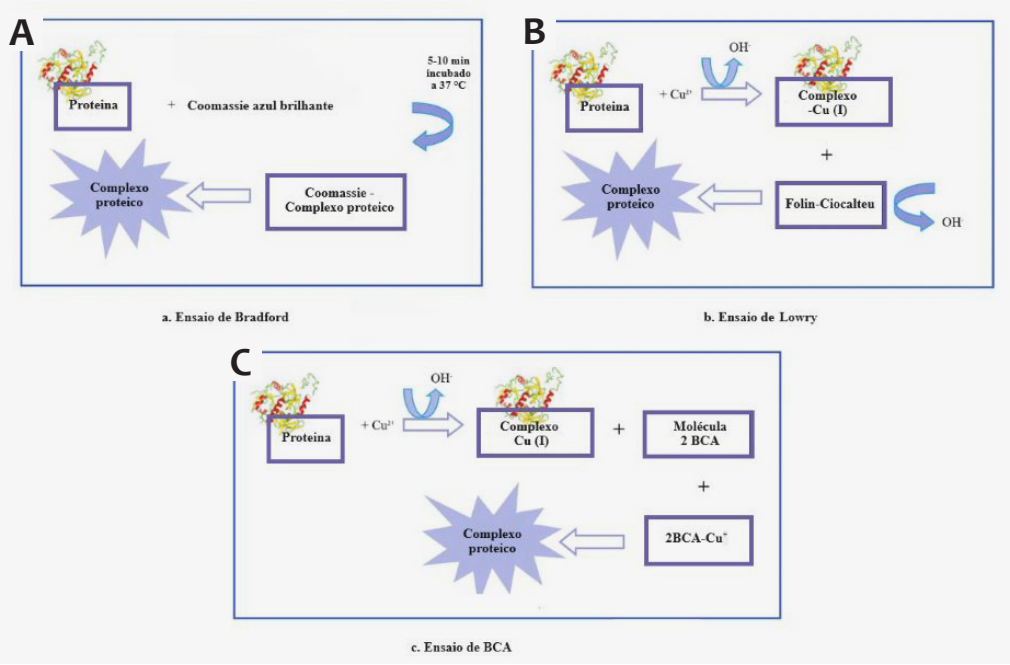

FIGURE 2: Characteristics of protein loss tests.
a) Bradford;
b) Lowry;
c) BCA

Physical and mechanical properties

The mechanical strength of the hair fiber can be assessed using methods based on its elastic and plastic properties, using a tension force. The plasticity of the hair fiber allows it to extend by about 2% of its original length. As the load exerted on the fiber continues, the plastic phase begins, and the hair stretches approximately 25 to 30% of its length before breaking.[34-36] Table 5 summarizes the methods of physical analysis of the hair fiber.

CONCLUSION

This article presents the main hair fiber assessment techniques that the cosmetics industry and research centers use, which are still not very accessible or well known in the dermatological field.

Currently, new technologies have been highlighted in the outpatient dermatology field, complementing the assessment and diagnosis of hair health, allowing for a better understanding of disorders and damage to the hair shaft, leading to more specific and effective treatments. ●

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Mohs surgery for the treatment of eccrine spiroadenoma: a case report

Cirurgia de Mohs para tratamento de espiroadenoma écrino: um relato de caso

Review Article

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ABSTRACT
Eccrine spiradenoma is a rare benign epithelial neoplasm derived from the ductal and secretory portions of the eccrine sweat glands. It is characterized by slow growth and may, in some cases, undergo malignant transformation. This report describes a case involving a male patient with a painful, slow-growing lesion present for 3 years. The nodular, lobulated lesion was located on the left frontal region. Due to the left. On account of location, size, and vascularization of the lesion, as well as the need to preserve the facial musculature and ensure complete tumor removal of the tumor with minimal functional damage, Mohs surgery was chosen as the treatment technique.
Keywords: Mohs surgery; Skin; Sebaceous Glands

RESUMO
O espiroadenoma écrino é uma neoplasia epitelial benigna rara, derivada de porções ductais e secretoras de glândulas sudoríparas écrinas. Caracteriza-se por crescimento lento e pode apresentar transformação maligna. Este relato descreve um paciente do sexo masculino, apresentando lesão nodular dolorosa de crescimento lento há 3 anos, localizada em região frontal à esquerda. Devido à localização, ao tamanho da lesão e à vascularização e para preservar a musculatura da face e realizar remoção completa do tumor com o mínimo de danos funcionais ao paciente, optou-se pela técnica de Mohs.
Palavras-chave: *Cirurgia de Mohs; Pele; Glândulas Sebáceas.*

INTRODUCTION

Eccrine spiradenoma is a rare benign adnexal neoplasm traditionally thought to arise from eccrine glands, although recent studies suggest that it may be of apocrine origin. First described in 1956 by Kersting and Helwig in 1956, their original report included a series of 114 patients. Most cases (97%) present themselves as a single mass, with an equal distribution between men and women.[1] Clinically, it appears as a pink to gray, solitary, small, painful nodule, typically pink to gray in color, and most often located on the upper ventral region of the body.[1] However, recent studies report that eccrine spiradenomas are more likely to occur on the upper limbs.[2,3,4] The present report has described a case presented here describes a solitary lesion in the frontal region, which is a rare location for this tumor. The varied presentations of eccrine spiradenoma make it difficult to classify clearly. Yoshida et al.[4] has proposed a categorization system based on clinical and histological findings. The clinical classification includes solitary or multiple forms, with additional distinctions to describe their appearance and define the distribution pattern (linear, zosteriform, nevoid, or blascoid). Histologically, eccrine spiradenomas are classified as either benign or malignant, with further distinctions based on histological characteristics (common, vascular, or cystic).[5] Due to its many possible presentations, the differential diagnosis can be challenging. Accurate diagnosis is crucial, given the potential for malignant transformation.[6] Immunohistochemistry can be particularly helpful, especially in malignant cases of malignancy.[6] The primary treatment for both benign and malignant eccrine spiradenomas is the surgical excision. Other treatment options include radiotherapy, carbon dioxide laser ablation, or chemotherapy in cases of multiple or malignant lesions.[6] Some authors recommend combining surgical excision (using complex linear closures and random pattern cutaneous flaps for reconstruction) with carbon dioxide laser therapy, resulting in good cosmetic outcomes.[7] Because of the potential for malignant transformation, wide surgical excision at the same surgical time or Mohs micrographic surgery is often considered the best approach, as these methods offer conservative treatment, low recurrence rates, and minimize the risk of malignancy.[6] In the case presented here, the eccrine spiradenoma was successfully treated using the Mohs technique, achieving complete lesion removal with excellent cosmetic results and preservation of frontal muscle function.

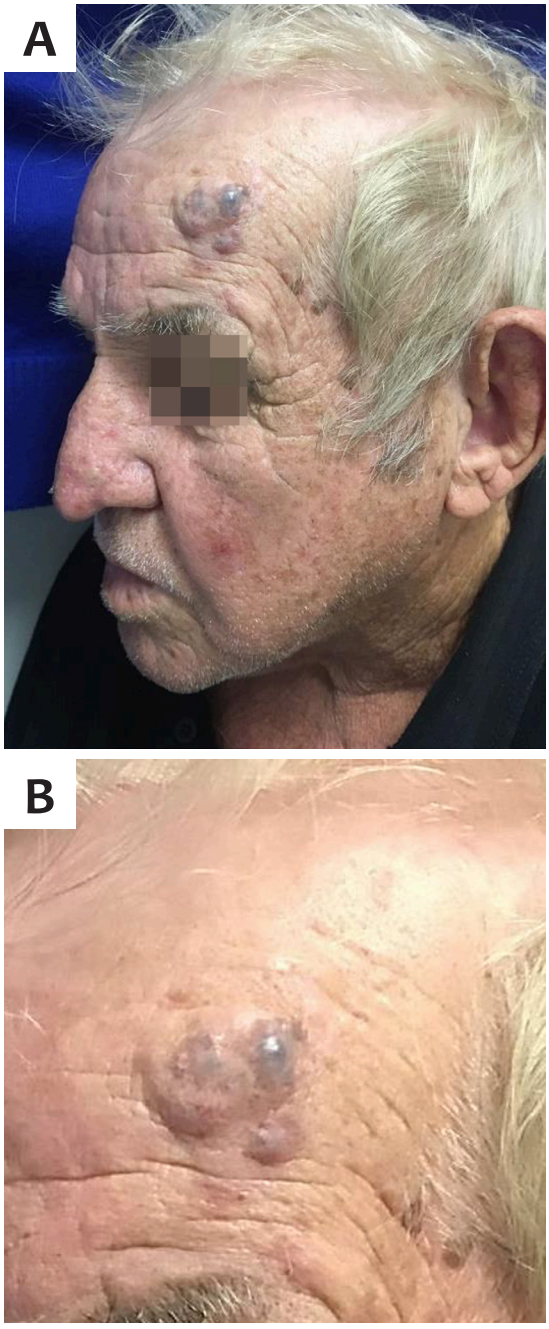

FIGURE 1: A e **B** - Lobulated nodule with areas of pink and blue-greyish coloration, located on the left frontal region. Close-up view of the lesion

CASE REPORT

A 72-year-old male patient was referred to the Dermatology Service due to a painful lesion in the left frontal region that had been slowly growing for approximately three years. Upon examination, a nodular, lobulated lesion was observed, measuring 2.0 × 1.8 cm. The lesion was covered by normal skin, with blue-greyish, painful areas, adhered to deeper tissues, and exhibited limited mobility (Figures 1). The initial differential diagnosis included common tumors of the cutaneous appendages, such as cylindroma, eccrine carcinoma, papillary hidradenoma, and eccrine spiradenoma as well as other possibilities, such as B-cell lymphoma, amelanotic melanoma, and cutaneous metastasis. An ultrasound of the lesion revealed hypoechogenic oval images with lobulated contours, in the frontal region, underlying the skin lesion. The lesion measured 2.2 × 2.0 × 1.0

cm at its largest axis, with flow to the Doppler study, showing blood flow. The imaging also indicated a clear cleavage plane from the adjacent cortical bone and preserved muscle planes. An incisional biopsy was performed, revealing diffuse proliferation of ovoid, monomorphic cells, some with a basaloid appearance, arranged in lobes with hyalinized septations. These findings were consistent with the diagnosis of eccrine spiradenoma (Figure 2A). Due to the size of the lesion, location, and vascularity of the lesion, Mohs micrographic surgery was selected as the best treatment approach. This technique was chosen to preserve the frontalis muscle while ensuring complete tumor removal and maximizing tissue preservation. The lesion was also subjected to histopathologic examination of the lesion and immunohistochemistry (Figure 2B and C). Surgical markings were made (Figure 3) and the procedure was performed in an outpatient setting by a dermatologic surgeon with a pathologist involved throughout the surgery. The lesion was divided into five fragments to assess the lateral margins, as determined by palpation and lesion topography, and by two fragments to assess the deep margins. In the first stage of surgery, all lateral margins were free of neoplasia, but two deep fragments have showed positive muscle invasion by an eccrine spiradenoma. Therefore, the surgical margin was extended deeper, and the entire muscle layer was removed. In the second stage, all specimens from the extended margins were free of neoplasia. The tissue was sent for immunohistochemical analysis, which confirmed ductal differentiation was confirmed with epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA) markers. The immunophenotypic profile in combination with the morphologic findings confirmed the diagnosis of eccrine spiradenoma. The final defect was reconstructed with a rotational flap, with primary closure of the edges of the lesion margins to preserve the position of the ipsilateral eyebrow (Figures 4 and 5).

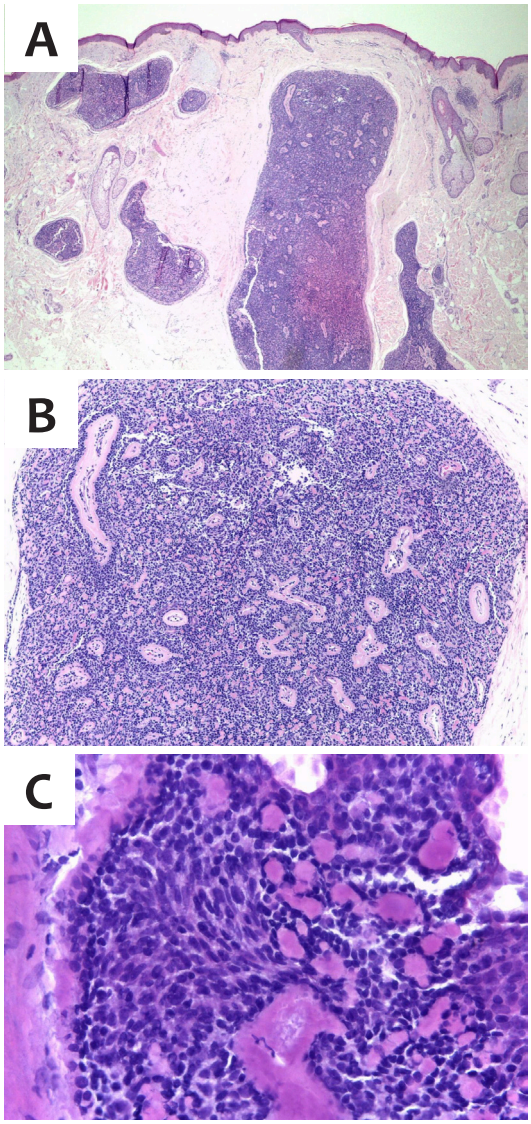

Figure 2: A, B and C - Histologic sections of excised specimens stained with Hematoxylin-Eosin. The tumor involves the dermis, hypodermis, and striated skeletal muscle tissue. It shows basaloid keratinocytes, interspersed lymphocytes, ductal differentiation, and hyalinized basal membrane material, forming a few large nodules in the dermis with a trabecular pattern

DISCUSSION

Eccrine spiradenoma is a rare benign tumor that can occur at any age, although it is most commonly seen more frequently between the second and fourth decades of life, with no gender predominance.[8] Clinically, spiradenomas present as a dermal or subcutaneous papules or nodules that can appear anywhere on the body. Rarely, these lesions can grow to several centimeters in diameter and may be painful. Due to the nonspecific nature of the clinical presentation, biopsy is required for the diagnosis.

Figure 3: Surgical marking for lesion excision

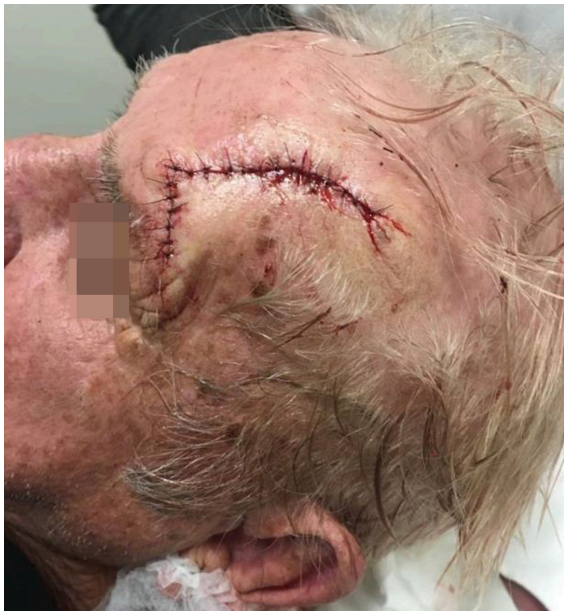

Figure 4: Rotation flap. Immediate post-surgery

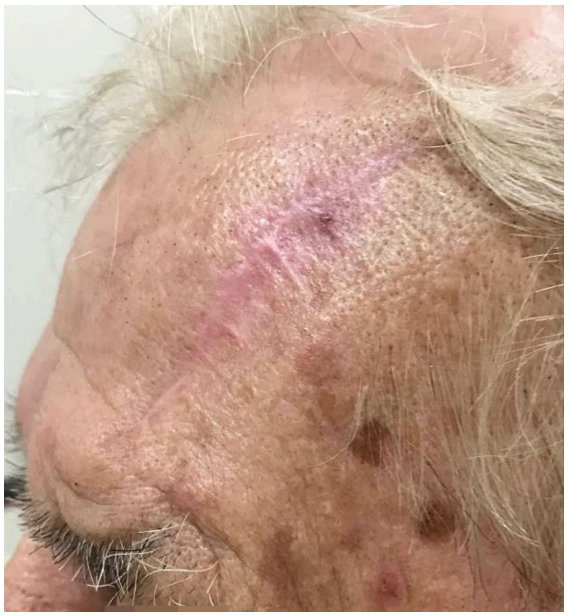

Figure 5: Three months post-operative

However, eccrine spiradenoma should be considered in the setting of a nodular, bluish, and painful lesion. Spiradenomas may present as solitary or multiple lesions, and in some cases may be associated with other tumors such as cylindroma and trichoblastoma. When multiple lesions are present, Brooke- Spiegler syndrome should be considered as a possible diagnosis.[9] Histologically, eccrine spiradenomas are usually found in the subcutaneous fat layer, with well-defined margins and a lobulated appearance. Blood flow is often observed in the peripheral region of the tumor, with or without central blood flow.[3] In this case, the central region.[3] The present work shows a tumor involved the dermis, hypodermis, and striated skeletal muscle tissue, complicating the therapeutic approach challenging. The use of ultrasound as a prognostic tool has been reported in some studies and correlates well with histologic findings. Ultrasound can help assess the extent of the tumor, identify possible recurrence, and determine any association or not with trichoepithelioma or cylindroma.[3,4] Treatment for benign or malignant eccrine spiradenomas typically involves conservative excision or simple enucleation.[9] Other options, particularly for multiple or malignant cases, include a combination of surgical treatments, radiation therapy, carbon dioxide laser ablation, or chemotherapy if multiplicity or malignancy.[6,7]

CONCLUSION

This article presents the clinical case of a 72-year-old male patient with a painful lesion on his forehead that was definitively diagnosed as an eccrine spiradenoma by biopsy incisional biopsy. The Mohs technique was chosen for treatment, and margin expansion was necessary due to the tumor's invasion of the skeletal muscle layer. Complete excision of the lesion was achieved with preservation of frontal muscle function and an excellent cosmetic results. Eccrine spiradenoma has an unclear etiology and presents in different clinical forms, requiring histologic confirmation to determine the most appropriate therapeutic approach, as conservative treatment options are available. Case reports such as this one are essential to guide treatment decisions and shed light on the different therapeutic options for managing this rare condition. ●

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The effectiveness of secretomes delivery using microneedling compared to laser-assisted drug delivery for facial skin rejuvenation: a systematic review

A eficácia da administração de secretomas usando microagulhamento ou laser para o rejuvenescimento da pele facial: uma revisão sistemática

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ABSTRACT

This study compared the effectiveness of secretome delivery using microneedling versus laser-assisted drug delivery for facial skin rejuvenation. The review included seven studies that demonstrated that both approaches were effective in delivering secretomes. However, microneedling had a higher patient satisfaction rate and fewer reported adverse events. We concluded that micro needling may be a more patient-friendly and safer option for facial rejuvenation. Further studies with larger sample sizes and extended follow-up periods are needed to confirm these results.

Keywords: Secretome; Laser Therapy; Systematic Review; Skin.

RESUMO

Este estudo comparou a eficácia da administração de secretomas utilizando a técnica de microagulhamento versus a administração assistida por laser para o rejuvenescimento da pele facial. A revisão incluiu sete estudos que demonstraram que ambas as abordagens são efetivas na entrega de secretomas. No entanto, o microagulhamento apresentou uma taxa de satisfação do paciente mais alta e menos eventos adversos relatados. Conclui-se que o microagulhamento pode ser uma opção mais amigável e segura para o rejuvenescimento facial. Estudos adicionais com amostras maiores e períodos de acompanhamento mais longos são necessários para confirmar esses resultados.

Palavras-chave: *Secretoma; Lasers; Revisão Sistemática; Pele.*

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INTRODUCTION

Skin aging is a natural process caused by a combination of extrinsic and intrinsic factors, leading to wrinkles, loss of elasticity, and other visible changes.[1,2] One strategy to combat aging is the use of stem cells, such as amniotic membrane stem cells-conditioned medium (AMSC-CM), adipose-derived mesenchymal stem cells (ADMSCs), and human umbilical cord-derived mesenchymal stem cells-conditioned medium (hUC-MSCs-CM).[3,4] To reduce wrinkles and other photoaging-related facial deformities, AMSC-CM, ADMSC-CM, and hUC-MSCs--CM can stimulate dermal collagen production, growth factor, chemokines, dermal fibroblast proliferation and migration, and epidermal keratinocyte migration.[5,6,7]

Several treatments, such as microneedling and laser therapy, can promote skin rejuvenation. The fractional CO_2 and erbium lasers are emerging technologies that show potential for improving skin rejuvenation.[7] The microthermal zone (MTZ) of ablation in the skin facilitates penetration of topical big therapeutic molecules from the surface to the layer of interest while shortening the healing time following laser-induced tissue injury.[8,9] This study aims to compare the effectiveness of secretome delivery using microneedling versus laser-assisted drug delivery (LADD) for facial skin rejuvenation.

METHOD

A systematic review through various stages: (Figure 1)

Search strategy

We conducted a comprehensive investigation in 2023 to explore the efficacy of delivering secretome through microneedling or laser-assisted drug delivery (LADD) therapy for skin rejuvenation. The search utilized keywords such as "SECRETOME", "MESENCHYMAL STEM CELL-CONDITIONED MEDIUM", "AMSC-CM", "ADMSC-CM", "hUC-MSCs-CM", combined with "MICRONEEDLING", and "LASER ASSISTED DRUG DELIVERY", including synonyms. Electronic databases, including Pubmed, Cochrane Central Database, ClinicalTrials.gov, and Mendeley, were consulted from their inception up until June 2023. We assessed the retrieved records systematically using predetermined inclusion and exclusion criteria. Initially, four authors (LPM, MT, RJ, and EK) independently scanned all abstracts to identify relevant studies. In case of discrepancies, the remaining two authors (YK and MT) were involved in the final judgment and eligibility assessment by reviewing the full-text articles. Figure 1 provides a flowchart outlining the literature search strategy, following the Preferred Reporting Items for Systematic Reviews guidelines.

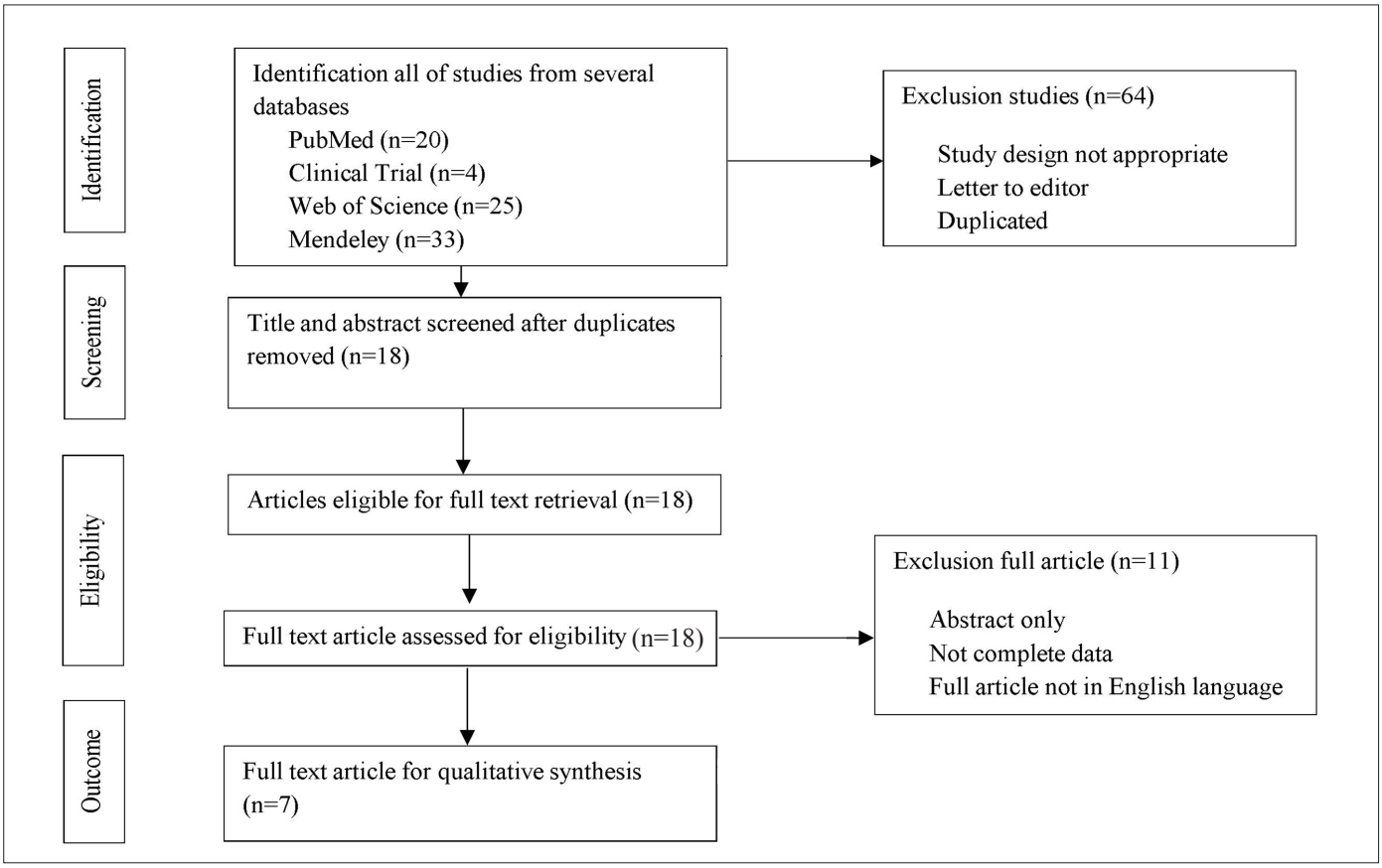

FIGURE 1: The flow diagram of meta-analysis

Selection Criteria

This study included all publications in 2023 that investigated the effectiveness of secretome delivery using microneedling or LADD therapy for skin rejuvenation. The selected publications consisted of original studies, excluding review articles, meta-analyses, epidemiological studies, abstracts only, non-English manuscripts, and editorials.

Data Extraction

Two independent authors (MT and LPM) performed the data extraction and quality assessment using a standardized extraction method in an Excel application.

Bias Analysis

We used the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) analysis to assess bias in several journals. Table 1 shows that all journals explicitly defined their population, intervention, comparison, and outcome criteria. Although original studies were the most prevalent, some journals exhibited bias in different aspects. One journal displayed biases in participant data, another had bias related to the intervention, one journal had biases due to missing data, and another had biases associated with reporting. Overall, all the included studies received low scores, indicating a risk of bias.

RESULTS

Study selection

Figure 1 provides an overview of the process used to select the studies. Initially, the search identified a total of 82 articles, and after removing duplicates, 18 potentially relevant articles remained. Upon reviewing the titles and abstracts, 64 articles were excluded, resulting in seven studies that met the inclusion criteria. There were no disagreements during the study selection process.

Table 1 presents the characteristics of the seven studies that met the inclusion criteria. These studies encompassed various types, including prospective studies, randomized controlled spit-face studies, and analytical experimental controlled clinical trials. Most cases and studies were conducted in Indonesia, with one study from China. Among the 268 patients included in the studies, 240 were women, while the study by Liang ***et al.*** did not specify the gender of the 28 participants. The studies used microneedling, fractional CO_2 laser, and fractional erbium:YAG laser. The secretomes employed in the studies included AMSC--CM, ADMSCs, and hUC-MSCs-CM.

The effectiveness of included studies

Table 3 shows that microneedling and LADD proved to be effective therapies for delivering secretomes. Microneedling and LADD significantly reduced wrinkles and pore size, improved pigmentation and UV spots, and enhanced moisture and elasticity starting at six weeks.

Adverse events of included studies

Table 2 indicates that both groups experienced adverse events, including erythema, pain, burning sensation, itch, and urticaria. Also, the LADD group reported acne eruption. Microneedling exhibited a higher patient satisfaction rate and lower reported adverse events than the LADD group.

Table 1. ROBINS-I Analysis

Study	Confounding Bias	Participants Bias	Intervention Bias	Missing Data Bias	Outcome Bias	Reporting Bias	Overall Risk Bias
Sari *et al.*, 2021[10]	No	No	No	NI	No	No	Low
Yusharyahya *et al.*, 2023[11]	No	No	Yes	NI	No	Yes	Low
Prakoeswa *et al.*, 2021[12]	No	No	No	NI	No	No	Low
Praharsini *et al.*, 2020[13]	No	Yes	No	NI	No	No	Low
Widianingsih *et al.*, 2019[14]	No	No	No	NI	No	No	Low
Liang *et al.*, 2022[15]	No	No	No	Yes	No	No	Low
Prakoeswa *et al.*, 2018[3]	No	No	No	NI	No	No	Low

Note: Bias analysis showed that all journals have clear population, intervention, comparison, and outcome. These journals were mostly the original study for this research. There were 1 journal with participants' data bias, 1 journal with intervention bias, 1 journal with missing data bias, and 1 journal with reporting bias. All of the included studies have a low score according with overall risk bias.

Table 2. Research characteristics involved in the study and side effects of each study

N.	Study (author, year)	Study Design	Country	Gender (M/F)	Type of Stem Cell	Intervention	Study Duration	Number of Session	Session Interval	2 weeks					
										Erythema	Pain	Burning Sensation	Itch	Urticaria	Acne Eruption
1	Sari *et al.*, 2021[10]	Prospective study	Indonesia	F (60)	AM-SC-CM	Fractional CO_2 and MN	12 weeks	3 sessions	FL: 1 month MN: 2 weeks	N/A	N/A	N/A	N/A	N/A	N/A
2	Yusharyahya *et al.*, 2023[11]	Randomized split-face clinical trial	Indonesia	F (30)	ADMSCs	Fractional CO_2 and MN	6 weeks	3 *sessions*	2 weeks	MN: 0 (0.0%); FL: 2 (6.7%)	MN: 15 (50.0%); FL: 30 (100.0%)	MN: 4 (13.3%); FL: 22 (73.3%)	MN: 1 (3.3%); FL: 2 (6.7%)	N/A	N/A
3	Prakoeswa *et al.*, 2021[12]	One group pre and post-test design model	*Indonesia*	F (60)	AM-SC-CM	*Erbium:YAG and MN*	*8 weeks*	3 *sessions*	4 weeks	N/A	N/A	N/A	N/A	N/A	N/A
4	Praharsini *et al.*, 2020[13]	Controlled split-face	*Indonesia*	F (33)	*AM-SC-CM*	*Erbium:YAG Fractional*	*8 weeks*	3 *sessions*	4 weeks	N/A	N/A	N/A	N/A	1	N/A
5	Widianingsih *et al.*, 2019[14]	Randomized, controlled split-face study	*Indonesia*	F (9)	*AM-SC-CM*	*Erbium:YAG Fractional*	*24 weeks*	3 *sessions*	4 weeks	9 (100%)	7 (77,7%)	N/A	N/A	N/A	2 (22%)
6	Liang *et al.*, 2022[15]	Controlled and prospective study	*China*	PEOPLE (28)	*hUC-MSCs-CM*	*MN*	*10 weeks*	5 *sessions*	2 weeks	1	N/A	N/A	N/A	N/A	N/A
7	Prakoeswa *et al.*, 2018[3]	Analytical experimental controlled clinical trial	*Indonesia*	F (48)	*AM-SC-CM*	*MN*	*8 weeks*	3 *sessions*	2 weeks	1	N/A	N/A	N/A	1	N/A

**N/A: Not available*

Table 3: Results of research interventions

N.	Study	Type of Stem Cell	Intervention	Outcome											
				Wrinkle		Pore Size		Pigmentation		UV Spot		Moisture		Elasticity	
				MN	FL	MN	FL	MN	FL	MN	FL	MN	FL	MN	FL
1	Sari *et al.*, 2021[10]	AM-SC-CM	Fractional CO2 and MN	11.90± 7.345 vs 0.50 (-11-17)	6.73± 2.586 vs. 1.00 (-4-19)	51.20 ±6.723 vs. -2.00 (-9-8)	49.60 ±4.924 vs. 3.50 (-1-10)	N/A	N/A	14.87 ±8.569 vs. 0.00 (-17-9)	7.77± 3.588 vs. 0.00 (-10-8)	N/A	N/A	N/A	N/A
2	Yusharyahya *et al.*, 2023[11]	ADM-SCs	Fractional CO2 and MN	3.50 (9.25) vs. −2.50 (7.00)	2.5 (8.00) vs. −1.00 (9.00)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3	Prakoeswa *et al.*, 2021[12]	AM-SC-CM	Erbium:YAG and MN	Janus 1 vs. 2: p value: 0,216; Janus 1 vs. 3: p value: 0,429; Janus 2 vs. 3: p value: 0,846	Janus 1 vs. 2: p value: 0,043; value: 0,043; Janus 2 vs. 3: p value: 0,000	Janus 1 vs. 2: p value: 0,084; Janus 1 vs. 3: p value: 0,032; Janus 2 vs. 3: p value: 0,029	Janus 1 vs. 2: p value: 0,023; Janus 1 vs. 3: p value: 0,023;	N/A	N/A	Janus 1 vs. 2: p value: 0,38; Janus 1 vs. 3: p value: 0,258; Janus 2 vs. 3: p value: 0,258	Janus 1 vs. 2: p value: 0,04; Janus 1 vs. 3: p value: 0,00; Janus 2 vs. 3: p value: 0,00	N/A	N/A	N/A	N/A
4	Praharsini *et al.*, 202013	AM-SC-CM	Erbium:YAG Fractional	N/A	4.28 ± 0.38 vs. 4.09 ± 0.20	N/A	6.52 ± 0.57 vs. 5.79 ± 0.7	N/A	4.35 ± 1.41 vs. 3.09 ± 0.68	N/A	N/A	N/A	42.2 ± 7.64 vs. 59.1 ± 7.94	N/A	48.2 ±14.1 vs. 61.7 ± 13.1
5	Widianingsih *et al.*, 2019[14]	AM-SC-CM	Erbium:YAG Fractional	N/A	19.7778 ±3.89801 vs. 18.6667 ±4.63681	N/A	48.3333 ±4.21307 vs. 47.1111 ±3.68932	N/A	N/A	N/A	13.1111 ±6.99007 vs. 11.4444 ±4.06544	N/A	N/A	N/A	N/A
6	Liang *et al.*, 2022[15]	hUC-MSCs-CM	MN	17.21 (13.24) vs. 18.18 (13.38)	N/A	23.55 (10.52) vs. 14.05 (6.11)	N/A	23.55 (10.52) vs. 24.40 (10.77)	N/A	24.39 (7.11) vs. 14.47 (5.38)	N/A	2.18 (5.80) vs. 2.07 (6.78)	N/A	0.56 (0.07) vs. 0.57 (0.06)	N/A
7	Prakoeswa *et al.*, 2018[3]	AM-SC-CM	MN	13.92 ± 6.639 vs. 12.13 ± 7.011	N/A	53.17 ± 4.565 vs. 49.63 ± 11.193	N/A	N/A	N/A	17.17 ± 8.646 vs. 14.54 ± 8.748	N/A	N/A	N/A	N/A	N/A

*N/A: Not available

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Table 4: The comparison of microneedling with laser therapy

Comparison	Microneedling	LADD
Type of treatment	Non-laser-based treatment	Laser-based treatment
Technique	Uses a device with tiny needles to create microinjury for providing skin access to topical drugs	Uses a laser to create microthermal zone for providing skin access to topical drugs
Targeted	Wrinkle, fine lines, acne scars, overall skin rejuvenation	Wrinkle, fine lines, age spots, acne scars
Recovery time	Minimal downtime, some redness and mild swelling	Several days to a week for redness and peeling
Pain/discomfort	May cause mild to moderate discomfort during the treatment	May cause discomfort during and after the treatment
Effectiveness	Effective, but may require several treatments for best results	Highly effective, noticeable, results in a few weeks
Cost	Less expensive to laser therapy	Expensive

The comparison of microneedling and laser therapy

Table 4 reveals that LADD was slightly more effective than microneedling in facial skin rejuvenation, although the difference was not statistically significant. Microneedling demonstrated fewer adverse events and lower costs compared to LADD.

DISCUSSION

Microneedling and LADD procedures have been used in cosmetic dermatology for several goals, including skin aging therapy. Both methods successfully construct vertical microtunnels into the dermis, allowing transdermal topical drug delivery.[6-8]

LADD is widely known for its capacity to increase collagen formation and remodeling, allowing photoaged skin's aberrant collagen fibers to rearrange as needed while microneedle creates microinjury and generates a regulated skin injury with little epidermal damage, which stimulates the dermal wound healing cascade (inflammation, proliferation, and remodeling).[1,2,6]

Mild erythema, localized edema, and skin peeling are the most frequent and anticipated adverse events of microneedling and typically resolve within 48 to 72 hours.[6] Compared to microneedling, LADD had more unfavorable effects, such as longer erythema, discomfort, burning sensation, and itch. In light of these findings, dermatologists can select between Microneedling and LADD to distribute secretome, given that LADD may not be available in every clinic due to high costs, while microneedling may be available in all settings. Microneedling is a beneficial option over more invasive procedures such as laser skin resurfacing and deep chemical peeling due to its quick post--treatment recovery, low adverse events profile, and remarkable clinical results.[2,5-7] To improve the therapeutic effect further, the AMSC-CM, ADMSCs, and hUC-MSCs- CM are delivered through laser channels. These cells exert their anti-wrinkle effects by upregulating procollagen type I production and inhibiting matrix metalloproteinase 1 (MMP- 1) secretion, which is responsible for the degradation of collagen fibers. The current study breaks down the skin barrier.[4,5]

CONCLUSION

Microneedling and laser-assisted drug delivery are effective methods for delivering secretomes for skin rejuvenation. However, microneedling may be a more patient-friendly and safer option. Further studies with larger sample sizes and longer follow-up periods are needed to confirm these findings. ●

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Nanotechnology-based cosmetics: regulation, claims, and cosmetovigilance

Cosméticos baseados em nanotecnologia: regulamentação, alegações e cosmetovigilância

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ABSTRACT

The rapid expansion of the cosmetics industry has been accompanied by an increasing demand for innovative and customized products based on scientific base. One of the innovative products is a nanotechnology-based product. This article discusses any potential risks associated with nanotechnology-based cosmetics use, how the government should regulate the product to protect the public and promote public understanding. The government should create effective regulations, but these regulations must not be detrimental to manufacturers. The government has an essential role in establishing effective regulations for both consumers and producers. In addition, the government should encourage manufacturers to provide rational claims and effective advertising.

Keywords: Cosmetics; Nanotechnology; Safety; Pharmacovigilance.

RESUMO

A rápida expansão da indústria cosmética foi acompanhada por uma crescente demanda por produtos inovadores e customizados. Um dos produtos inovadores é um produto baseado em nanotecnologia. Este artigo discute os riscos potenciais associados ao uso de cosméticos baseados em nanotecnologia e como o governo deve regulamentar o produto e promover a compreensão do público. O governo deve criar regulamentações eficazes, mas esses regulamentações não devem ser prejudiciais aos fabricantes. O governo tem um papel fundamental em estabelecer regulamentações eficazes, tanto para os consumidores quanto para os produtores. Além disso, o governo deve incentivar o fabricante a fornecer alegações racionais e publicidade eficaz.

Palavras-chave: *Indústria cosmética; Nanotecnologia; Segurança; Farmacovigilância.*

Review Article

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INTRODUCTION

Cosmetics encompass a vast array of products that are primarily intended for external use and are intended to cleanse, perfume, alter the appearance of, neutralize aromas emanating from, or more generally maintain the health of the body parts to which they are applied. As a result of globalization, the function of these products is swiftly transforming, and their use is increasingly regarded as essential to personal health. The rapid expansion of the cosmetics industry has been marked by a growing demand for innovative and customized products based on ever-increasing scientific knowledge. One of the innovative products is based on nanotechnology.[1]

Nanotechnology is a new field that has been intensively researched over the past several decades. According to an inventory compiled by an initiative on emerging nanotechnologies, the global market contains more than 1,800 nanotechnology-based consumer products manufactured by over 620 companies in 32 countries.[2] Nanotechnology is the study of nanostructures, which, by definition, are any material that is at least 100 nanometres in size or smaller. The optical, thermal, electrical, and magnetic properties of nanostructures are distinctive. In cosmetics, numerous nano-delivery systems, such as liposomes, nano-emulsions and nanocrystals, lipid nanoparticles (NPs), polymeric NPs, and microparticles, are utilized. The primary benefits of using nanocomponents in cosmetics are: improving the stability of some unstable cosmetic ingredients in formulations[1]; enhancing the permeability of some active ingredients[2]; enhancing the efficacy and tolerance of UV absorbers[3]; and making products more aesthetically pleasing[4], such as converting the active minerals in mineral sunscreens into smaller particles so they do not leave visible white patches on the face.[3] However, the use of very small particles in consumer products has raised safety and environmental concerns.[4] NP skin penetration and toxicological effects are unknown, but a variety of local, chronic, metabolic, and photoinduced toxicities are possible.[5]

Another concern is the public's comprehension of how a producer's claim can be affected by label and commercial branding. Government should also provide well-regulated rules for labelling and claims that give marketers opportunities to advertise and at the same time educate the public about the risks and benefits of using cosmetics containing nanotechnology. In addition, the government should educate the public more about nanotechnology in cosmetics that they may use on a daily basis.

Prior to being registered or marketed, cosmetics did not require any clinical tests to determine their safety for human use. The majority of novel cosmetics, including those containing active ingredients and nanotechnology, are created using only animal testing. Therefore, it is vitally essential for the government to closely monitor any reports of cosmetic use-related adverse effects. A competent cosmetovigilance system can encompass this monitoring.

Some research has been held to discuss the assessment and mitigation of risk related to nanotechnology and cosmetic, such as that done by Lohani et al., Nohynek et al., Ferraris et al., Singh & Nanda, and Gupta et al.[6–9] However, they did not mention that public awareness itself plays a crucial role in identifying risks and the need for cosmetovigilance to monitor the cosmetics' long-term safety. This article discusses any potential risks associated with the use of nanotechnology-based cosmetics, how the government should regulate the product to safeguard the public, and how the government should increase public understanding and awareness of nanotechnology-based cosmetics on the market. As well as pharmacovigilance, the government should collect and manage all reports related to cosmetic use in a coordinated system.

The "nano" term

Because the definition of what constitutes a nanomaterial is presently evolving, it is difficult to determine how many nanomaterials are used in cosmetic products. The use of the prefix "nano" in cosmetic advertising and labelling may differ from how regulatory authorities use the term.[10] According to the Indonesian Food and Drug Agency (Indonesian FDA) statute, nanomaterials are materials that are insoluble or bio-persistent and are intentionally made with one or more external dimensions, or internal structures, with a scale of 1 to 100 nm, or with a scale of more than 100 nm but has very different characteristics from the starting material.[11]

The European Union (EU) regulation define the same scope. According to EC Regulation 1223/2009, nanomaterial is a material that is insoluble or bio-persistent and intentionally manufactured with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm.[12,13] By that description of nanomaterial, the Cosmetics Regulation in EU primarily provides guidelines for the incorporation of compounds, such as nanomaterials that are deliberately manufactured and insoluble/partially soluble or bio-persistent (e.g., metals, metal oxides, etc.). Conversely, nanoscale materials that are soluble, degradable, and/or non-persistent in biological systems (e.g., liposomes, emulsions, plant-derived vesicles, etc.) are not nanomaterials and, as such, are not governed by this regulation.[13,14]

In the other hand, the FDA does not presently have a definition of a nanomaterial, but in June 2014 it issued final guidance to help provide regulatory clarity in FDA's regulation of nanotechnology-containing products.[10] The use of nanomaterials in cosmetics is governed by the Indonesian FDA statute number 21/2022 regarding cosmetic notification. It is stated that cosmetics containing nanomaterials are classified as having an uncertain safety profile, necessitating additional data and a review of their safety.

Marketed products

Almost every category of personal care products on the market contains engineered NPs, from sunscreens and anti-aging creams to toothpastes.[8] An environmental working group issued a report in May 2006: "Nanomaterials, sunscreens and cosmetics:

small ingredients – big risks." The report included deodorants, soaps, toothpastes, shampoos, hair conditioners, sunscreens, anti-wrinkle creams, moisturizers, foundations, face powders, lipstick, blush, eye shadow, nail polish, fragrances, and aftershave lotions. Involved materials include various metal oxides and various lipid formulations with nanoscale particles.[15]

In 2006, Estée Lauder introduced a variety of NP-containing products to the nano-market. According to Singh & Nanda,[8] formulations containing NPs allow products, such as anti-wrinkle creams, to penetrate the epidermis more deeply. The largest cosmetics company in the world, L'Oréal, has patented the use of numerous nanosome particulates as nutrient delivery systems. They created RevitaLift Anti-Wrinkle Cream and RevitaLift Double Lifting, both of which contain nanosomes of Pro-Retinol-A.[6] Nano Emulsion Multi-Peptide Moisturizer is manufactured by Hanacure and contains a high concentration of peptides.[16] Tiande has also marketed the microcapsule collagen-based Nano Corrector lifting.[17] Lancome introduced Soleil Instant Cooling Sun Spritz SPF 15, containing vitamin nanocapsules, and Primordiale Optimum Lip, containing vitamin E nanocapsules.[6]

Christian Dior of France, Procter & Gamble, Shiseido, and Estée Lauder are also incorporating NPs into their cosmetics. The other major leaders in this field are Colorescience, Revlon, Pureology, La Prairie, Neutrogena, Johnson & Johnson, Caudalie, Chanel, Beyond Skin Science LLC, SkinCeuticals, The Body Shop, Dr Brandt, Prestige, Sircuit, Dermazone Solutions, Crown Laboratories, Birch Trees, Nucelle, Skin Ceuticals, Rosacea Care, Image skincare, Almay, Barneys New York, Bellapelle Skin Studio, AmerElite Solutions, AmorePacific, Cell Rx, and Avon. Moreover, many boutique lines sell nanotechnology-based cosmetics.[8]

Current regulation

The majority of manufacturers comply with EU legislation, commercializing nanomaterials that are already authorized and for which Scientific Committee on Consumer Safety has conducted a comprehensive risk assessment. Several industries have recently shifted their focus towards nano-spectrum materials that are soluble, biodegradable, and/or non-persistent in biological systems in order to avoid all regulatory concerns. Due to their origin, these substances (such as nanoliposomes) are not considered nanomaterials.[13,14]

Cosmetics in the United States do not require premarket approval. However, manufacturers must ensure that their products are not mislabeled or tampered with (FDA, 2014c). In June 2014, the FDA published new guidance titled "Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology".[18] It applies to all pharmaceuticals, medical devices, culinary products, and cosmetics and provides a broad definition of 'engineered nanomaterials' between 1 and 100 nm in size. In addition, it suggests taking into account whether a material or final product exhibits size-related properties, even if its dimensions lie outside the nanoscale range (up to 1 μm). Similar to European regulations, the terms "engineered nanomaterials" and "intentionally manufactured material" have been implemented. They refer to objects that have been manipulated intentionally using nanotechnology, excluding naturally occurring nanostructures.[18] The aforementioned document is supplemented by the FDA's guidance on the safety of nanomaterials in cosmetic products",[19] which cites a number of other documents, such as the International Cooperation on Cosmetic Regulation (ICCP) report.[20] The ICCP report provides a summary of the analytical methodologies used to evaluate nanomaterials. Since there is no requirement for FDA approval, all liability for cosmetics rests with the manufacturer.[21]

Risk to consider

NPs are able to cross membranes and access cells, tissues, and organs that are inaccessible to larger particles because of their small size and structure. They can enter cells, causing additional injury or cell death.[22,23] Indonesian-FDA statute number 17/2022 establishes the item and concentration limits for nanomaterial use in cosmetics. All possibilities of these nanomaterials entering the nasal cavity are ruled out.[11] NPs typically enter the body via three distinct routes: inhalation, ingestion, and dermal absorption. Inhalation is the most widely recognized route of exposure to airborne NPs. Consumers may inhale nanomaterials when using products containing them. For instance, nanoscale titanium dioxide (TiO2) sunscreen sprays may cause the inhalation of nanomaterials, which may travel through the nasal nerves to the cerebrum (brain) and penetrate the blood and various organs, causing serious side effects.[24,25] Depending on their aerodynamic dimensions, inhaled nanomaterials can deposit anywhere along the respiratory tract, not just in the alveoli. Due to their minute size, only a fraction of nanometric particles can reach extrapulmonary organs. This entails migration of some solid particles, translocation to the blood and lymphatic systems through the pulmonary epithelial layers, and translocation to the central nervous system, through the nerve endings of the olfactory nerves, along the neuronal axons.[25]

However, there are additional toxicology risks, such as a mild risk of skin surface effect for any excipient that can damage skin layers and the possibility of the substance entering the bloodstream via transdermal activity, particularly with regard to cosmeceuticals, which refer to preparations that contain therapeutically active ingredients that have specific remedial effects upon topical application, in contrast to conventional cosmetics.[9,26] The term "cosmeceutical" derives from the combination of cosmetics and pharmaceutical information.[27] When cosmeceuticals are combined with nanotechnology, they become nano-cosmeceuticals, which are cosmetic formulations incorporating nano-drug delivery systems to transport cosmetic active molecules to the appropriate skin tissues, which could induce more undesirable side effect, since some penetration enhancers or carrier systems have been demonstrated to facilitate epidermal absorption of an active constituent to enter the bloodstream,[28]

as shown in a study conducted by Cevc et al. demonstrating the ability of transfersome vesicles to disrupt and destabilize stratum corneum, then confirmed the presence of intact vesicles in the bloodstream.[29] Several studies executed by other researchers on various types of ultra-deformable vesicles have yielded comparable results, including Niu et al. and Manconi et al.[30,31] Therefore, one must be concerned about the prospect of a substance that enters the bloodstream causing an undesirable systemic effect.

Concerns have been raised regarding the potential dangers associated with the skin penetration of a number of cosmetic products containing chemical active ingredients or bioactive NPs (known as cosmeceuticals) .[6] Active Compounds such as alpha hydroxy acid (AHA), an exfoliant that can remove the top layer of skin to cure scars, wrinkles, acne, and to lighten the skin. As eliminating skin could be viewed as affecting body structure, AHA could be considered a drug by the FDA, despite being advertised in cosmetics. Therefore, AHA is classified as a cosmeceutical because it possesses both cosmetic and pharmaceutical properties.[32] Tranexamic acid,[33-36] retinoids,[37] hydroxycinnamic acid,[38] and some bioactive ingredients such as phlorotannin[39] have been also formulated and marketed as cosmetic products. Other compounds that function as moisturizers, antioxidants, anti-wrinkles, depigmenting agents, anti-cellulite agents, and sunscreens, are frequently used to formulate into some carrier system and become nano-cosmeceuticals.[37] However, many of these chemical additives are toxic to the human body, posing health risks ranging from moderate hypersensitivity to life-threatening anaphylaxis or fatal intoxication.[40] Therefore, any cosmetic containing an active ingredient, particularly one whose safety is unclear, should be given careful consideration.

Registration

Some points need to be considered in product registration or notification, such as: what is the exposure, is it assimilated, and if so, how much reaches the viable cells, and is it intrinsically toxic? The following are examples of more specific concerns regarding the safety of nanotechnology or NPs in cosmetic products:

Do cosmetic formulations containing nano-sized components (vesicles or droplets) entail additional risks compared to conventional cosmetics?

Does the increased skin penetration of nano-sized cosmetic formulations increase the risk of skin sensitization or systemic exposure?

Are insoluble NPs in sunscreens intrinsically more dangerous than microparticles or bulk material?

Do topically administered insoluble NPs remain on the skin surface or are they capable of penetrating the skin barrier of normal or compromised skin to reach systemic compartments of the organism?[5]

Nanomaterial penetration is an issue of concern in scientific discourse for at least two primary reasons: the toxicological consequences associated with nanotechnology and the need to reveal the function of nanomaterials as carriers that improve the bioactive agent's penetration.[1] Numerous beauty products claim to be based on sophisticated scientific research, giving consumers the impression that they are as effective and thoroughly tested as pharmaceuticals. In contrast, the cosmetics industry does not want its products to be regulated similarly to pharmaceuticals, as this would necessitate extensive, time-consuming, and expensive clinical trials to determine efficacy. It is therefore the responsibility of regulatory agencies to determine whether a product, despite its claims, is a cosmetic or should be classified as a drug due to its therapeutic effect.[41]

Regarding any risk calculated, several tests and documents must be completed by applicant during registration, such as: physicochemical laboratory tests, since properties of a product affect the body cumulatively, and safety in vivo or in vitro tests.

Claim and advertising

The informational value of a cosmetic advertising claim is the most significant factor in determining whether consumers try the advertised product.[42] The Indonesian-FDA regulation governing cosmetic labeling and claims is Indonesian-FDA statute number 3/2022, which established the prohibited and permitted claims for cosmetics and mentioned any permissible details and prohibited cosmetic claims. In fact, it is more of a broad guideline that does not specify in detail the permissible claims for each product category. In essence, it is up to the producer to construct a persuasive line to convince consumers to use their product. In Indonesia, producers are not required to obtain approval for labeling. They just release it to the market, and the Indonesian FDA conducts a post-market surveillance. The government, through the Indonesian FDA, perpetually educates cosmetic manufacturers on how to advertise and market their products in compliance with the law.

With the accelerated development of nanotechnology and pharmaceutical ingredients in cosmetics, the industry is becoming increasingly competitive. Because cosmeceuticals claim to contain properties of both cosmetics and pharmaceuticals, they may constitute a "grey area" because they cannot be classified as either cosmetics or pharmaceuticals.[32] As a result, consumers may be required to ingest these products with little guidance and a heightened level of caution.[42] In the other hand, consumers cannot presume the veracity of cosmeceutical claims or the efficacy of these products.[27] Furthermore, Indonesian FDA should renew their regulation on labeling and claim that put a special part of cosmetic with nanotechnology more especially on cosmeceutical.

Advertising's purpose is to induce immediate action, to create liking and preference for a product, to generate product awareness,[43] and to educate the customers about the functionality of the product. It brings the existence of certain products to the attention of the intended consumers and informs the consumer and influences their purchasing behavior in various ways.[44] In other words, good advertising can increase public aware-

ness of nanotechnology-based cosmetics, allowing consumers to comprehend the risks and benefits of using these products. Additionally, they can safeguard themselves against the use of high-risk products. Government should encourage producers to create enlightening advertising in order to foster a positive advertising environment. As mentioned by Protopapa & Plangger, educating marketing practitioners is a crucial component of this transition toward more diverse and inclusive marketing.[43]

These days, advertising communication activities are compelled to use multiple media, traditional and new media. New media is a novel form of communication founded on digital technology and network technology, with smart terminals as the target of communication. Diversified and personalized interaction forms create a rich brand experience, allowing consumers to receive brand-delivered information more directly and become secondary communicators more independently, thereby creating a virtuous circle of joint image communication.[45] Therefore, government should exert greater effort to regulate advertising in all media.

Cosmetovigilance

With high development of cosmetics with nanotechnology, negative effects of cosmetics continue to exist in the consumer population.[40] In occupational hygiene, one must bear in mind that the direct human health risk posed by a nanomaterial depends on exposure probability and, if applicable, exposure concentration and duration. Second, it depends on whether these materials, once inside the body, manifest specific nanostructure-related behaviour.[25] Similar to other maladies, cosmetic-related disorders also result in pharmacoeconomic loss.[46]

The concept of pharmacovigilance is relatively new and distinct from industry surveillance, whose primary purpose is to use safety information for commercial gain. Cosmetovigilance is the public health surveillance of cosmetic products with the goal of protecting public health. For the purposes of cosmetovigilance, causality is defined as the examination of the relationship between a cause (cosmetic product) and an effect (manifestation). There are numerous techniques for determining causality, the majority of which are founded on the evolution of semiological and chronological elements.[46]

Although a study conducted in Sweden between 1989 and 1994 on the utility of implementing a cosmetovigilance system received a small number of adverse effect notifications and thus concluded that cosmetovigilance was of little value, the study did find that cosmetovigilance was necessary.[47]

Future perspective

Prior to marketing a cosmetic product in Indonesia, the producer is required to notify the Indonesian FDA, through the Cosmetic Notification System. The procedure is so expedient, requiring no more than 14 days to evaluate the document before releasing the approval letter. Unless the product contains nanomaterials, additional time is required to assess its safety.[48]

The Indonesian FDA encourage the producer to disclose whether or not their products contain nanomaterials or materials modified by nanotechnology.

However, according to Singh & Nanda, the cosmetics industry has been reluctant to disclose the use of nanoscale synthetic materials.[8] Therefore, the registration officer should have extensive knowledge of nanotechnology in order to conduct screening prior to receiving the registration document. If there is any chance that the product is related to nanotechnology, the industry must be consulted. In addition, the cosmetics industry and other stakeholders should be able to identify potential nanomaterial safety concerns and to discuss various regulations and recommendations imposed by various regulatory agencies.[9]

People need more information and education about the potential benefits and risks of nanotechnology. The Indonesian FDA may utilize any method to disseminate information, including social media and collaboration with public influencers. People can protect themselves and comprehend what to do with their product if they have adequate knowledge. ●

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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 the studied cases; critical literature review; critical revision of the manuscript.

Tri Wagiyanti
Preparation and writing of the manuscript.

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Examine the slide instead of just reading the report!

Examine a lâmina e não apenas leia o laudo!

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ABSTRACT

Histopathology reports are the pathologist's description of a microscopic morphological image, which can be understood as long as the basic elements of the histological structures are known. However, actually viewing the morphological image can be more helpful in understanding what is really being described, similar to the examination of radiograms, which is directly performed by the orthopedist despite the report being made by the radiologist. This article discusses this scenario, with the aim of encouraging surgeons to view and inspect morphological images to improve their understanding of the clinical-surgical status and their analysis of the state of the surgical margins or the histological subtype.

Keywords: *Mohs Surgery; Official laboratory; Pathology; Reoperation; Skin Neoplasms*

RESUMO

Laudos histopatológicos são descrições, realizadas pelo patologista, de um quadro de morfologia microscópica, que podem ser compreendidos desde que os elementos básicos das estruturas histológicas sejam conhecidos. Porém, a visualização da imagem morfológica em si pode ser mais útil no sentido de entender o que realmente está sendo descrito, a exemplo do exame do quadro radiológico, que é diretamente realizado pelo ortopedista apesar de o laudo ser feito pelo radiologista. Este artigo discorre sobre esta realidade, tentando estimular o cirurgião a praticar essa visualização, a fim de melhorar a compreensão da situação clínico-cirúrgica, assim como da análise do estado das margens cirúrgicas ou do subtipo histológico.

Palavras-chave: *Cirurgia de Mohs; Laboratório Oficial; Patologia; Reoperação; Neoplasias Cutâneas*

Review Article

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INTRODUCTION

Years of experience with surgeons from the most diverse specialties have revealed one fact to us: only a few of them can properly process a surgical specimen and interpret the histopathological findings. Although this is not absolutely necessary, most surgeons only interpret reports and would be unable to argue with the pathologist if they received a false positive report, as they have rarely experienced the routine of histotechnology. Only micrographic surgeons are slightly more experienced in examining histological sections, so the pathologist's report, which rarely describes possible technical artifacts or other biases, becomes an unassailable truth, despite the footnote routinely stating that, in case of any questions, the pathologist should be informed and the case revised.

In our medical literature review on the subject, we hardly found anything specifically about this fact, and sometimes, surreptitiously, possible errors in histotechnical manipulation are poorly analyzed[1] or dismissed as "unlikely".[2]

This short review seeks to encourage surgeons to get used to examining the histological sections of their own surgeries and, over time, to realize that there are a significant series of events that can interfere with the pathologist's report. The pathologist, in turn, can be misled even by a lack of adequate information from the surgeon who sent the material. It's worth noting that every Anatomic Pathology laboratory has its own, often standardized, routine, but the rule is that pathologists routinely receive a large number of ready-made slides of the most varied tissues and cases, processed by their histology technicians. The greater the volume of cases in a department, the greater the chance of errors. No one is infallible. The histopathological sections on the slide, which are the product of histological processing, must be interpreted in the light of all the phenomena that can make the report as accurate as possible. No wonder some laboratories always put a note in their reports: "every histopathological examination must be correlated with the patient's clinical history, otherwise the interpretation of the result is only relative."

HISTOPATHOLOGICAL PROCESSING

In laboratory routine, the surgical specimen first needs to be fixed. Formalin (37% formaldehyde, diluted in a 9:1 or 10% ratio) is usually used.[3,4] Buffered formalin is ideal, because if immunohistochemistry (IHQ) is required; unbuffered formaldehyde can be harmful.[5,6] Fixation time is also important. It should be a minimum of six hours and a maximum of 72 hours so that the antigens are preserved. Once this time has elapsed, the results of histochemical or immunohistochemical staining may be affected. The volume of formalin required for proper fixation should be given special attention, with the ideal parameter being at least 10 times the volume of tissue to be fixed. After the specimen has been resected, it should be placed in the fixative (formalin) within a maximum of 30 minutes.[7,8,4] The process of fixation in formalin will start the hardening process to enable the extremely fine cut it will undergo on the microtome. The length of time it remains in formalin depends on the size of the piece. The larger the piece, the longer the time. Formalin penetrates the tissue at around 1mm/hour. A 2cm specimen takes, on average, 24 hours for the desired initial fixation, while a 10cm specimen would take three to five days.[9] Prolonged time in formalin (longer than five days) can lead to deformation of the surgical specimen, sometimes requiring artifices to maintain the shape of the specimen, such as placing a weight on it or even fixing it to a rigid surface in the desired direction, even before it is introduced into the formalin.[10] The size of the container that will hold the surgical specimen is also important, as small vials for large specimens may contain an insufficient amount of formalin for good fixation, and deform the specimen if it remains in the vial for longer than necessary. Ideally, the surgical specimen should not be compressed inside the flask and should retain its original shape with a sufficient amount of formalin. Fixation will be completed over the course of around 10 to 12 hours, during which time the specimen will be dehydrated by immersion in alcohol, clarified, and paraffinized until the rigidity required for cutting is achieved. This is usually done automatically in a tissue processor called "technicon."[3,4,7,9,10]

One of the most important steps in histotechnology is painting the surgical edges. Without this, the edge can be fragmented during cutting or processing, and the pathologist may find it difficult to analyze, as they may not be referring to the true surgical edge.[4,9] Depending on the situation, the surgeon can paint the surgical edge to suit their liking, which is much better than just placing a surgical wire in a certain position in an attempt to orient the specimen. Drawing a picture of the different colors with the request for the examination can be very useful for the pathologist. Preferably, the surgical edge should be painted before fixation or before the specimen is placed in the "technicon" so as not to contaminate areas unrelated to the surgical edge, such as the cleavage surface, for example.[4,8,9,10]

Once the specimen has been completely fixed and the surgical edges painted, cleavage (sampling) is performed. Many technicians perform the cleavage right after painting the surgical edges, fixing the paint immediately with acetic acid. The cleavage surface should not be painted and should be rectilinear during cutting. It is also important that the cleavage is performed with a single cut and with the specimen properly fixed; otherwise, a softened surface can deform the specimen, making it difficult to recognize the true surgical edge.

The next step is to embed the specimen in liquid paraffin, ensuring that when it solidifies, the surface desired for cutting fits as perfectly as possible to the straight edge of the paraffin block, preventing the block from being worn down too much during cutting in order to obtain the desired cut. An inclusion lacking the necessary care can leave the specimen poorly positioned in the paraffin block, resulting in an inadequate cutting surface. This is extremely important for cuts parallel to the orientation of the surgical margin ("in face" cuts), which are widely used in peripheral micrographic surgery methods (Mohs and Tübingen Pie).[11]

The paraffin block is then fixed to the microtome to make the cuts. Depending on the application, such as "in face" cuts, the initial adjustment of the movable head of the microtome must be made in such a way as to cut the entire desired surface on the first attempts. Otherwise, excessive wear on the block could compromise the correct assessment of the surgical edge. Most technicians are skilled and careful, but when the volume of work increases, the speed of processing can generate more wear, as it is easier just to rough up the block than to carefully adjust it, check for wear, adjust it again, until the first cut reaches the entire surface to be examined. Too much wear and our "in face" surgical edge is gone. Once the desired cut has been obtained, it is picked up and placed on the slides, where it will be stained. A coverslip is added to protect the cuts and the process is finished.

All this processing has been described here because it is essential that the attending physician is aware of every technical detail so that, when examining the slide, they can realize when these steps may not have been properly followed. Pathology laboratories receive a large number of exams of the most varied types every day and it is not uncommon for some technical flaws to be found which can distort the pathologist's report regarding the state of the surgical margins. The pathologist was not present at the surgery and often did not receive any information about the perioperative procedure that could have influenced his judgment. This is not about "doubting the technical capacity of laboratories," because mistakes, who does not make them? The duty of the zealous surgeon would only be to better investigate the situation, and the more information he has or can gather from what has already been done, the better for the patient. We all know that the surgical specimen is never examined in its entirety (not even in micrographic surgery!). Thus, the histopathology report that assesses the surgical margin is actually a logical abstraction of the pathologist's judgment of the histopathological picture and its relationship to the surgical edges, which may represent the real picture (correct report) or contain a false negative or false positive. Figure 1 summarizes the stages of histological laboratory processing of the surgical specimen.

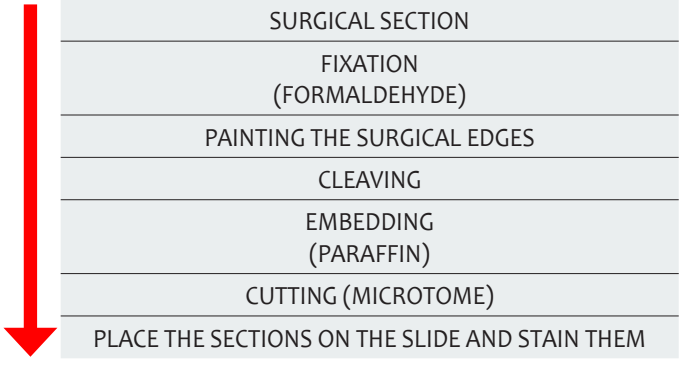

Figure 1: Stages of histotechnical processing. They should occur in the sequence indicated by the arrow

THE FALSE NEGATIVE

Patients who have undergone conventional surgery based on the concept of a safety margin and who, typically one to two years later, develop a tumor with the same histopathological characteristics at the same site as the primary tumor, are diagnosed as having a recurrent tumor. How can this be explained if the histopathology report from the previous surgery was "free margins?" Most surgeons are well aware of this situation, because they know that the statement in the report that the margin is free refers to a non-full sample. What many surgeons are not aware of is that, in most cases, this sample is not even 1% of the total surgical margin. There are certainly highly careful laboratories that routinely perform total inclusion with thin slices, especially when the pathologist performs the macroscopy and is dedicated to a specific sub-area such as Dermatopathology. However, the routine of large laboratory groups, which are increasingly common in the market, is to have trained macroscopy technicians to standardize the process, lacking the appropriate technical expertise (medical) to interpret the data in the request and the diagnostic hypotheses and thus decide on a more "customized" form of sampling for each case.[4,9] It should also be pointed out that total inclusion often implies a greater number of blocks, with costs that multiply and cause financial losses. But the fact is that many surgeons know that if the sample is not totally representative, a small portion of these results may represent a false negative, i.e. a portion of the tumor was left in the patient, although the report was "free margins." This would justify tumor recurrence. Once there are clinical signs compatible with a tumor at the previously operated site, the decision to reoperate the patient is easy to make. This situation is more frequent the more infiltrative the tumor is.

The report has to include the information, not always observed by the surgeon, about whether the specimen has been fully included or not. The acronyms generally used are: TI (totally included; total inclusion), PI (partially included; partial inclusion); WR (with reservation of material from macroscopy) or LR (lacking reservation of material from macroscopy and therefore totally included) can also be used. The laboratory must not discard the remains of the macroscopy samples for six months, so that the pathologist can, upon request, complete the inclusion of the entire specimen.[4] However, lack of familiarity with histotechnology processing means that many surgeons fail to correctly interpret the macroscopy items on the report.

Figure 2 is an example of a false negative.

THE FALSE POSITIVE

While the false negative is only noticed when the tumor recurs, the false positive is based only on the histopathological report, since this information will be available a few days after the surgery. At first, this comes as a surprise to both the patient and the surgeon, as the concept of a safety margin, which was initially considered "safe," has not proven to be effective in completely removing the tumor. The clinic no longer helps and what

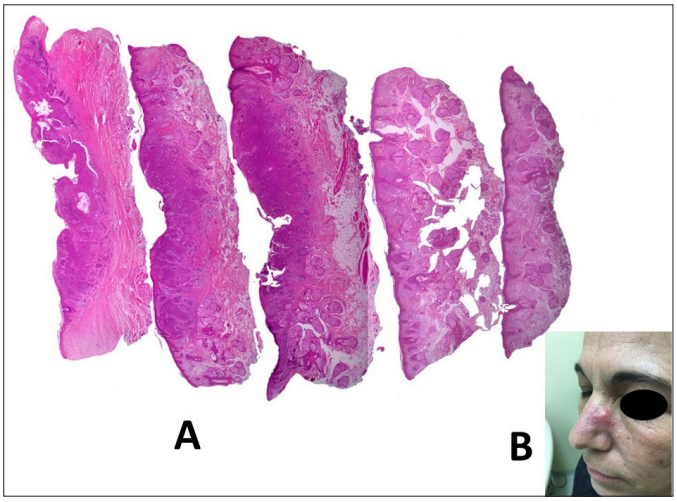

FIGURE 2: As you can clearly see, the pathologist's report was correct: infiltrative basal cell carcinoma (BCC) with free margins **(A)**. However, a year later, the patient developed a tumor at the same surgical site, and the biopsy revealed that it was an infiltrative BCC **(B)**. This means that the small sample size of the conventional surgery could not demonstrate that the margins were actually compromised, thus generating a false negative result. Another important detail: the arrangement of the sections suggests that the sampling was of the "bread loaf" type, and although the surgical edges are not painted, they should be. Hematoxylin & eosin staining 20x

we have is a newly acquired scar. Most surgeons do not have any questions about this report, as they cannot argue with the pathologist because they are not used to examining slides with histopathological sections. The surgeon is left with two options: observe or reoperate.

Is observing wrong or risky? It has long been said that only a third of tumors with reports of compromised margins result in clinical recurrence.[12-16] Many surgeons choose to observe. Some because they are suspicious of the report without contesting it. Others believe that skin cancers (mainly basal cell carcinomas) have a "benign behavior, as they do not cause metastases" and that a recurrence would not be a problem.[16] Thus, in the absence of clinical signs, waiting for progression does not seem to be a course of action that will worsen the patient's long-term prognosis. However, we have to remember that observation is not treatment, especially if the condition really requires re-intervention.

Perhaps the crucial question that should be answered is: is there really a possibility that the patient has a residual tumor, or could this report represent a false positive? In our experience, false positives can occur in three common cases:

- Technical artifacts
- The type of view of the pathologist
- Coincident margin

Artifacts of technique

A very common artifact of technique is the failure to demarcate surgical edges with ink or even the contamination of surfaces with ink which are not surgical edges (free edge or even cleavage surface) (Figures 3, 4, 5).

Type of view (or interpretation) of the pathologist

Many pathologists use different terminology that can mean "compromised margins" to surgeons, such as the term "exiguous margins" or margins smaller than 1mm. In micrographic surgery, especially when using the Munich method, a margin of 1mm can be more than enough, and pathologists unaccustomed to interpreting this variation of micrographic surgery could be unsure about stating that the margins are free. Several times I have taken reports of compromised margins to the pathologist and, examining them with a microscope, I was told that "they thought it best to judge the margin compromised because the tumor was so close," even though in the histological sections the tumor mass would not touch the surgical edge. It is therefore important to know what interpretation the pathologist usually gives to these cases, as the professionals involved have different interpretations (Figure 6).

Coincident margin

Some pathologists use the term "coincident margins" when the tumor only appears to touch the surgical edge focally. Others prefer to judge this as a compromised or focally compromised margin. Undoubtedly, this can represent a dilemma when, in fact, the tumor only tangents the surgical edge, but does not

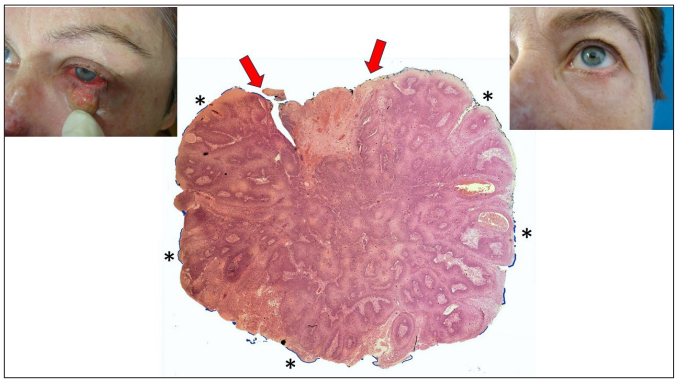

FIGURE 3: The patient had an exophytic tumor on the lower eyelid. The dermatologist shaved the base of the lesion and placed the specimen in formaldehyde. The histology technician received the spherical material and mistakenly painted the entire surface (asterisks). The only place that should have been painted, to mark the surgical edge, was between the red arrows. The pathologist reported it as a "coincident margin." Follow-up for 13 years showed no recurrence. False positive due to technical artifact. Hematoxylin & eosin staining 20x

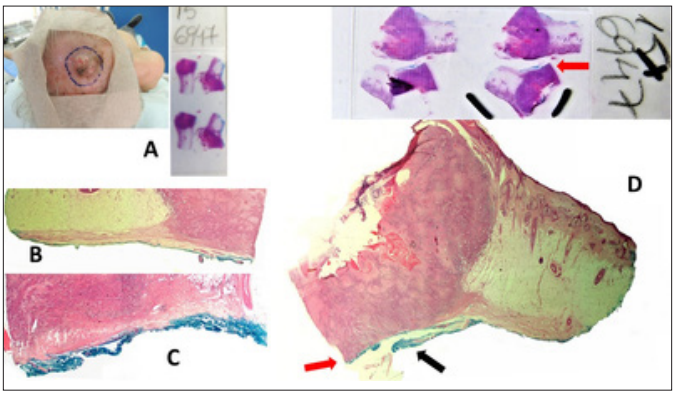

Figure 4: A patient with a squamous cell carcinoma (SCC) clinically non-adherent to the periosteum was submitted to conventional surgery with safety margins and immediate grafting. After examining the two slides shown here, the anatomopathological report suggested that the deep margin had been compromised. On slide **A**, note that the ink does not touch the tumor (**B** and **C**). On the other slide, the ink clearly touches the tumor (**D**) (red arrows). However, there has been a detachment of the deeper surface, from the cleavage of the piece. This layer should have been below the tumor, but it retracted after the piece was cleaved. The technician said that the piece was painted after the cleavage and not before, thus contaminating the deepest part of the tumor with the paint, due to the retraction of the deepest layer, which is the only one that really represents the surgical edge and should have been painted (black arrow). The patient was followed up for more than seven years and had no recurrence. False positive due to technical artifact. The pathologist agreed with the arguments presented and then modified the report. I personally operated on the patient and checked the histopathology. Hematoxylin & eosin staining 20x

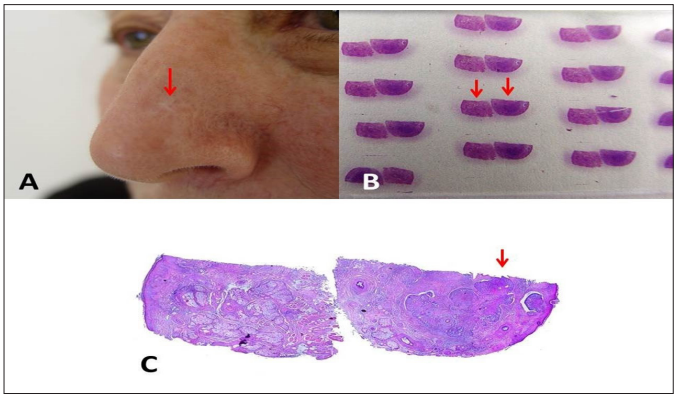

Figure 5: Patient referred for micrographic surgery due to a report of compromised margins. Clinically, we observed only a small scar (red arrow), with no clinical or dermoscopic signs suggestive of tumor persistence (A). Direct examination of the sections on the slide clearly shows straight surfaces, typical of cleavage of the specimen (red arrows) (B). Examination of the sections (C) shows no ink marking the surgical edge, with the tumor touching the straight surface of one of the fragments, which is matched by the straight surface of the other fragment, the latter with no tumor. I took the cuts and the report to the pathologist, who apologized for the mistake. The patient has never recurred after more than eight years of follow-up. Hematoxylin & eosin staining 20x

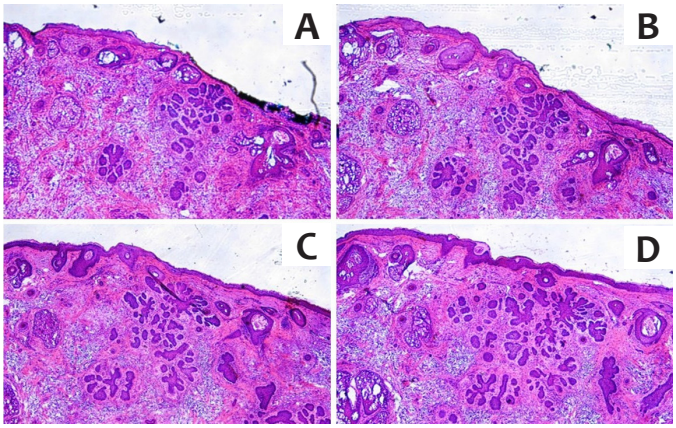

Figure 6: Sequence of histological sections using the Munich method, with a 50 MICRA interval between sections. The BCC is approaching the surgical edge and lies a few microns from the surgical edge (**A** and **B**). In sections **C** and **D**, the epidermis closes the surgical edge, and the tumor is still not touching the epidermis, as its origin is not at this point. Many pathologists not used to this type of analysis would report "compromised margins" or "thin margins," and the surgeon would have to interpret the report. In this way, the pathologist's view can be a false positive. Hematoxylin & eosin staining 20x

go beyond it. When examining cases like these, the pathologist's interpretation of a compromised margin is undoubtedly correct, but I've never seen a pathologist write a report stating that it could be a false positive. One of the characteristics of the tumor edge in these circumstances is its rounded or curved appearance. Straight tumor borders coinciding with the surgical edge should really be interpreted as true compromised margins (Figure 7). In some cases, due to the architecture of the lesion, it is easier to imagine that this border is just coincidental (e.g. clearly nodular basal cell carcinoma). However, in micronodular, infiltrative cases or those with small blocks, it can be difficult to say that the margin is only coincidental, excluding the possibility of residual blocks remaining in the patient's surgical bed. For this reason, the

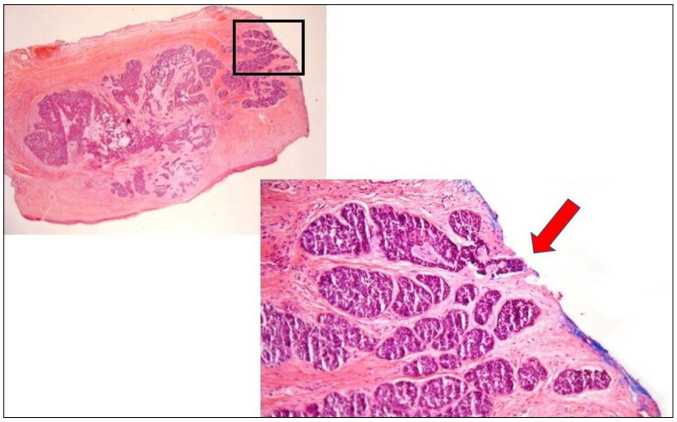

Figure 7: Coincident margin. Only a few pathologists describe this case as a coincidental margin (red arrow). The tumor clearly touches the surgical edge, yet the edge is rounded, giving the impression that it may have stopped right there. If this image, and its interpretation as a coincident margin, represents the actual picture, there is no residual tumor in the patient, which is another cause of a false positive. However, this really is a dilemma for pathologists or surgeons, because the tumor touches the surgical edge and we have no way of proving that it ended exactly at this point. However, note that basal cell carcinoma predominantly has expansive growth, which increases the chance of interpreting a coincident margin and, consequently, the chance of a false positive. If the predominant histological type was infiltrative, this interpretation would be more risky. Hematoxylin & eosin staining 20x

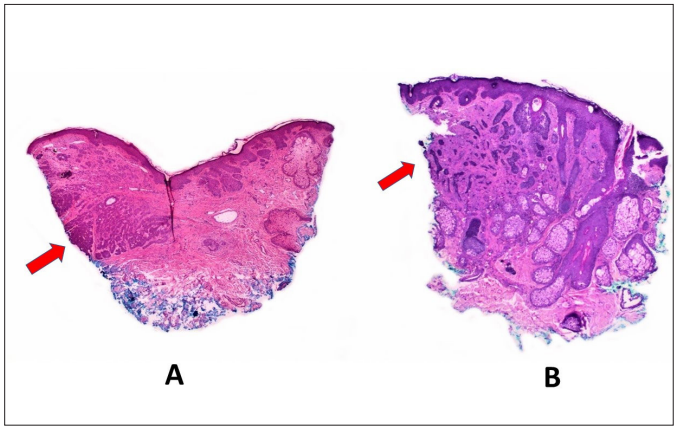

Figure 8: Typical examples of compromised margins. In **A**, the tumor mass is as if cut along its length, appearing straight for a good length of the surgical edge, giving no impression of focal involvement. In **B**, the BCC is quite infiltrative, touching the surgical edge with small tumor fragments protruding into it (arrow). Hematoxylin & eosin staining 20x

Figure 9: When you read the text describing a picture with palm trees, a cove with white sands, a blue sea and sky, mountains in the background... is that how you pictured the description? In other words, a picture is worth 5,000 words

histological subtype and the architectural pattern of the tumor should be highly valued in the interpretation.

COMPROMISED MARGINS

The margin is compromised when the surgical edge, which should be painted, coincides with the tumor edge, which is generally straight (i.e. giving the impression of having been cut). The tumor is otherwise quite infiltrative, so that digitiform projections of it appear sectioned at the surgical edge. Many pathologists do not mention the amount of tumor in the sections that touch the surgical edges, thus failing to distinguish even a possible case of a focal coincident margin as described above, from a case in which a large amount of tumor tissue affects the surgical edge. Surgeons who are aware of this situation may feel more confident about reoperating if they notice that a large amount of tumor tissue has touched the surgical edge (Figure 8).

DIVERGENT HISTOPATHOLOGICAL INTERPRETATIONS

A histopathological image is nothing more than a morphological analysis. The terminology used in histopathological language can be understood by associating its meaning with a pathology. For example, when the pathologist refers to "basaloid cells arranged in blocks with a palisaded periphery, surrounded by stromal retraction," we all interpret this as a description of basal cell carcinoma. But we really have no idea what the pathologist is actually describing (the image per se). We like to play this joke in lectures. Everyone knows palm trees, a mountain, a cove of white sand, a blue sky.... We immediately put all these elements together in a picture and imagine what is being described. Look at figure 9. It contains all these elements. Is that exactly how you imagined it? In other words, a picture is worth 5,000 words!

We all know that irregularly growing (infiltrative) tumors are more unpredictable in the way they expand, unlike expansive tumors, which tend to be more regular. This is important when it comes to surgical planning, i.e. whether or not we can use the safety margin concept correctly.[1] Similarly to the imagery puzzle presented here, the pathologist's description may not fit very well with what the surgeon can perceive by examining the patient's clinical-surgical case and viewing the histopathological image directly. And if the pathologist describes the histological subtype of the tumor! Many reports lack this description, which can even be hampered by the type of material sent to the pathologist, such as fragmented or tiny biopsies.

FINAL COMMENTS

It is very important to say that this text has absolutely no intention of instilling distrust in histopathology reports, but rather of drawing the attention of surgeons to the limitations that a pathologist may have in interpreting or describing them. Almost never have pathologists been upset that a doctor has asked to see the slides. On the contrary, most pathologists encourage this interaction. How often have we had productive conversations in favor of the patient's well-being when questions have been raised and resolved?

A close analogy is the interpretation of radiological images taken directly by orthopedists and the report issued by radiologists. In this case, we are dealing with known anatomy, unlike the abstract images of a histopathological image. The fact that orthopedists directly examine the image and only then quickly read the report cannot be interpreted as a sign of distrust of the radiologist's report.

It is a lot harder to write a text about this without being misunderstood than it is to talk about it in a lecture or to practice it for years. A concise and objective form that contains everything we have observed over years of practice is difficult to find. However, we believe that this short review can encourage the reader to embark on this journey and get used to examining the histopathology of their own cases. We are confident that you will see a lot that you had not expected and that you will be surprised that such disagreements in interpretation are not so rare. Observing the facts and seeking to understand them has always been the aim of science. If there are unanswered questions, what is wrong with raising them?

Another fact to be discussed is the scarcity of literature on the specific subject described here. Perhaps this has to do with the risk of being misinterpreted, as mentioned above. We are unaware of any publication with this clear objective and perhaps this article is original.

All this accumulated knowledge has come from our experience in micrographic surgery. More histotechnology and histopathological knowledge would be very useful for surgeons, which is precisely what micrographic surgeons do. We always encourage micrographic surgeons to make their own cuts and this is closely related to all the questions we are asking in this short review.

Finally, we would like to introduce the subject to give you a better understanding of the meaning of the term "compromised surgical margins". For most surgeons, this means further intervention, as most are unable to interpret a false positive. This review also has this objective: to encourage physicians to look a little further in order to better understand this phenomenon. ●

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Recombinant enzymatic products in Dermatology

Produtos enzimáticos recombinantes em dermatologia

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.2024160306

ABSTRACT

Esthetic dermatology is a growing field, and different noninvasive therapies are gaining attention. The objective of this narrative review was to update current evidence-based knowledge about recombinant enzymes. The PubMed, SciELO, Cochrane Central, and Imbiomed databases were searched for meta-analyses, systematic reviews, randomized controlled clinical trials, observational registries, and preclinical data published in English, Spanish, and Portuguese. Effectivity, safety, and tolerability of recombinant hyaluronidases, lyases, collagenases, and lipases, including their combinations, were evaluated and confirmed in diverse indications. Further research could increase current knowledge on this constantly developing and promising therapeutic area.

Keywords: Lyases; Collagenases; Hyaluronoglucosaminidase; Lipase.

RESUMO

A dermatologia estética é um campo em crescimento, e diferentes terapias não invasivas estão ganhando atenção. O objetivo desta revisão narrativa é atualizar o conhecimento baseado em evidências sobre as enzimas recombinantes. Uma pesquisa bibliográfica de metanálises, revisões sistemáticas, ensaios controlados e randomizados, registros observacionais e dados pré-clínicos publicados em inglês, espanhol e português foi realizada nas bases de dado PubMed, SciELO, Cochrane Central e Imbiomed. A eficácia, segurança e tolerabilidade das hialuronidases, liases, colagenases e lipases recombinantes, incluindo suas combinações, foram confirmadas em diversas indicações. Espera-se que novas pesquisas aumentem o conhecimento sobre essa área terapêutica promissora e em constante desenvolvimento.

Palavras-chave: *Liases; Colagenase microbiana; Hialuronoglucosaminidase; Lipase.*

Review Article

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INTRODUCTION

The definition of beauty has puzzled the minds of artists, mathematicians, and beauty professionals alike for the past seven centuries, starting with Pacioli's divine proportions. Current beauty standards can be related to concepts such as youth, health, and symmetry. Progress towards these apparently simple goals may be achieved through interventions ranging from minimally invasive or noninvasive options to radical, surgical solutions, the first of which are cost-effective and fast-acting therapies, thus gaining the trust of patients and surpassing the popularity of traditional, surgical options.[1] Techniques such as cryolipolysis, radio frequency, low-level laser therapy, and high-intensity focused ultrasound are reported to offer "significant and satisfying results without any adverse side effects".[2] Nevertheless, it is worth noting that these treatment strategies differ in terms of outcomes and tolerability profiles.

A novel class of injectable solutions relies on therapeutic enzymes, which act on their target with great affinity and specificity.[3] Therapeutic enzymes are synthesized in heterologous organisms with the help of biotechnology and genetic engineering, leading to the development of recombinant DNA products.[4] Recombinant DNA technology is a technique of gene cloning that leads to the production of a defined sequence of DNA, with its subsequent propagation and amplification in a suitable host cell or expression system (bacteria, yeasts, animal cells). This process culminates with the purification steps of centrifugation and/or filtration.[4] The resulting recombinant enzymes are obtained quickly, in large quantities, and with high purity levels. Bacterial enzymes are characterized by lower immunoreactivity than those of eukaryotic origin and, therefore, by a better safety profile. The absence of glycosylation in bacterial enzymes is related to the lack of organelles (Golgi apparatus and endoplasmic reticulum in prokaryotic organisms) in which the post-transcriptional process of glycosylation takes place.[5]

The main objective of this narrative review is to update current evidence-based knowledge about recombinant enzymes in Dermatology.

METHODS

A literature search for meta-analyses, systematic reviews, randomized controlled clinical trials, observational registries, case reports, and preclinical data was performed in biomedical databases (PubMed, SciELO, Cochrane database, and Imbiomed), focusing on the use of recombinant enzymes in Dermatology; "lyase", "hyaluronidase", "collagenase", and "lipase" and their corresponding translations were defined as keywords. Publications in English, Spanish, and Portuguese from January 2011 to January 2023 were considered. All authors have reviewed the relevant contents before writing this objective, comprehensive narrative synthesis of published information.

RESULTS

Hyaluronidases and lyases

The skin's extracellular matrix (ECM) provides a structural framework and plays a role in regulating cellular proliferation, adhesion, and migration. The main components of the ECM are collagen, elastin, and proteoglycans, to which glycosaminoglycan (GAG) chains are linked. The most expressed GAG in the dermis is hyaluronic acid (HA).[6] Human hyaluronidases enzymatically degrade GAGs and hydrolyze HA, increasing both skin and connective tissue permeability. Six hyaluronidases have been identified in humans (HYAL1, HYAL2, HYAL3, HYAL4, and PH- 20).[7]

Both hyaluronidases and lyases degrade HA. Hyaluronidases are part of the broader group of lyases, which may degrade several substrates, including GAGs different from HA. It is worth noting that high-purity recombinant lyases like PB72K are characterized by a different amino acid sequence when compared with human hyaluronidases. PK72K lyase acts on local permeability and allows the reduction of edematous components at a tissue level.[6–9]

Progressive loss of HA is a hallmark of skin intrinsic aging (reduced biosynthesis of HA in fibroblasts) and extrinsic aging (progressive degradation of HA due to exogenous factors, such as recurrent and prolonged exposure to ultraviolet radiation).[6]

Local injection of HA-based fillers is the current preferred treatment for soft tissue augmentation, deep skin hydration, and facial contouring. However, this procedure may be associated with adverse events, including superficial placement leading to skin discoloration (Tyndall effect), the use of excessive product and granulomatous foreign-body reactions.[10] Hyaluronidase is used for the management of complications resulting from filler injections. Its efficacy has been demonstrated by Vartanian et al., who performed a randomized, controlled trial including 12 subjects receiving two 0.2 mL injections of stabilized HA in the proximal forearm. Up to three days after injection, skin scores were determined on a scale based on the size of dermal augmentation. Participants were randomly divided to receive 0.5 mL of 75 units of hyaluronidase or normal saline as a placebo. After one week, hyaluronidase-treated patients experienced an 80% decline in skin scores, compared to 10% among controls ($p < 0.001$). Ninety days after treatment, no palpable HA remnant was identified in 92% of subjects.[11] It is worth noting that, in contrast to calcium hydroxylapatite or poly-l-lactic acid-based fillers, HA-based filler effects may be reversed with hyaluronidase treatment.[6]

Hypertrophic scars are characterized by an altered ECM and may develop after injuries, burns, surgery, and several inflammatory processes. These scars remain a therapeutic challenge. Hyaluronidases regulate the level of HA mostly by its degradation, but the role of these enzymes in the wound healing processes is less evident. Products of hyaluronidase degradation seem to stimulate angiogenesis, contributing to wound healing. In a clinical study, treatment of hypertrophic scars with hyaluro-

nidase injections led to changes in scar consistency and a significant reduction in height, independently of their pretreatment elevation.[12] These results are consistent with in vitro and in vivo data showing that hyaluronidases accelerate wound closure in a full-thickness excisional model. This action is mainly associated with regulation of the inflammatory response by mediating pro and anti-inflammatory cytokines, lipid mediators (derived from arachidonic acid) and transcription factors. Moreover, hyaluronidase contributes to the balance between biosynthesis and deposition of collagen.[8]

Collagenases

Collagenases are part of the matrix metalloproteinases group and participate in physiological processes related to collagen biosynthesis, integrity or rearrangement. Collagen represents 30% of the total protein content of the human body.[13] The human skin expresses three collagenases that may initiate degradation of type I fibrillar collagen (MMP-1, MMP-8, MMP-13).[14] All these isoforms prompt collagenolysis by single scissions across the three chains that integrate the collagen molecule in distinct loci from the N-terminus; nevertheless, collagenase posterior action on alpha chains is poor, and subsequent collagenolysis is mainly mediated by gelatinases.[15] By contrast, collagenases synthesized by bacteria from the Clostridioides genus (clostridial collagenases), like collagenases G/H PB220, are able to induce multiple scissions in the collagen triple helix and complete collagenolysis, resulting in several small peptides.[15] In addition, clostridial collagenases reduce the expression of other fibrosis-related molecules, including fibronectin, smooth-muscle actin, and transforming growth factor beta. Notably, the presence of collagen metabolites stimulates fibroblast activity for the formation of new fibers with improved functionality.

In the skin, fibrotic responses to an injury are characterized by scar formation, with excess collagen deposition and a lack of dermal appendages. The process leading to fibrosis is still poorly understood and may be related to cell lineage reprogramming and fibroblast heterogeneity.[16] Hypertrophic and keloid scars have been associated with excessive collagen deposition and reduced native collagenase activity.[14] Keloid fibroblasts have a higher rate of proliferation, more excessive deposition of ECM proteins, and increased expression of myofibroblast biomarkers. The main drawback of keloid treatments, including surgical excision and intralesional corticosteroid injections, is the high recurrence rate.[17] As an isolated therapeutic approach, collagenases have been proposed for the management of these difficult-to--treat lesions and also for enzymatic debridement of burns.[18-20]

Lipases

Lipases catalyze the hydrolysis of triglycerides to smaller molecules (free fatty acids and glycerol). Human lipase activity is determined by modulating factors, including the metabolism of insulin, diet, and physical activity. On the contrary, bacterial lipases, such as recombinant PB500 lipase, do not require cofactors and have a broad substrate specificity.[21]

Adipose tissue accumulates in larger quantities in several areas, predominantly the abdominal and gluteal regions, thighs, periarticular region, retro-orbital areas, as well as on the face and visceral structures. Accumulation of triglycerides may lead to an increment of volume and proliferation rate of adipocytes; triglyceride hydrolysis mediated by lipase induces the formation of easily diffusible metabolites that may be eliminated by lymphatic drainage for further metabolic degradation.[14] In each area, adipose tissue accumulation is characterized by a different profile of adipokine expression.

Intradermal or hypodermic application of lipase to induce fat dilution in areas including the neck, arms, abdomen, and thighs has shown important clinical effectiveness with a good safety profile. Lipases also reduce the size of localized fat deposits or in case of post-lipoplasty imperfections, making this strategy a valuable complement or even an alternative for patients looking for minimally invasive treatments.[14] In addition, one or more injections may be considered for nonobese individuals requiring a mild reduction of adipose tissue, with lower risk than invasive procedures.[14]

Rational and clinical applications of combined enzymatic therapies

The combination of nonfunctional collagen degradation (recombinant collagenases G/H PB220), fat reduction (recombinant lipase PB500), and GAGs hydrolysis (recombinant lyase PB72K) represent a rational, pathogenic-based, and synergic strategy for approaching several esthetic concerns. In addition, the incorporation of high molecular weight HA (HMWHA) into this combination is associated with superior results. HMWHA is characterized by anti-inflammatory properties, contrasting with the potent proinflammatory activity of low molecular weight HA. HMWHA also modulates angiogenesis and cell migration, in relation to skin repair processes. Antioxidant, antiplatelet and inhibitory actions on endothelial cell proliferation and migration have also been identified.[22,23]

Combined enzyme therapy (CET) is a suitable treatment for facial rejuvenation and double chin. As a result of aging, dental alveolar regression leads to flattening of the malar region, with subsequent deepening of the nasolabial folds. This remodeling process causes an imbalance in the upper, middle, and lower thirds of the face.[24] Also linked to aging, a double chin develops due to weakening of the ligaments, loss of skin tone and flaccidity of the facial and cervical subcutaneous adipose tissue.[25,26] Therefore, several components (including connective and adipose tissues) are involved in the pathogenesis of both conditions, which may be targeted by CET.

Edematous fibrosclerotic panniculopathy (EFP) is another esthetically important condition, currently considered as a metabolic disorder of adipose tissues. EFP is probably multicausal, and related factors include connective tissue architecture, estrogen action, microvascular alterations, and genetic and

hormonal characteristics.[27] As a consequence, local hypoxia is induced, leading to a fibrotic response with thick bundles and collagen septa that finally connect the subcutaneous fat to the skin, producing the classical EFP appearance.[12] Ongoing studies and future publications will add more medical evidence on the benefits of CET in patients with EFP.

Additionally, in a clinical multicentric study conducted by Castro-García et al., 42 patients who reported 44 scarring fibrotic lesions (hypertrophic, atrophic or keloids) were treated with a combination of HA, collagenase, lipase, and hyaluronidase, administered with a blanching technique. Fibrosis was evaluated with the Vancouver score and the patients' perceptions were quantified with the Patient and Observer Scar Assessment Scale (POSAS). Prespecified visits were scheduled at day 15, 30, 45, and 60. Combined therapy with HA and recombinant enzymes was associated with relevant improvement, starting at the first control visit. These benefits included the domains of the Vancouver scale (pigmentation, lesion height, vascularization, flexibility) and POSAS (pain, itching, color, stiffness, thickness, irregularity).[28]

CET targeting several components of the MEC is a suitable strategy for treating patients with abnormal wound healing, including keloids. These pathological scars are correlated with an abnormal fibroproliferative response, in which raised scar tissue grows excessively and invasively beyond the original wound edges. Keloids may occur following a triggering stimulus (dermal injuries or inflammatory processes). Environmental factors (type of injury), anatomical location, and genetic predisposition are involved in keloid pathogenesis.[29] As previously cited, collagenases G/H PB220 degrade nonfunctional collagen fibers, while lyase PB72K leads to better tissular penetration and HMWHA modulates local angiogenesis. This enzymatic synergy addresses several patient complaints simultaneously.

Safety and tolerability

Hyaluronidase is associated with a low risk of adverse events. Reports of complications are usually linked with hypersensitivity reactions. Severe forms (facial angioedema, anaphylaxis) have been reported with an estimated incidence rate of 0.1%; nevertheless, such cases are associated with higher doses used to facilitate anesthesia. The risk of allergic reactions has significantly reduced with the use of recombinant formulations. Hyaluronidase is contraindicated in patients who have previously developed hypersensitivity reactions to bee or wasp stings.[30] Collagenase therapy is generally well tolerated. In a real-world setting, the most common treatment-related adverse events are injection site-related and typically resolve before the next treatment session.[31]

Lipase therapy is considered safe, with a good tolerability profile. By contrast, deoxycholic acid, also indicated for fat reduction, has been associated with disruption of adipocyte cell membranes and local tissue responses involving macrophage infiltration, with risk of necrosis.[32]

In the combined therapy study by Castro-García et al., 91% of participants reported local pain as an adverse event, taking into consideration the long-term history of the scarring lesions. Pain was progressively reduced during follow-up, consistently with fibrosis improvement. Local reactions were reported by 75% of patients (erythema, local pain, edema) and spontaneously resolved after 48 hours from the application. No participant withdrew from the study due to adverse events.[28] Enzymatic recombinant therapy is contraindicated during pregnancy and breastfeeding and should not be administered in case of local irritation or infection. Caution is advised in patients with autoimmune diseases and those who had recently received vaccines.

Discussion and conclusion

Esthetic Dermatology is a growing field, and different noninvasive therapies are gaining attention. Enzymes obtained through recombinant DNA technology are safe and effective as injectable products, yielding progressively beneficial results. These enzymes may be used as stand-alone products or as part of recombinant CET, with indications ranging from localized excessive adipose tissue to keloid scarring. Different published and ongoing studies have confirmed the effectivity of recombinant CET with diverse indications, including facial rejuvenation, double chin, hypertrophic scars, and EFP. While current minimally invasive and surgical treatment strategies have variable outcomes and several tolerability issues,[3] recombinant enzymes represent a safe treatment when administered by trained healthcare professionals. It is concluded that enzymatic therapy represents an important advance in the cosmetic field, taking into consideration that these pharmaceutical products act on their targets with great affinity and specificity. It is expected that further research will increase current knowledge of this constantly developing and promising therapeutic area. ●

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Exosomes in dermatology: A review of their role in skin diseases and rejuvenation

Exossomos na Dermatologia: revisão de sua ação em doenças cutâneas e rejuvenescimento

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ABSTRACT

Exosomes are small extracellular vesicles, released by different types of cells, that play roles in intercellular communication. In the skin, exosome-mediated information transfer and intercellular communication are necessary for the maintenance of cellular function and tissue homeostasis. Recently, several studies have demonstrated the involvement of exosomes in skin diseases and rejuvenation, including potential therapeutic uses. In this context, we address recent research on exosomes in dermatology by reviewing the role of exosomes in skin diseases and rejuvenation.

Keywords: Exosomes; Skin; Rejuvenation.

RESUMO

Os exossomos são pequenas vesículas extracelulares, liberadas por diversos tipos de células, que atuam na comunicação intercelular. Na pele, a transferência de informação mediada por exossomos e a comunicação intercelular são necessárias para a manutenção das funções celulares e homeostase tecidual. Recentemente, diversos estudos têm demonstrado o envolvimento dos exossomos nas doenças dermatológicas e no rejuvenescimento, incluindo possibilidades terapêuticas. Dessa forma, iremos abordar, a seguir, pesquisas recentes sobre exossomos na Dermatologia, por meio de trabalho de revisão sobre a ação dos exossomos em doenças cutâneas e rejuvenescimento.

Palavras-chave: *Exossomos; Pele; Rejuvenescimento; Dermatopatias.*

Review Article

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INTRODUCTION

The skin is the physical, chemical, and immune barrier of the human body, preventing loss of substances to the environment. However, it has several other functions, such as tissue repair, perspiration, and temperature and pressure detection, in addition to promoting structural support. The performance of these multiple functions is affected by several factors, ranging from environmental to hormonal. Recent studies have indicated a role of exosomes in physiological and pathological processes of the skin. Their findings have brought a new perspective to understanding the molecular mechanisms involved in these processes.[1]

Exosomes are small extracellular vesicles, released by different types of cells, that effect intercellular communication through the delivery of bioactive proteins, lipids, RNAs, and DNA from donor cells to recipient cells, being able to both regulate cellular physiological events and participate in pathological processes.[2] The recognition of exosomes by cellular targets is specific and involves the following events: recognition between receptor surfaces, direct fusion of the exosome with its target on the cell membrane, and absorption into the target cell by endocytosis. Given their abilities, exosomes are important mediators of intercellular communication and are involved in multiple processes, including immune response, angiogenesis, and inflammation. Cells secrete exosomes as a means of presenting signaling molecules to tissues or to other cells with regulatory functions.[3]

In the skin, exosome-mediated information transfer and intercellular communication are necessary for the maintenance of cell functions and tissue homeostasis. Studies have shown that transport of endogenous exosomes occurs in multiple types of skin cells and is implicated in the molecular mechanisms of cutaneous diseases.[4] Furthermore, the content of exosomes (known as cargo) can be a potent biomarker for the diagnosis and treatment of cutaneous disorders and diseases. Exosomes secreted by stem cells can be used for therapeutic purposes in regenerative and aesthetic medicine.[5] Within this context, in the following sections, we will address recent research on exosomes and the skin by reviewing the literature on the interactions of skin exosomes and their roles in skin diseases and rejuvenation.

Exosomes: definition and biological characteristics

The first evidence of the existence of extracellular vesicles was recorded in the early 1960s, but little was known on the subject.[6] Major discoveries occurred in the late 1980s, when a study on the maturation of sheep reticulocytes revealed the mechanism of exosome formation. These investigators demonstrated that small vesicles were formed within endosomes and then released into the extracellular environment by exocytosis (hence exosomes).[7] Years later, a study proposed that exosomes were small transporters carrying mRNA and microRNA that enabled remote genetic communication.[8] Developments in exosome research since then have led to a new paradigm in several fields of medicine. Because they are derived from different cells or tissues, exosomes exert multiple actions and may be associated both with physiological cellular functions and with disease states.[9]

Extracellular vesicles (EVs) play an important role in intercellular communication. They are stratified by size into exosomes (60 to 180 nm in diameter), microvesicles (50 to 1000 nm), or apoptosomes (50 to 5000 nm). Exosomes are secreted by most cells and contain a variety of proteins and nucleotides.[10] Damaged organs secrete signals that induce stem cells to produce RNA and protein-containing exosomes, in order to facilitate the maintenance of tissue homeostasis. The composition of exosomes is influenced by inflammatory signals such as lipopolysaccharides, tumor necrosis factor-alpha, interferon gamma, and hypoxia. In addition, other physiological factors and cellular conditions also affect exosome release, such as intracellular calcium levels, cellular energy, membrane phospholipids, membrane-associated enzymes, cytoskeleton-membrane interactions, and other effects of exocytosis, hypoxia, and oxidative stress.[11] Exosomes are loaded with bioactive components for intercellular communication and gradually mature as they are delivered to multivesicular bodies by internal budding. This process prevents the cytoplasmic degradation of exosomes by lysosomes. Multivesicular bodies then fuse with the plasma membrane and are secreted into the microenvironment (extracellular space or bodily fluids), carrying RNAs and proteins depending on the type of cell which secreted them.[13] The cargo of exosomes consists of biologically active substances, including proteins, mRNA, microRNA, cytokines, and transcription factors. Circulating exosomes are recognized by multiple receptors on cells, which then

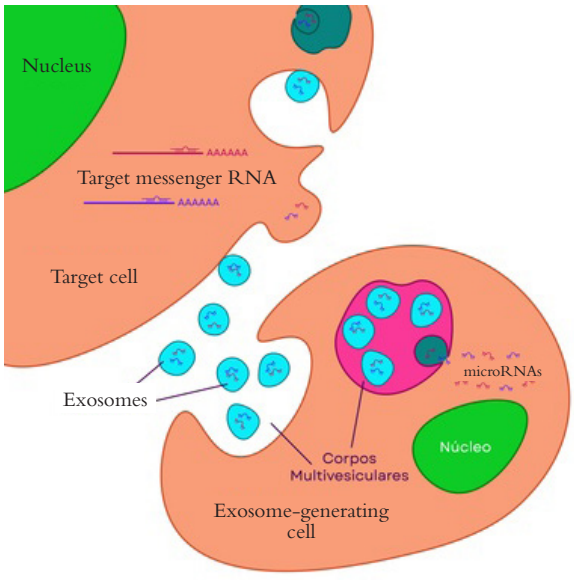

FIGURE 1: Cellular mechanisms of exosome formation, secretion, and reception

receive their cargo (Figure 1). Exosome uptake occurs by three mechanisms: endocytosis, ligand-receptor uptake, and fusion.[14]

Exosomes and skin physiology

The skin, known for being the largest organ in the body, is composed of the epidermis, the dermis, and the subcutaneous tissue. The outermost layer of the skin, the stratum corneum, is 10 to 20 μm thick and consists of 10 to 15 layers of dead cells. The second layer, the viable epidermis, is 100 to 150 μm thick and is composed predominantly of keratinocytes at various stages of differentiation, in addition to melanocytes, Langerhans cells, and several other types of cells.[14] The third layer, the dermis, is rich in extracellular matrix (ECM) proteins and growth factors, due to the presence of several fibroblast lineages. The deepest layer, the hypodermis or subcutaneous tissue, is composed of adipocytes, mesenchymal stem cells (MSCs), and connective tissue.[15] The different cell types present in the skin layers, including keratinocytes, fibroblasts, and macrophages, have the ability to communicate with the environment and mount complex responses to internal and external stimuli.[16] Thus, different types of skin cells secrete exosomes to other cells or bodily fluids in order to participate in biological activities.[4]

The development of the skin, especially the epidermis, is essential for survival. The balance between cell renewal and differentiation must be regulated by stem and progenitor cells.[17] Exosomes are abundantly loaded with epidermal progenitor cells and are essential to preventing premature differentiation of progenitor cells. Wnt signaling pathways play an important role in skin development and renewal processes. In a prior study, Wnt protein transport was found to be mediated by exosomes.[18]

Skin pigmentation is also regulated by keratinocyte-derived exosomes that carry specific mRNA and bind to melanocytes. In addition, exosomes are capable of affecting angiogenesis, cell proliferation and differentiation, apoptosis, and inflammation.[5] Fibroblast-derived exosomes have been shown to increase collagen and elastin synthesis, and may act in rejuvenation and wound-healing processes.[19] They have also been implicated in the regulation of skin inflammation, since exosomes from adipose tissue-derived mesenchymal stem cells downregulate the expression of inflammatory cytokines such as IL-4, IL-23, IL-31, and TNF-α. It has also been suggested that exosomes secreted by mesenchymal stem cells can balance the Th1 and Th2 immune responsess.[20]

Exosomes and mesenchymal stem cells

Mesenchymal stem cells (MSCs) are multipotent stem cells defined by their ability for self-renewal, multilineage differentiation potential, and paracrine regulation. Due to their ease of isolation, in vitro expansion, and multipotent origin, MSCs have become established as a particularly important stem cell type in the field of regenerative medicine, including tissue repair.[21] In addition to their classic origin in the bone marrow, MSCs are also present in adipose tissue, muscle, umbilical cord blood, and various other organs and tissues. Stem cells have excellent therapeutic effects in promoting tissue remodeling, neovascularization, soft-tissue regeneration, bone and cartilage repair, rejuvenation of various tissues, and hair-follicle regeneration. Currently, stem cells are mainly used to facilitate the healing of skin wounds via their multifactorial paracrine effects. However, therapeutic use of stem cells in wound healing is limited by difficulties in storage, potentially tumorigenic mutations, immune rejection, and ethical issues.[22]

Since exosomes are the products of their parent cells, MSC-derived exosomes (MSC-exos) have unique biological functions similar to those of MSCs. Indeed, stem cell-derived exosomes are essential mediators of the paracrine effects of stem cells.[23] MSC-exos also contain cytokines such as vascular endothelial growth factor (VEGF), transforming growth factor β1 (TGF-β1), interleukin-6 (IL-6), interleukin-10 (IL-10), and hepatocyte growth factor (HGF), which facilitate angiogenesis and immunomodulation.[24] The main packaging components of MSC-exos, including metabolites, proteins, DNA, and non-coding RNAs (ncRNAs), can be internalized by recipient cells such as fibroblasts, keratin-forming cells, immune cells, and endothelial cells (ECs) and further promote improved tissue repair. Furthermore, the efficacy of repair mediated by MSC-exos can be improved by targeted editing of exosome content, pretreatment of MSCs, or artificial modification of exosome surface receptors.[25]

In summary, MSC-exos may have specific advantages over MSCs for dermatological applications. Adipose-derived stem cells (AD-MSCs), bone marrow-derived MSCs (BD-MSCs), and human umbilical cord MSCs (hUC-MSCs) are the most frequently used exosome-producing cells. However, MSC-exos have specific mechanisms which make their use a promising cell-free therapeutic strategy for skin regeneration.[26]

Given the various effects of exosomes in skin cells, we will now address its action on cutaneous diseases and rejuvenation.

Exosomes and cutaneous diseases

Scarring

Several studies have demonstrated the therapeutic role of exosomes at various stages of wound healing. During the inflammatory phase, exosomes have been shown to modulate immune cells and local tissue cells, helping prevent an uncontrolled inflammatory response. During the proliferation phase, exosomes act to close up the scar by activating endothelial cells and fibroblasts. This activation promotes a proangiogenic milieu and initiates extracellular matrix deposition. Finally, during the remodeling phase, exosomes influence the balance between matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases, which facilitates the achievement of excellent tissue healing. Exosome therapy also increases tissue healing by stabilizing and stimulating a wide variety of mediators involved in

each of these phases.[27]

In a systematic review, Sousa *et al.* (2023) highlighted the great potential of exosomes as therapeutic options for chronic nonhealing wounds. In summary, exosome therapy has shown consistent positive results, including increased wound closure rates, stimulation of local angiogenesis and re-epithelialization, and increased collagen deposition. Furthermore, exosomes have demonstrated the ability to reduce scar formation, alleviate local inflammation, promote increased formation of granulation tissue, and increase the proliferation and migration of dermal fibroblasts. These findings highlight the therapeutic efficacy of exosomes in promoting wound healing. In the last 5 years, there have also been significant advances in combining exosomes with innovative engineering strategies. Exosome-based therapies have emerged as promising tools for wound healing, with advantages such as abundant sources; ease of preparation, storage and transportation; and minimal immunogenicity.[28]

Healing is a process that at least partially comes down to an exosome-mediated interaction between various skin cells, including keratinocytes, fibroblasts, endothelial cells, adipocytes, macrophages, and other immune cells. Li *et al.* suggested that macrophage-derived exosomes are capable of promoting the healing of diabetic wounds, with marked pro-angiogenesis and proliferative effects and attenuating the secretion of cytokines and pro-inflammatory enzymes.[29] Kim *et al.* found that subcutaneous administration of M2 macrophage-derived exosomes (M2-exos) in a mouse wound model markedly decreases and increased the local populations of M1 and M2 macrophages, respectively, thus contributing to a successful conversion of M1 to M2 macrophages.[30] Finally, exosome-guided reprogrammed M2 macrophages improved fibroblast migration, collagen deposition, and endothelial cell tube formation in wound healing. Interestingly, exosomes derived from mesoglycan-treated, exosome-containing keratinocytes were able to induce increased expression of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) in human fibroblasts and endothelial cells, thereby increasing angiogenesis and stress fiber formation, in vitro.[31] This finding revealed an autocrine loop with a positive impact on re-epithelialization which is implicated in wound healing. Furthermore, Zhao *et al.* discovered that exosomes derived from human umbilical vein endothelial cells (HUVECs) could accelerate wound healing, both in vitro and in vivo, and promote the proliferation and migration of keratinocytes and fibroblasts, two important types of effector cells for skin regeneration.[32]

Atopic dermatitis

Exosomes play a critical role in the pathogenesis of inflammatory and autoimmune cutaneous diseases. AD-MSCs can exert an important paracrine effect by secreting active soluble factors and exosomes that modulate inflammation and may thus be an option for treating atopic dermatitis. Cho *et al.* found that injection of ADSC-exos was able to improve atopic dermatitis in mice treated with house dust mite antigens by reducing serum levels of IgE, eosinophils, and pro-inflammatory cytokines such as IL-4, IL-23, IL-31 and TNF-α, thus improve pathological symptoms in AD skin lesions.[33] Shin *et al.* found that, in an oxazolone-induced dermatitis model, subcutaneous injection of ADSC-exos markedly reduced transepidermal water loss, while also improving stratum corneum moisture and markedly decreasing levels of inflammatory cytokines such as IL-4, IL- 5, IL-13, TNF-α, IFN-γ, IL-17 and thymic stromal lymphopoietin (TSLP), indicating that ASC-exos effectively restored the epidermal barrier functions in AD by promoting ceramide synthesis.[34]

Psoriasis

Psoriasis is at least partly attributable to immune system dysfunction; therefore, exosomes can act by modulating the production of pro-psoriatic cytokines. Phospholipase A2 is highly overexpressed in psoriasis. It was recently discovered that mast cells produce exosomes containing phospholipase A2, generating neolipid antigens and leading to recognition by active CD1 cells, which results in the production of interleukins IL-22 and IL-17, involved in the pathogenesis of psoriasis. Cutaneous T cells from patients with psoriasis were found to exhibit increased sensitivity to phospholipase A2 versus control T cells, suggesting that mast cell exosomes are important mediators in the pathogenesis of psoriasis and that inhibition of phospholipase A and CD1 exosomes may be therapeutic strategies in psoriasis.[35]

As targeted anti-IL-17 and anti-IL-23 therapies have proven effective in psoriasis, it can be assumed that manipulating the function of the exosomes of dendritic cells (which release IL-23, which in turn controls the release of IL-17 and IL-23) 17) may be a promising avenue to treat this common chronic disease. Along these lines, Jiang *et al.* demonstrated that exosomes isolated from psoriasis-like keratinocytes and treated with a "psoriatic cytokine cocktail" (IL-17A, IL-22 and TNF-α) are critical actors in the induction of psoriatic inflammation, through activation and infiltration of T cells and neutrophils. Increased expression of inflammatory cytokines (IL-6, IL-8 and TNF-α) has been reported after stimulation with keratinocyte-derived exosomes, suggesting that control of these Evs may have therapeutic potential to treat psoriasis.[36]

Indeed, epidermal keratinocyte-derived exosomes have been found to exacerbate skin lesions in a psoriasis-like mouse model. Keratinocytes interact with infiltrating immune cells (such as neutrophils and mast cells) via exosomes, positively affecting the epidermal microenvironment in psoriasis. Shao et al. found that exosomes secreted by neutrophils harvested from patients with generalized pustular psoriasis could be internalized by keratinocytes and increase the expression of inflammatory molecules in these keratinocytes via activation of signaling pathways, such as IL-1β, IL-36 G, IL-18, and TNF-α.[37]

It has been demonstrated that IFN-γ can mediate exosome secretion in cells that play a critical role in the patho-

genesis of psoriasis, activating innate and adoptive immune cells, such as dendritic cells, lymphocytes, neutrophils, NK cells and macrophages.[38] Evidence further suggests that RNAs transported by exosomes play a critical role in regulating inflammatory responses against endotoxin and in several diseases, including psoriatic arthritis. A recent study showed that plasma exosomal microRNAs play a critical role in the pathogenesis of autoimmune diseases, including psoriasis, and can be used as biomarkers of disease or prognosis.[39]

Nonmelanoma skin cancer

Exosomes play an important role in anti-skin cancer therapy. Zhao et al. reported that exosomes are critical to 5-aminolevulinic acid photodynamic therapy (ALA-PDT) of cutaneous squamous cell carcinoma (SCC), as they mediate its antitumor action via induction of dendritic cell maturation and TGF-β1 fibroblast secretion, providing a new strategy for antitumor immune response.[40] Chang et al. identified clustered exosomes from fibroblasts and keratinocytes in patients with basal cell carcinoma (BCC), demonstrating an increase in proliferation, metabolic activity, migration, and invasion capacity of exosomes in patients with BCC compared to a control group without BCC.[41]

Merkel cell carcinoma (MCC) is an aggressive cancer, with a poor prognosis, for which biomarkers to allow early detection and assessment of treatment response are lacking. Konstantinell et al. investigated exosomes from four different MCC cell lines and identified 164 common proteins, many of which were involved in tumor progression and metastasis, demonstrating the importance of obtaining information on the protein cargo of exosomes and laying the foundation for identification of exosome proteins that might measured in biopsy specimens as prognostic and diagnostic biomarkers to assess the progression of MCC.[42]

Melanoma

Recently, the importance of melanoma-derived exosomes in the progression of this cancer has become more evident due to their role in various stages of metastasis, including induction of migration, invasion, primary niche manipulation, immune modulation, and pre-metastatic niche formation. In a review on the role of exosomes in melanoma progression, Isola et al. concluded that tumor-derived exosomes participate as cellular messengers and are involved in several steps that are essential for successful metastasis. Some melanoma exosome-specific proteins found in patients' circulating exosomes are now known to correlate with prognosis; this evidence shows the great potential of using exosomes to detect cancer and estimate prognosis. The field of research into the role of exosomes in cancer progression is expanding and being increasingly explored, as exosomes emerge both as a druggable target and as a tool to deliver anticancer drugs directly to tumors.[43]

Disorders of pigmentation

Human keratinocytes release exosomes that modulate pigmentation. Exosomes transport specific RNAs to melanocytes and modulate pigmentation status by altering gene expression and tyrosinase activity. Thus, they can act both to inhibit and to stimulate melanogenesis. Kim et al. showed that keratinocyte exosomes can inhibit melanogenesis by decreasing levels of microphthalmia-associated transcription factor – the main transcriptional regulator of melanogenesis – in melanocytes.[44] Lo Cicero et al. found that exosomes from UVB-stimulated keratinocytes increased tyrosinase activity in melanocytes. Furthermore, transfection of melanocytes with keratinocyte-specific pre-mRNAs increases melanin production and microphthalmia-associated transcription factor gene expression. Thus, keratinocyte exosomes have roles in delivering RNA cargo to alter melanocyte pigment production in microphthalmia-associated transcription factor-dependent and microphthalmia-associated transcription factor-independent pathways.[5]

Takano et al. found that exosomes from UVB-irradiated keratinocytes significantly activated melanocytes, suggesting quantitative changes in exosomes secreted by keratinocytes homeostatically regulate human skin color development.[45] Liu et al. also suggested that crosstalk between keratinocytes and melanocytes in the epidermal melanin unit occurs via exosomal mRNAs, reporting that keratinocyte exosomes induced a significant decrease in melanin production and tyrosinase expression in melanocytes.[46] Despite this evidence, additional studies of this nature are needed to gain insight into how exosomes can be used to manipulate pigmentation in hypo- and hyperpigmentation disorders.

Systemic lupus erythematosus (SLE)

Circulating exosomes have been shown to be immunologically active and their levels to correlate with disease activity in SLE patients. SLE exosomes mediate increased production of TNF-α, IL-1β, and IL-6, all of which may play a role in the inflammatory process of SLE.[47] In a review on the role of exosomes in SLE, Fei et al. reported that exosomes play important roles in the occurrence and development of lupus via several molecular mechanisms that significantly mediate its progression. They further concluded that exosomes have attracted increasing attention from pharmacologists and drug developers as potential drug carriers, as it has been demonstrated that exosomes provide substantial benefits in the targeted delivery of drugs and biomolecules, making them excellent candidates for the treatment of SLE and other autoimmune diseases.[48]

Systemic sclerosis

Exosomes from patients with systemic sclerosis contain mRNAs with a profibrotic profile and induce a profibrotic phenotype in normal fibroblasts in vitro. Wermuth et al. discovered that serum exosomes from systemic sclerosis had profibrotic mRNAs. Exosomes isolated from patients with systemic sclerosis stimulated profibrotic gene expression (type 1 collagen and

fibronectin) in human dermal fibroblasts. Thus, exosomes are involved in the pathogenesis of systemic sclerosis and may be a promising therapeutic target.[49]

Hair growth

Dermal papilla cells (DPCs) play an important role in hair follicle stem cell (HFSC) differentiation. In the resting phase, HFSCs are located in the bulge region of the follicles. During apoptosis of matrix cells, the dermal papilla (DP) migrates upward and, upon reaching the bulge, releases signals that stimulate the differentiation of HFSCs and trigger follicle regeneration.[50] Exosomes play an important role in cell-to-cell communication. Research in mice has shown that DPC exosomes (DPC-exos) induce the anagen phase while delaying the catagen phase of hair follicle growth, producing longer hair strands and larger bulges, as well as improve outer root sheath cell proliferation and migration in vitro. These effects were found to be mediated by β-catenin and hedgehog signaling. These findings highlight a novel role for exosomes in regulating hair follicle growth and development and provide a potential avenue for treating hair loss.[52]

Yan et al. showed that HFSC differentiation could be induced by culturing DPCs with DPC-exos coupled to the surface of the HFSCs. Using high-throughput micro RNA (miRNA) sequencing, 111 miRNAs were identified that were significantly differentially expressed between DPC-exos and DPCs, and the predicted target genes of the top 34 differentially expressed miRNAs suggested that DPC-exos regulate the proliferation and differentiation of HFSCs via genes involved in cellular signal transduction, regulation of fatty acid expression, and cell-to-cell communication.[53]

A recent study by Wang et al. evaluated the use of DPC-exos in the treatment of male pattern baldness in an animal model. The results showed significant hair regeneration in the group treated with DPC-exos, which probably activated VEGF and AKT1 expression, protecting DPCs and restoring hair growth.[54]

Exosomes and rejuvenation

Skin aging is a complex mechanism that involves intrinsic and extrinsic processes, which manifest clinically as loss of epidermal and dermal thickness, deepening of rhytids, enlargement of pores, depigmentation, and decreased soft-tissue elasticity. This is a multifactorial process, but one key component – the senescence of vitally important cells such as keratinocytes, fibroblasts, and melanocytes – is believed to be mediated by miRNA dysregulation. Consequently, structural and functional changes occur in the extracellular matrix, such as a decrease in the organization and production of collagen, elastin, and proteoglycans, all of which are necessary for the tensile strength, elasticity, and moisture of young skin. Many factors are known to exacerbate aging, including oxidative stress, DNA damage, telomere shortening, miRNA regulation, accumulation of advanced glycation end products, genetic mutations, and inflammation. Exosomes are believed to act mainly on oxidative stress and inflammatory pathways, impacting both the extracellular matrix and collagen.[55]

The potential therapeutic utility of exosomes has increased interest in the proliferation of fibroblasts and stimulation of their migration. In vitro and in vivo studies with UVB photoaging models showed that exosome treatment protects cells from UVB damage by decreasing proinflammatory mediators such as tumor necrosis factor alpha (TNF-α), while upregulating TGF-β and tissue inhibitor MMP (TIMP).[56] These mechanisms lead to the reversal of senescence in fibroblasts, upregulating the production of type I collagen, elastin, and fibronectin, and downregulating expression of type III collagen.[57]

Guo et al. successfully isolated ADSC-exos and found they were able to attenuate the senescence of human dermal fibroblasts (HDFs) and stimulate HDF migration. In addition, the ADSC-exos increased expression of type I collagen and reduced reactive oxygen species (ROS) and senescence-associated β-galactosidase (SA-β-Gal) activity in HDFs. They further demonstrated that ADSC-exos inhibited expression of senescence-related proteins (p53, p21, and p16). These broad anti-senescence effects of ADSC-exos in HDFs may herald a new cell-free antiaging strategy.[58]

Oh ***et al.*** showed that exosomes derived from human pluripotent stem cells inhibit UVB damage to dermal fibroblasts and overexpression of matrix-degrading enzymes, in addition to restoring the expression of type I collagen in senescent dermal fibroblasts, suggesting therapeutic potential in rejuvenation.[56]

Recent studies evaluating topical exosomes in conjunction with nonsurgical facial treatments have demonstrated synergistic effects.[59,60] Chernoff found that combining topical exosomes with facial microneedling produced greater skin quality, tone, texture, vascularity, clarity, and overall patient satisfaction compared to microneedling alone.[59] Duncan added topical exosomes after facial rejuvenation procedures such as laser resurfacing and found faster recovery and fewer side effects compared to resurfacing alone.[60]

CONCLUSION

Exosomes play a key role in skin physiology, skin diseases, and rejuvenation. Although research and scientific evidence are still recent, their importance in Dermatology has been consolidated. In this sense, exosomes represent a new perspective that encompasses cellular and molecular mechanisms involved in skin processes and provides the possibility of revolutionary therapies in the near future.

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Probiotic innovations: bacillus species in dermatology and cosmetology

Probiotic innovations: bacillus species in dermatology and cosmetology

Review Article

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ABSTRACT
In recent years, the use of probiotics in dermatology and cosmetology has been demonstrating a notable rise, offering both preventive and therapeutic benefits for the skin. The intestinal microbiota plays crucial roles, including enzymatic degradation of dietary fiber, starch, proteins, and fats, as well as the synthesis of vitamins B, K, nicotinic acid, amino acids, and various metabolites. The use of multicomponent probiotics composed of strains of the genus Bacillus is a promising way to optimize the positive effects of these microorganisms in dermatological and cosmetic practice and avoid their undesirable effects.
Keywords: Bacillus; Probiotics; Dermatology; Cosmetic Microbiology.

RESUMO
Nos últimos anos, o uso de probióticos em dermatologia e cosmetologia tem demonstrado um aumento notável, oferecendo benefícios preventivos e terapêuticos para a pele. A microbiota intestinal desempenha papéis cruciais, incluindo a degradação enzimática de fibras alimentares, amido, proteínas e gorduras, bem como a síntese de vitaminas B, K, ácido nicotínico, aminoácidos e vários metabólitos. A utilização de probióticos multicomponentes compostos por cepas do gênero Bacillus é uma forma promissora de otimizar os efeitos positivos desses microrganismos na prática dermatológica e cosmética e evitar seus efeitos indesejáveis.
Palavras-chave: *Probióticos; Dermatologia; Bacillus; Microbiologia de Cosméticos.*

INTRODUCTION

According to the Consensus Statement proposed by the International Scientific Association for Probiotics and Prebiotics (ISAPP), the term "probiotic" should be applied to living microorganisms that, when consumed in adequate quantities, have a positive effect on the health of the host.[1] This definition is also employed by the World Gastroenterological Organization.

In recent years, the use of probiotics in dermatology and cosmetology has been demonstrating a notable rise, offering both preventive and therapeutic benefits for the skin. This trend has been extensively explored in current publications.[2] It is noteworthy that these beneficial effects are achieved not only by oral intake of probiotic microorganisms, but also by their direct contact with the skin. It is also worth emphasizing that not only compromised skin, but also healthy skin, exhibits favorable responses to the ingestion of probiotic bacteria.[3]

The extensive adoption of probiotics in dermatology and cosmetology is supported by basic research findings which have highlighted the presence of functional and metabolic connections between the gut microbiota and skin health (known as the "gut-skin axis"). These studies have also elucidated the antioxidant, anti-inflammatory, antiproliferative, and histoprotective properties of the normal intestinal and skin microbiota, as well as its ability to safeguard connective tissue biopolymers and impede aging of the skin.

Current knowledge of the relationship between the gut microbiota and skin health

The human gastrointestinal tract harbors more than 100 trillion microorganisms primarily consisting of bacteria, although viruses, fungi, and protozoa are also present.[4] In the colon, the density of bacterial cells is estimated to range from 10^{11} to 10^{12} per ml, making this segment of the intestine one of the most densely populated microbial ecosystems on Earth. Almost 10 million genes have been identified in the gut microbiome, while the human genome consists of approximately 23,000 genes.[4]

The intestinal microbiota plays several crucial roles, including enzymatic degradation of dietary fiber, starch, proteins, and fats, as well as the synthesis of vitamins B and K, nicotinic acid, amino acids, and various metabolites. It also serves to safeguard the host organism against pathogenic microorganisms through mechanisms such as microbial antagonism, pH regulation, production of antimicrobial compounds, and modulation of cell signaling. Thus, the intestinal microbiota has a profound impact on both innate and adaptive immunity.[5]

Alteration in the species composition and spatial distribution of the intestinal microbiota, known as dysbiosis, can result in disruption of the barrier function of the colon[6] and is implicated in the pathogenesis of various conditions, including pseudomembranous (or "antibiotic-associated") colitis, ulcerative colitis, colorectal cancer, obesity, type 2 *diabetes mellitus*, atherosclerosis, steatohepatitis, autoimmune diseases, osteoarthritis, and disorders of the nervous system such as multiple sclerosis, neurodegenerative diseases, epilepsy, depression, autism, and schizophrenia.[6-9]

Microorganisms are known to colonize the human intestine at birth. During early development, the composition of the gut microbiome undergoes changes until it reaches a relatively stable state. The human intestine contains approximately 1000 different species of bacteria classified into phyla such as Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, Verrucomicrobia, Fusobacteria, Tenericutes, Spirochaetes, Cyanobacteria, and Saccharibacteria.[10] One of the most notable alterations in the gut microbiome is the Firmicutes/Bacteroidetes ratio, as an increase in Firmicutes has been reported in cases of obesity.

It has been established that the gut microbiome synthesizes a minimum of 30 bioregulatory compounds, including short-chain fatty acids, secondary bile acids, trimethylamine, cortisone, glucagon-like peptide-1, peptide YY, ghrelin, and leptin, as well as several neurotransmitters such as gamma-aminobutyric acid, serotonin, dopamine, and norepinephrine.[11] Certain members of the intestinal microbiota can respond to host-secreted hormones. These bioregulators, generated by the gut microbiota, enter the bloodstream and can influence distant organs and systems, including the skin.[12]

Table 1 provides an inventory of metabolic products originating from the intestinal microbiota that possess the capability to traverse the intestinal barrier, access the systemic circulation, and impact the skin.[12]

Numerous studies have shown the mutual relations between the colon microbiota and the functional and metabolic state and structure of the skin through the impact of the former on the immune system.

Short-chain fatty acids (monocarboxylic acids with a chain length of up to 6 carbon atoms) are the byproducts of the fermentation of undigested polysaccharides by intestinal bacteria. Among these compounds, acetate, propionate, and butyrate dominate in the gastrointestinal tract, constituting more than 95% of the total, with formate, valerate, caproate, and others comprising the remaining fraction.[13] Acetate and propionate are primarily produced by representatives of the Bacteroidetes phylum, while bacteria of the Firmicutes phylum, including representatives of the Bacillales and Lactobacillales, are the main sources of butyrate[14], a key enhancer of epithelial barrier function.[15] Excessive fat and sugar consumption with insufficient fiber intake, as is typical in the Western diet, disrupts the balanced Firmicutes/Bacteroidetes ratio. This is accompanied by an increase in the permeability of the intestinal barrier that contributes to the development of inflammatory and immune diseases.[16] The amount of short-chain fatty acids also decreases with the development of intestinal dysbiosis associated with the use of broad-spectrum antibiotics.[17]

Recent research has demonstrated that dietary fiber and short-chain fatty acids are able to modulate the immune respon-

Table 1: Potential impact of metabolites produced by intestinal microbiota on the intestine and skin (adapted from[12])

Bacterial metabolites	Documented or likely impact on the intestine	Documented or likely impact on the skin
Short-chain fatty acids	Anti-inflammatory effect	Anti-inflammatory effect
Gamma-aminobutyric acid	Modulation of neurotransmitters	Anti-pruritic effect
Dopamine	Modulation of neurotransmitters	Suppression of hair growth
Serotonin	Modulation of neurotransmitters	Melanogenesis
Phenol and para-cresol	Biomarkers of intestinal dysbiosis	Disruption of epidermal barrier function

se in various inflammatory conditions, extending their impact beyond the intestine to distant organs like the lungs[18] and skin.[19] The anti-inflammatory effect of these acids is attributed to the inhibition of the histone deacetylase enzyme by butyrate and propionate[20], as well as the activation of metabotropic G-protein-coupled receptors such as GPR109A (known as the niacin receptor) by butyrate, and GPR41 (commonly referred to as the free fatty acid receptor 3, FFAR3) and GPR43 (FFAR2) by acetate, propionate, and butyrate. The inhibition of histone deacetylase with concurrent activation of histone acetyltransferase results in epigenetic post-translational modifications, accompanied by a reduction in the expression of proinflammatory cytokines, consequently restraining the systemic inflammatory response.

It has been revealed that GPR109A can activate colon macrophages and dendritic cells, promoting the differentiation of T-regulatory lymphocytes, which are responsible for producing the anti-inflammatory cytokine interleukin (IL)-10.[21] Additionally, this receptor is able to block lipopolysaccharide (LPS)-induced activation of the transcription factor kappa B (NF-ϰB).[22] The signaling pathway associated with this receptor plays a key role not only in colon inflammation but also in the development of various skin conditions, including psoriasis, inflammatory disorders such as incontinentia pigmenti, sunburn, allergic contact dermatitis, autoimmune diseases, and skin cancer.[23] This suggests that GPR109A could be a promising therapeutic target for the treatment of skin diseases.

Recent evidence highlights that children and infants with dermatitis or a predisposition to allergic sensitization have a gut microbiota with diminished capacity for producing short-chain fatty acids, notably butyrate.[24] These findings support the hypothesis that a low fiber intake, typical of Western lifestyles, may contribute to impairment of the skin barrier and subsequent susceptibility to early allergen sensitization. In line with this, Trompette *et al.*[25], using an experimental model of atopic dermatitis, demonstrated that a diet enriched in fermented dietary fiber reduced systemic allergen sensitization and disease severity. The authors attribute this effect to the production of short-chain fatty acids, particularly butyrate, which enhances the functionality of not only the intestinal barrier but also the skin barrier through the induction of epidermal keratinocyte differentiation and the production of essential structural components of the epidermis.

Other metabolites produced by the intestinal microbiota have been found to impact skin function. For instance, bacterially produced gamma-aminobutyric acid (GABA), similarly to its endogenous counterpart, acts as an inhibitory neurotransmitter and thus possesses the ability to suppress neurons responsible for signaling skin itching.[26] In a mouse model of atopic dermatitis, GABA demonstrated the ability to ameliorate skin lesions by rebalancing the levels of T helper cells of the Th1 and Th2 types, with a shift towards a predominance of Th1 cells.[27] GABA is also able to inhibit matrix metalloproteinase-1 (MMP-1), an enzyme involved in the breakdown of type I collagen, and increase the expression of human type I collagen (COL1A1 and COL1A2). These processes play an important for maintaining skin elasticity.[28]

In turn, dopamine directly influences human hair follicles, inhibiting hair growth by inducing the catagen (resting stage) that is important for prevention of hirsutism and hypertrichosis.[29] Serotonin is able to enhance melanogenesis through the activation of 5-HT_{2A} receptors.[30]

The development of intestinal dysbiosis alters the systemic impact of gut microbiota metabolites. In such conditions, the blood plasma concentration of bioactive toxins, specifically phenol and para-cresol, which are byproducts of aromatic amino acids, rises. At present, these compounds are considered biomarkers for intestinal dysbiosis. Recent research has demonstrated their ability to reduce skin hydration and disrupt the epidermal barrier function due to derangement of keratinocyte differentiation.[31]

Pathogenetic significance of the gut-skin axis

Regulating interactions between the host and microbiota stands as a fundamental role of the immune system, and regions inhabited by commensals, such as the skin and intestine, house a substantial portion of the body's immune cells. Given the predominant activity of the immune system, commensal microbial communities significantly influence mucosal immunity. Limiting the contact between microorganisms and the intestinal epithelial membrane to minimize inflammatory reactions and microbial

translocation is crucial for maintaining the host's homeostatic balance. To achieve this segregation, the intestinal epithelial cell barrier, mucus layer, T cells, secretory immunoglobulin A, and dendritic cells collaborate to establish a protective structure termed the mucosal firewall. This structure restricts the movement of commensal bacteria to lymphoid tissues, thus preventing the development of inflammation.[10] Furthermore, intestinal cells in their normal state demonstrate relatively low expression of Toll-like receptors, particularly types 2 and 4; this is associated with insensitivity to bacterial LPS enhanced by the production of IL-10 and TLR-inhibitory peptide by the colon mucosa.

The ability of the symbiotic microbiota to inhibit the translocation of NF-ϰB to the nucleus and thus eliminate the expression of several proinflammatory and prooxidant proteins, as well as histolytic enzymes, contributes to the protection of the host against inflammatory reactions to commensal microorganisms.[32]

However, any alteration in the gut microbial diversity can increase the vulnerability of the host and impair the immune tolerance of the intestinal mucosa,[33] potentially impacting skin health.[34]

This condition significantly diminishes the anti-inflammatory properties of the normal microbiota and creates an environment for the passage of molecular structures associated with microorganisms – known as microbe-associated molecular patterns (MAMPs), such as LPS, peptidoglycan, flagellin, bacterial DNA, etc. – across the compromised intestinal epithelial cell barrier and into the systemic bloodstream. This can subsequently lead to the onset of a systemic inflammatory response.[35]

For instance, the DNA of intestinal microbiota representatives has been detected in plasma samples from patients with psoriasis. In a study involving 54 patients and 27 healthy controls, bacterial DNA was identified in 16 out of 54 patients with psoriasis, while none was observed in the control group. Furthermore, patients with psoriasis were found to have an increase in markers of systemic inflammatory response (γ-interferon, IL-1β, IL-6, IL-12, and tumor necrosis factor-α) compared to healthy controls. Bacterial DNA sequencing revealed the presence of the same type of microorganisms commonly found in the intestinal microbiota.[10] Thus, the intake of MAMPs into skin tissues results in the development of inflammation, structural damage, and compromised epidermal barrier function.[12] Based on contemporary theories, the development of intestinal dysbiosis involves a series of pathophysiological events that contribute to skin damage[10,36]: increased permeability of the intestinal barrier permitting the passage of microorganisms and their byproducts, leading to B-cell hypersensitivity, T-cell deterioration, and reduced secretion of secretory immunoglobulins A; dysbiotic intestinal microbiota, toxic products, neurotransmitters, and altered immune cells reach the skin tissue through the circulatory system. This transition shifts the skin condition from a state of health, characterized by a balanced microorganism composition and an appropriate level of antimicrobial peptides (from both human and bacterial sources) to a dysbiotic state; finally, MAMPs from the dysbiotic intestinal and skin microbiota trigger signaling cascades, such as NF-ϰB-dependent pathways, resulting in the degradation of skin connective tissue, disruption of the epidermal barrier function, inflammatory and immune-mediated skin damage, and development of skin diseases and/or aging.

It is important to note the bidirectional nature of the gut-skin axis. Exposure of the skin to ultraviolet B (UVB) radiation has been shown to enhance the diversity of the gut microbiome, likely mediated by vitamin D production.[37] Indeed, the concentration of vitamin D in human serum was found to correlate with the relative abundance of the genera Lachnospira and Fusicatenibacter. Furthermore, disruptions in the skin barrier can potentially contribute to pathological processes in the intestine that are not directly linked to dysbiosis. For instance, sensitization of the body to epicutaneous exposure to peanut protein can result in immunoglobulin E-mediated intestinal infiltration by mastocytes.[38]

Use of probiotics in dermatology and cosmetology

The probiotics most commonly used in dermatology and cosmetology include some species of Lactobacillus, Bifidobacterium, Enterococcus, and certain representatives of the Bacillus genus. Notably, a systemic course of probiotics is emerging as a novel approach to preserving skin health and function.

In recent years, several randomized, placebo-controlled clinical trials have yielded compelling evidence for the efficacy of oral probiotics in managing conditions such as atopic dermatitis[39,40] and psoriasis.[41] These studies report that the use of probiotic microorganisms significantly improves the quality of life of patients, reduces disease severity and the risk of relapse, and normalizes inflammatory biomarker levels. Furthermore, a study has provided supporting evidence for a therapeutic benefit of a topical preparation containing Enterococcus faecalis fermentation products on the skin microbiome and the management of acne vulgaris.[42] The Italian dermatologist Christian Diehl conducted a comprehensive analysis of the mechanisms responsible for anti-inflammatory and antioxidant effects of probiotics on the human and mammalian body.[2] These mechanisms encompass: the production of various metabolites with anti-inflammatory and antioxidant properties, including butyrate, folate, and glutathione, by probiotic microorganisms such as Bifidobacteria and Lactobacillus fermentum; inhibition of NF-ϰB-dependent production of pro-inflammatory cytokines, matrix metalloproteinases, and reactive oxygen and nitrogen species by Bacillus spp. activation of the Nrf2-Keap1 signaling pathway – an antioxidant response element (Bacillus spp. strain LBP32); a histoprotective effect, which entails the inhibition of matrix metalloproteinase expression (seen in *L. acidophilus* and *L. plantarum)*, along with anti-elastase and anti-collagenase activity (notably in *L. casei*, *L. diolivorans*, *L. rhamnosus*, and lactobacillus *exopolysaccharides*); inhibition of enzymes responsible for the production of reactive

oxygen species, including NADPH oxidase and cyclooxygenase-2 (seen in *L. fermentum* CECT5716, *L. coryniformis* CECT5711, and L. gasseri CECT5714); chelation of metal ions, specifically Fe2+ and Cu2+ cations (*Streptococcus thermophilus* 821, L. casei KCTC3260, and *L. helveticus* CD6); and expression of enzymatic antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase (seen in *L. fermentum* and *L. lactis*). In animal experiments, probiotic bacteria have demonstrated the ability to provide photoprotective effects when applied to the skin (e.g., *Bifidobacterium* breve, *L. johnsonii*, *L. plantarum* HY7714, and *L. acidophilus*), accelerate the healing of skin wounds (as observed with *L. plantarum*), improve skin barrier function (*Streptococcus thermophilus*, *L. plantarum*, and *Bifidobacterium* breve), and enhance skin hydration (*Bifidobacterium*).[2] The ability of probiotics to improve skin hydration and prevent photoaging was confirmed in a randomized, double- blind, placebo-controlled clinical trial in which *L. plantarum* HY7714 was taken orally by participants with dry skin and wrinkles.[43] The laboratory of Theofilos Poutahidis discovered a rejuvenating effect of probiotic bacteria on the skin and fur of elderly mice.[44] According to the investigators, consumption of probiotic yogurt causes a shift in the anagen phase (the active phase of hair growth) with sebocytogenesis that leads to the formation of thick and shiny fur due to induction of the anti-inflammatory cytokine IL-10 and the neurohormone oxytocin by bacteria. In older male mice treated with probiotics, there was an observed increase in subcuticular folliculogenesis when compared to the control group.[44] Additionally, the shinier hair in the female experimental group was considered by the researchers as a sign that correlates with fertility. However, it is important to note that probiotic bacteria can have side effects when taken orally, including septic conditions (in cases of intestinal barrier dysfunction and immunodeficiency), immune and metabolic disorders, and outcomes resulting from horizontal gene transfer.[45] There have been reported cases of bacteremia and sepsis associated with the consumption of probiotics containing *L. acidophilus, L. casei*, *S. boulardii*, *L. rhamnosus*, Bifidobacterium breve, and Bacillus subtilis.

In the context of using probiotics for inflammatory skin diseases, lactobacilli may pose a certain risk due to their ability to activate the production of proinflammatory cytokines by type 1 T-helper cells.[46] Moreover, *L. reuteri* has been found to stimulate autoimmune responses in a mouse model of lupus erythematosus.[47]

Modern literature sources criticize the idea that probiotic microorganisms can be effectively introduced to a stable biofilm formed by the resident microbiota. Furthermore, species within the Lactobacillus and Bifidobacterium genera are known for their very slow growth and marked sensitivity to gastric juice when taken orally, which impedes their passage through the gastrointestinal tract.[48] It is widely accepted that the impacts of probiotic bacteria are primarily related to their direct effect on epithelial and immune cells, as well as the maintenance of problematic microbiota through the exchange of gases and metabolites.[49]

Thus, the current scientific literature substantiates a need to search for effective probiotic agents suitable for oral and topical administration in dermatology and cosmetology, while maintaining a high safety profile. In this context, the use of representatives of the transient microbiota – in particular, spore-forming bacteria within the Bacillus genus – as probiotics appears quite promising. These microorganisms, despite their brief residence in the intestine and their inability to integrate into the biofilm, have the potential to positively influence its function, fortify epithelial barriers, and counteract immune, inflammatory, and metabolic disorders associated with intestinal and skin dysbiosis, as well as underlying diseases and age-related changes.

Bacteria of the Bacillus genus as probiotics: potential applications in dermatology and cosmetology

The genus Bacillus comprises 77 species, constituting a substantial group of gram-positive, rod-shaped microorganisms that are primarily aerobic, but can tolerate anaerobic conditions, and form heat-resistant endospores.[50] These bacilli, alongside lactobacilli, constitute the major components of the colon microbiota. By producing catalase and subtilisin, bacilli can promote the growth and viability of Lactobacillus culture. It is noteworthy that certain bacilli, such as *B. subtilis var. natto,* have been used in the fermentation of Asian foods since time immemorial. Most commercial Bacillus-based probiotics contain *B. subtilis, B. polyfermenticus*, or *B. clausii*, and some include *B. cereus*, *B. coagulans*, *B. pumilus*, and *B. licheniformis*, whose spores exhibit stability during storage and resistance to temperature variations, gastric acidity, and bile.[51]

Upon reaching the mucous membranes of the oral cavity and pharynx and encountering the gastric milieu, these spores become activated and begin vegetative growth. Analysis of fecal samples has revealed that probiotic strains of *B. cereus*, *B. clausii,* and *B. pumilus* can persist in the gastrointestinal tract of mice for up to 16 days.[50] A number of reviews and original publications highlight the benefits of probiotic strains of Bacillus, the most important being their safety even at high concentrations, their antagonism to a wide range of pathogenic and opportunistic microorganisms, their ability to synthesize useful biologically active compounds, their positive impact on the immune status of the host organism, and their antimutagenic, antioxidant, anti-inflammatory, histoprotective, and antiproliferative properties. Bacillus strains also exhibit resistance to lytic enzymes, ensuring high viability in the gastrointestinal tract, and are environmentally safe.[51]

According to recent studies, about 800 substances that can be produced by bacilli possess antibacterial properties. Among these compounds are bacteriocins, which are ribosomal peptides or proteins undergoing post-translational modifications (subtilin, erycin *S, coagulin*, and megacin), as well as antibiotics (bacillisin and surfactin).[52]

The prospects for applying Bacillus bacteria as probiotics

in dermatology and cosmetology have significantly expanded, primarily due to their remarkable antioxidant, anti-inflammatory, immunomodulatory, histoprotective, and antiproliferative properties. Many of these properties can be attributed to the ability of bacilli to produce exopolysaccharides (EPS), high-molecular-weight byproducts of bacterial metabolism.[53] For instance, EPS derived from B. subtilis have been shown to effectively regulate cytokine production by T-helper types 1 and 2[54], promote the polarization of macrophages toward the M2 phenotype[55], and reduce the expression of key components in proinflammatory signaling pathways, including transcription factors NF-κB and STAT6, as well as Janus kinase 1 (JAK1).[56] These transcription factors play pivotal roles in the pathogenesis of psoriasis and other inflammatory skin disorders, as well as age-related disorders. When B. subtilis was introduced into enterocyte cultures, a notable reduction in the production of proinflammatory IL-8 and inducible NO synthase isoforms in response to various stimuli (IL-1β, deoxynivalenol, and flagellin) was observed. This reduction was attributed to the inhibition of NF-κB activation, achieved by disrupting the degradation of the inhibitory protein IκB.[57] This study also demonstrated that certain strains of B. subtilis are able to enhance the integrity of the intestinal barrier by upregulating the expression of tight junction proteins. Moreover, probiotic strains of this species demonstrate the ability to attenuate the degradation of connective tissue components within the extracellular matrix.[58]

A useful trait that favorably distinguishes B. subtilis is its ability to slow aging and extend life expectancy, as evidenced in a study using the nematode Caenorhabditis elegans as a model organism.[59] It is important to emphasize that this effect of B. subtilis primarily resulted from downregulation of the insulin-like growth factor signaling pathway, which is characteristic of the healthy longevity observed in centenarians. EPS derived from *B. amyloliquefaciens* can also reduce the expression of pro-inflammatory cytokines, phagocytic activity, and oxidative stress, effects associated with the inhibition of NF-κB signaling and extracellular signal-regulated protein kinase 1/2.[60] Moreover, EPS activates the nuclear factor erythroid 2-related factor 2 (Nrf2)-regulated antioxidant-response element, an NF-κB-antagonistic signaling pathway. Collectively, these mechanisms considerably reduce the manifestations of oxidative stress and the severity of inflammation.

Recently, the ability of *Bacillus spp*. probiotics to block the signaling system of pathogenic microorganism colonies has been discovered, which is implemented through the mechanism known as quorum sensing, a means of maintaining the "social behavior" of bacteria. This capability of bacilli is highly important for correcting skin dysbiosis and creating the prerequisites for incorporating specific strains of the Bacillus genus into topical probiotics and personal care products (body sprays, soaps, skin creams, toothpastes, toothbrush cleaners, etc.). At present, such species as *B. subtilis*, *B. licheniformis*, and *B. pumilus* are already being used for these purposes.[52]

One of the most promising approaches to maximize the positive impact of bacilli while mitigating potential side effects associated with their consumption (the risk of enterotoxin formation, antibiotic resistance, and biogenic amine production) is the development and application of multi-component probiotic formulations. Based on research conducted by Ukrainian scientists, the most balanced probiotic composition providing antioxidant, anti-inflammatory, immunomodulatory, histoprotective, and antiproliferative effects with a high safety profile is the product Remedium™, a formulation which includes five multidrug-resistant strains of the genus Bacillus (*B. subtilis*, *B. amyloliquefaciens, B. licheniformis*, *B. pumilus*, and *B. megaterium*)[50]. The safety of this probiotic composition has been validated by the U.S. Food and Drug Administration (FDA). One dose of the product contains 1.7×10^9 CFU/vial of live probiotic bacteria.

It is noteworthy that this medication contains two bacillus species, *B. subtilis* and *B. amyloliquefaciens*, which have proven pharmacological action associated with their impact on the NF-κB, STAT, and Nrf2 signaling systems. Another important effect of this preparation is its antibacterial properties, attributed to the antagonistic behavior of probiotic strains against a broad spectrum of opportunistic pathogens, particularly bacteria of the genera *Staphylococcus* and Proteus, as well as Candida fungi.[50]

CONCLUSIONS

The commensal microbiota in the colon maintains constant functional communication with skin cells and elements of its microbiocenosis, a phenomenon known as the gut-skin axis. This interaction occurs through the production of bioregulatory compounds (short-chain fatty acids, GABA, serotonin, dopamine, and others) and metabolites and involves the participation of both the innate and adaptive immune effectors. The development of intestinal dysbiosis alters the systemic impact of metabolites produced by the intestinal microbiota and increases the permeability of the intestinal barrier, allowing microorganisms, toxic substances, neurotransmitters, and modified immune cells to enter the bloodstream. These components then reach the skin through the circulatory system, disrupting its microbial community, connective tissue structure, and epidermal barrier function. These disruptions contribute significantly to the pathogenesis of skin diseases and hasten aging.

Contemporary literature consistently supports the practicality of using both oral and topical probiotics in dermatology and cosmetology. This approach yields notable benefits, such as improving patients' quality of life and ameliorating the course of inflammatory, immune, and hyperproliferative skin conditions (acne, atopic dermatitis, psoriasis, hidradenitis suppurativa, rosacea, seborrheic dermatitis, focal alopecia, and skin cancer), reducing the severity of these conditions and the likelihood of recurrence. Probiotics also provide protective effects against environmental factors and accelerate the process of skin wound healing.

Modern literature extensively substantiates the expedien-

cy of using probiotic strains of spore-forming bacteria of the genus Bacillus in dermatology and cosmetology based on their properties to restore the normal functioning of the gut-skin axis, suppress the growth of pathogenic microorganisms, decelerate aging, and provide significant antioxidant, anti-inflammatory, immunomodulatory, histoprotective, and antiproliferative effects, including those associated with impact on intracellular signaling systems.

The use of multicomponent probiotics composed of the most suitable strains of the genus Bacillus is a promising way to optimize the positive effects of these microorganisms in dermatological and cosmetic practice and avoid their undesirable effects.

Conflict of interest statement

The authors declare that there is no known conflict of interest regarding this article. ●

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Treatment of periorbital syringoma with intradermal botulinum toxin A monotherapy versus carbon dioxide laser: a case report

Tratamento de siringoma periorbitário com toxina botulínica A intradérmica em monoterapia versus laser de dióxido de carbono: relato de caso

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ABSTRACT

Syringomas are benign adnexal neoplasms that develop from eccrine sweat ducts. They are mostly found in early adulthood, with a female gender predominance. They typically occur on the face, particularly the periorbital region, which has a high demand for cosmetic enhancement. Management of periorbital syringomas is challenging, with no consistently effective treatment available. Intradermal injection of botulinum toxin A (BTX-A) is a new treatment modality for periorbital syringoma. We present a 53-year-old female patient with periorbital syringoma who was successfully treated with intradermal BTX-A monotherapy as a painless, cost-effective treatment that produced better long-term results than carbon dioxide laser.

Keywords: Botulinum Toxins, Type A; Syringoma; Carbon Dioxide

RESUMO

Os siringomas são neoplasias anexiais benignas que surgem a partir do ducto sudoríparo écrino. Em geral ocorrem no início da idade adulta, com predominância no sexo feminino; geralmente na face, principalmente na região periorbitária, que tem alta demanda por aprimoramento estético. O manejo é desafiador, sem tratamento consistentemente eficaz disponível. Injeção intradérmica de toxina botulínica A (BTX-A) é uma nova modalidade de tratamento para siringoma periorbitário. Apresentamos um siringoma periorbitário em mulher de 53 anos tratado com sucesso com BTX-A intradérmica como monoterapia indolor, custo-efetiva e com melhores resultados a longo prazo do que o laser de dióxido de carbono.

Palavras-chave: *Toxinas Botulínicas Tipo A; Dióxido de Carbono; Siringoma*

Case report

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INTRODUCTION

Syringomas are benign adnexal neoplasms that arise from eccrine sweat duct. The lesions manifest as small, hard, flesh-colored or yellow papules, often in multiples, with a symmetric distribution.[1] They are most common in early adulthood, with a female predominance, and are commonly found on the face, particularly the lower eyelids. Lesions in sensitive areas such as the periorbital region can cause psychological distress, so cosmetic repair is in high demand.[2,3]

Multiple therapeutic approaches have been attempted, including surgical procedures such as dermabrasion, excision, cryotherapy, electrocautery, electrofulguration, laser therapy, and chemical cautery, with the carbon dioxide (CO_2) laser being the most commonly used ablative laser therapy. All these approaches carry a significant risk of recurrence.[2,4]

Nonsurgical alternatives such as topical retinoids, dermabrasion, and intradermal botulinum toxin A (BTX-A) monotherapy have been used in the management of periorbital syringoma, but only in isolated case reports or small case series.[5,6] This entity continues to pose a therapeutic challenge, with no consistently effective treatment available.[7]

We present a case of a 53-year-old female patient with periorbital syringoma who was successfully treated with monotherapy intradermal BTX-A and showed superior result compared to CO_2 laser.

CASE REPORT

A 53-year-old female visited the Dermatology and Venereology clinic with a 9-year history of 1-to-3-mm, skin-colored papules in the area around the eyes. Initially small, the papules grew larger gradually. Despite no pain or pruritus, the lesions bothered her cosmetically. The patient had undergone CO_2 laser treatment 5 years before, but the lesions recurred. On dermatological examination, numerous skin-colored papules consistent with syringoma were seen in the periorbital region.

The patient consented to a split-face procedure using CO_2 laser on the left periorbital area and intradermal BTX--A on the right periorbital area. Written consent was obtained. Ablative CO_2 laser was performed on the left periorbital area until the syringoma resolved, with topical anesthesia given 30 minutes prior to the procedure. A 100-unit vial of BTX-A was diluted in 2.5 mL of preservative-free normal saline solution. A total of 24 international units (IU) were intradermally distributed using a 30 G×4mm needle and 1-cc syringe into 1-cm2 injection sites in the right periorbital area (2 IU per site), with ice application prior to injection. In comparison to CO_2 laser therapy, the patient found intradermal BTX-A injections to be more comfortable and less painful.

Significant improvement of the syringoma was achieved by both treatment modalities within different time frames. On the left periorbital region, which was treated by CO_2 laser, the lesion disappeared immediately, with a wound healing time of about 2 weeks, and reappeared 4 months later. On the right periorbital area, which was treated using intradermal BTX-A, improvement progressed gradually, with no reappearance at 7-month follow-up. (Figure 1)

DISCUSSION

Syringomas are benign adnexal tumors that clinically appear as yellowish or skin- colored papules 1-3 mm in size, most typically found in the lower periorbital region, and can cause significant cosmetic concerns. The goal of treatment is to improve appearance by eradicating the tumor in a minimally invasive fashion. Numerous treatment strategies with varying degrees of success have been described in the literature; the most common problem in the management of syringoma is recurrence.[7]

Botulinum toxin A is a neurotoxin with numerous dermatological applications which inhibits acetylcholine release from cholinergic nerve endings. This leads to chemodenervation, which modulates the autonomic regulation of eccrine glands.[8] BTX-A is being studied as a novel treatment modality for various skin conditions, including hyperhidrosis, hypertrophic scars and keloids, Raynaud phenomenon, oily skin, facial **flushing,** psoriasis, and cutaneous lesions (including periorbital syringomas).[9]

Although the exact mechanism by which BTX-A affects syringoma is unknown, it could be explained by inhibition of the SNAP-25 (synaptosomal associated protein of 25 kD) component of the SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complex, which prevents the release of acetylcholine from vesicles within the cytoplasm of nerve endings. This causes suppression of cholinergic terminals on autonomic nerves, which in turn control the secretion of eccrine sweat glands, from which syringoma is derived.[6] CO_2 laser, on the other hand, destroys the syringoma itself as the target tissue by heating and vaporizing intracellular water, but is associated with a high potential of recurrence. When employed

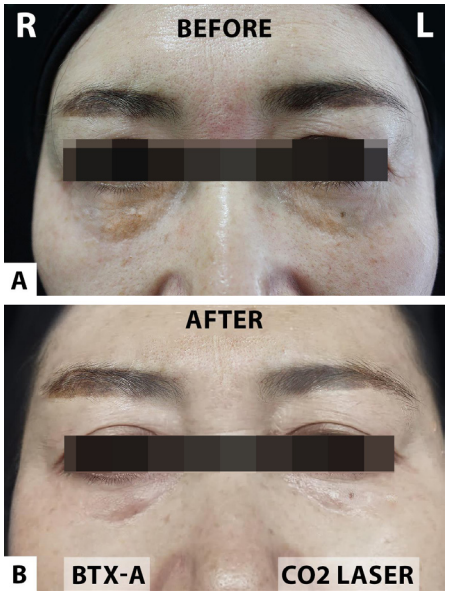

FIGURE 1: **A -** Before treatment. **B -** 7-month follow-up ater intradermal BTX-A on the right periorbital area and CO_2 laser on the left periorbital area

fractionally, CO_2 laser remains the treatment of choice, with intralesional electrocoagulation available as a second option with acceptable results and lower risk of complications.[7] A review article reported that CO_2 laser is the most commonly used ablative laser therapy; however, it is frequently associated with side effects such as scarring and dyspigmentation.[2,5] Previous clinical research with CO_2 laser showed that the fractional ablative method resulted in post-treatment erythema lasting a mean of 16.67 days, crusting for a mean of 5.87 days, and post-treatment hyperpigmentation in 14.3% of patients.[10]

In a retrospective study of 92 patients, Seo et al. compared CO_2 laser therapy with multiple perforations combined with botulinum toxin A. In a previous study, the authors had reported success with deep tumor eradication using a CO_2 laser with multiple perforations ("**multiple-drilling method**"), and in this later series, decided to add botulinum toxin A as an adjunct. Although the rate of recurrence was comparable in both groups, the rate of improvement was much higher in the combination therapy group.[8]

Fujigaki reported a case of localized syringomas in the periocular and upper lip region treated with 46 IU of BTX-A intradermally as monotherapy. At 8-month follow-up, the patient showed significant improvement.[6]

Intradermal BTX-A monotherapy could potentially become the treatment of choice in the management of syringoma, allowing selective eradication of dermal target lesions while preserving normal epidermal tissue.[3] In this case report, it was also shown to be a painless treatment with a better long-term outcome than carbon dioxide laser.

CONCLUSION

Intradermal BTX-A injection offers a painless and more cost-effective treatment option with better long-term outcomes compared to carbon dioxide laser in the management of periorbital syringoma.

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Therapeutic effect of botulinum toxin A on folliculitis dissecans of the scalp

Efeito terapêutico da toxina botulínica A em foliculite dissecante

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ABSTRACT

A patient with dissecting folliculitis of the scalp who did not respond to antibiotic therapy received four monthly sessions of intradermal administration of 100 IU of botulinum toxin A. Four months after treatment, a complete recovery of the affected area of the patient's scalp was observed. A biopsy taken from the affected area showed the presence of ***Staphylococcus lugdunensis*** and ***Staphylococcus aureus*** resistant to erythromycin. Botulinum toxin A had no effect on the viability or biofilm production of the ***Staphylococcus strains***, indicating that the healing effect of the toxin was associated with the host response alone.

Keywords: Botulinum Toxins Type A; Folliculitis; Alopecia; ***Staphylococcus aureus***; ***Staphylococcus lugdunensis***.

RESUMO

Um paciente com foliculite dissecante que não respondeu à terapia com antibióticos recebeu quatro sessões mensais de administração intradérmica de 100 UI de toxina botulínica A. Quatro meses após o tratamento, foi observada uma recuperação completa da área afetada do couro cabeludo do paciente. Uma biópsia da área lesionada mostrou a presença de Staphylococcus lugdunensis e Staphylococcus aureus, ambos resistentes a eritromicina. Observou-se que a toxina não teve efeito sobre a viabilidade ou produção de biofilme das cepas de Staphylococcus, indicando que o efeito curativo da toxina estava associado apenas à resposta do hospedeiro.

Palavras-chave: *Toxinas Botulínicas Tipo A; Foliculite; Alopecia; Staphylococcus aureus; Staphylococcus lugdunensis.*

Case report

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INTRODUCTION

Dissecting folliculitis of the scalp (DFS) is a rare cause of scarring alopecia characterized by neutrophilic inflammation, hair loss, perifollicular pustules, nodules, and abscesses.[1] Although these abscesses are sterile, they are frequently associated with secondary bacterial infection, mainly by ***Staphylococcus aureus***.[2] The conventional treatment for this disorder involves the use of topical and oral antibiotics, which may not be very effective in severe cases, for which surgical removal of the lesions needs to be considered.[3] Therefore, there is an urgent need to find new treatments to control the development of DFS. Several studies have demonstrated the effectiveness of botulinum toxin A as an alternative treatment for nonscarring androgenetic alopecia, which is not associated with infection.[4,5] We report the case of a patient with DFS who showed complete resolution of the condition after treatment with botulin toxin A.

CASE REPORT

A 37-year-old man with clinical symptoms of DFS was admitted to our clinic. The patient did not have associated comorbidities such as high blood pressure, diabetes, or obesity. Clinical examination revealed the presence of nodules, abscesses, and a patch of hair loss (Figure 1).

At admission, the patient was treated with tetracycline antibiotics (100 mg/day for 12 weeks) and received intralesional administration of corticosteroids and antibiotics, but did not respond to these treatments. Botulinum toxin A was considered an alternative treatment option. The patient received intradermal administration of 100 IU of botulinum toxin A (Allergan) at days 0, 30, 60, and 90. A diagram of the scalp area to be treated was previously defined by outlining the infection sites. Each injection site received a dose of 2.5 IU/100 μL of botulinum toxin A in sterile saline 0.9%. The patient did not receive any other type of treatment during this period. After treatment, the patient reported resolution of pain within the first 2 weeks. Four months after the initial treatment, the abscesses and swelling subsided and a significant increase in hair density was observed (Figure 2).

For microbiological analysis of the affected area, a punch biopsy of approximately 3 mm in size of the patient's scalp was performed before treatment with botulinum toxin A.[6-8] The results showed the presence of ***S. aureus*** and ***S. lugdunensis*** resistant to erythromycin (Table 1).

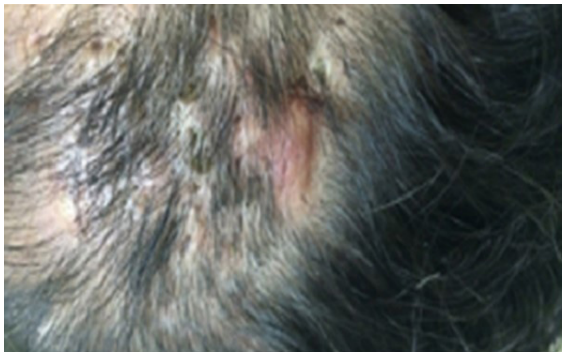

Figure 1: Macroscopic analysis of the scalp before treatment with botulinum toxin A

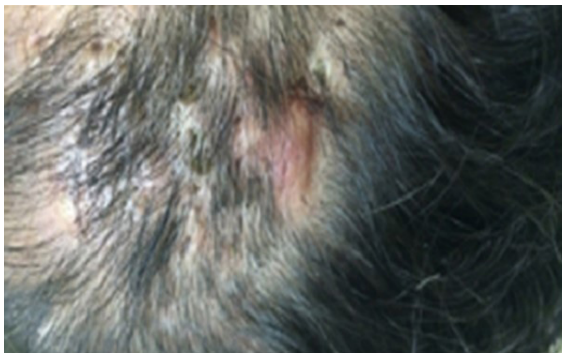

Figure 2: Macroscopic analysis of the scalp after 4 months of treatment with botulinum toxin A

The effect of botulinum toxin A on the growth (bacteriostatic effect) and killing (bactericidal effect) of ***S. aureus*** and ***S. lugdunensis*** was also investigated, by measuring the optical density of the bacterial culture and counting the number of colony-forming units, respectively.[9-11] In addition, the effect of botulinum toxin A on biofilm formation by the bacterial strains was determined by colorimetric assay, as described by Sheikl et al.[12] The results showed that botulinum toxin A had no effect on the viability of the ***Staphylococcus*** strains and did not influence their ability to form biofilm (Table 2).

Table 1: Antimicrobial Profile of the *Staphylococcus* strains derived from the patient's scalp legional area

	Erythromycin	Tetracycline	Doxycycline
Staphylococcus aures	R	S	S
Staphylococcus lugdunensis	R	S	S

R = Resistant *S = Sensitive*

Table 2: Influence of botulinum toxin A on bacterial viability and biofilm formation

	PROLIFERATION O.D. 595 nm				CFU				BIOFILM O.D. 595 nm			
	Without Toxin		With Toxin		Without Toxin		With Toxin		Without Toxin		With Toxin	
	Mea	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Staphylococcus aures	0,652	0,03	0,660	0,03	$2,65x10^8$	0,04	$2,73x10^8$	0,05	0,45	0,05	0,50	0,008
Staphylococcus lugdunensis	0,592	0,05	0,600	0,04	$9,8x10^7$	0,009	$9,67x10^7$	0,05	1,98	0,04	2,00	0,04

The Table shows the mean ± SD (Standard Deviation)
O.D.= Optical Density
CFU = Colony-forming Units
Obs: Positive for biofilm formation when the optical Density is higher than 0,5

DISCUSSION

DFS is a rare skin disorder that can cause significant emotional distress due to the appearance of the affected skin, as well as itching, pain, and permanent hair loss. It destroys hair follicles by causing deep follicular occlusion, followed by follicular rupture and deep inflammation of the hair bulb. Therefore, DFS is categorized as a type of cicatricial folliculitis.[13] Although DCS is commonly associated with ***S. aureus***, our report shows that S. lugdunensis can also be involved. In addition, our findings indicate that the healing effect of botulinum toxin A does not seem to be associated with the toxin's direct action on the pathogen, as it had no effect on the viability of the ***Staphylococcus*** strains found in the patient and on their ability to produce biofilm. In contrast, treatment with botulinum toxin A was highly successful, with the patient reporting resolution of pain within the first few days of treatment and full recovery after 4 months. Therefore, it seems that the healing effect of botulinum toxin A is associated with the host response. However, the mechanism of action of the botulinum toxin A remains unclear, as the toxin has the ability to interact with both neuronal and immune cells.[4] Nevertheless, several studies have indicated that, under conditions of altered immune response induced by the cholinergic anti-inflammatory pathway and the release of calcitonin gene-related peptide, botulinum toxin A can act locally as an antagonist agent.[4,14–17] Therefore, it is possible that the intradermal administration of botulinum toxin A in patients with DCS can shift the patient's dysfunctional inflammatory reaction to a competent immune response and, as a consequence, restore the normal functioning of the affected area of the scalp. However, further research is needed to fully understand the mechanisms behind the healing effect of botulinum toxin A and to establish protocols to optimize its use as a therapeutic tool for DFS.

CONCLUSION

Our findings suggest that botulinum toxin A is an effective alternative for the treatment of DFS in patients who do not respond to conventional treatment with antibiotics. ●

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Hair transplantation in transgender women: case report

Transplante capilar em transgêneros femininos: estudo de casos

Case report

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ABSTRACT
Hair transplantation is an option for anyone with Androgenetic Alopecia, including transgender patients who want to align their appearance with their gender identity. Thus, hair transplantation can help transform appearance and boost self-esteem, especially if hair loss is a source of gender dysphoria. We report two cases of hair transplantation in transgender patients with good results, using the Follicular Unit Extraction and Follicular Unit Transplantation techniques. Due to the scarcity of specific articles about hair transplantation in this population, we report these cases for a better understanding of the specific needs of these patients.
Keywords: Hair; Transplants; Transgender People; Gender Dysphoria; Gender Identity; Feminization.

RESUMO
O transplante capilar é uma opção para aqueles com alopecia androgenética, incluindo pacientes transgênero que desejam alinhar sua aparência com sua identidade de gênero. Assim, o transplante capilar pode ajudar a transformar a aparência e aumentar a autoestima, especialmente se a perda capilar é uma fonte de disforia de gênero. Relatamos dois casos de transplante capilar em pacientes transgênero, com resultados satisfatórios, usando as técnicas Follicular Unit Extraction e Follicular Unit Transplantation. Como há escassez de artigos específicos sobre transplante capilar nesta população, relatamos estes casos para maior compreensão das necessidades específicas destes pacientes.
Palavras-chave: Cabelo; Transplante; Pessoas Transgênero; Disforia de Gênero; Identidade de Gênero; Feminização.

INTRODUCTION

The term transgender refers to a person who does not identify with the biological sex assigned at birth. The transgender population corresponds to 0.69% of the Brazilian population.[1] To adapt to the gender with which they identify, some undergo treatments that include surgeries, hormonal therapies, and dermatological procedures. During this transition to alleviate gender dysphoria, multidisciplinary monitoring with psychologists, psychiatrists, endocrinologists, dermatologists, and plastic surgeons, among others, is critical. Facial feminization surgery is an example of a procedure to transition from male to female, as some facial features are more typical of a woman's face while others are of a man's face. One of these characteristics is the hair implantation line, which usually has an oval pattern in women and an M-shaped pattern in men.[2] Thus, hair transplantation is an option for patients with androgenetic alopecia or those who want a reduction in the forehead and /or the bitemporal recesses for a more feminine appearance. We report cases of hair transplantation in transgender patients with satisfactory results.

CASE REPORT

A 45-year-old transgender woman came to our Service with a history of androgenetic alopecia for five years and gender-affirming hormone therapy for two and a half years, in maintenance for a year and a half with estradiol valerate 6 mg, aldactone 200 mg and blister of estradiol 6 mg and 1.2 mg. She denied previous hair treatments other than topical minoxidil 5% for a year. The patient had anxiety and was taking desvenlafaxine 50 mg, and did not intend to perform other facial surgical procedures. She presented a hairline 7 cm distant from the diagonal to the angle and 7 cm from the anterior line to the glabella. She started clinical treatment with finasteride 2.5 mg/day, minoxidil 2 mg/day, and topical minoxidil 5%. After three months and having verified the stability of the condition and adherence to therapy without adverse events, we performed hair transplantation using the Follicular Unit Transplantation (FUT) technique to reduce the previous line, with 1,551 follicular units, totaling 2,896 hairs, with follow-up on the first day of postoperatively (Figure 1), one month, three months, five months, ten months, and one year after surgery (Figure 2).

A 37-year-old transgender woman with androgenetic alopecia, who already used dutasteride 0.5 mg and minoxidil lotion for seven months and had no intention of gender-affirming hormonal therapy, sought our Service. She presented an excellent donor area with follicular units with three hairs, good density, and a distance from the recess to the mid-pupillary line of 6.5 cm (Figure 3). We performed hair transplantation using the Follicular Unit Extraction (FUE) technique in the bitemporal region, maintaining the previous line. The design was 5 cm of bitemporal recess x 8.5 cm of anterior line x 8.5 cm from the glabella to the anterior line, and 1,750 follicular units were used, totaling 3,764 hairs (Figure 4). Follow-up took place on the first postoperative day, 15 days, three months, and six months after surgery (Figure 5) with excellent results.

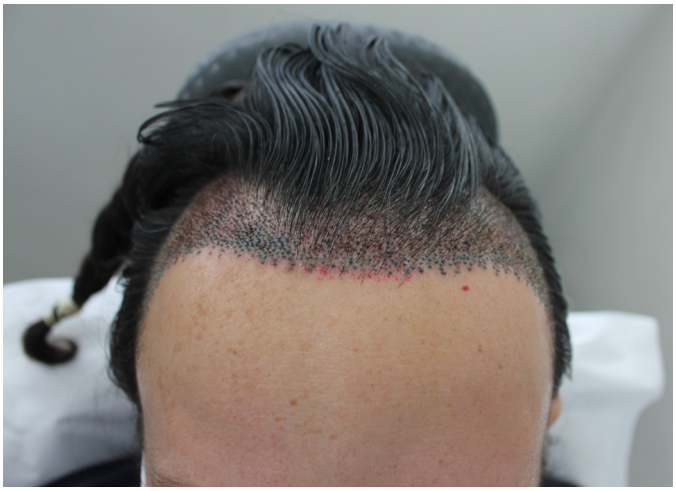
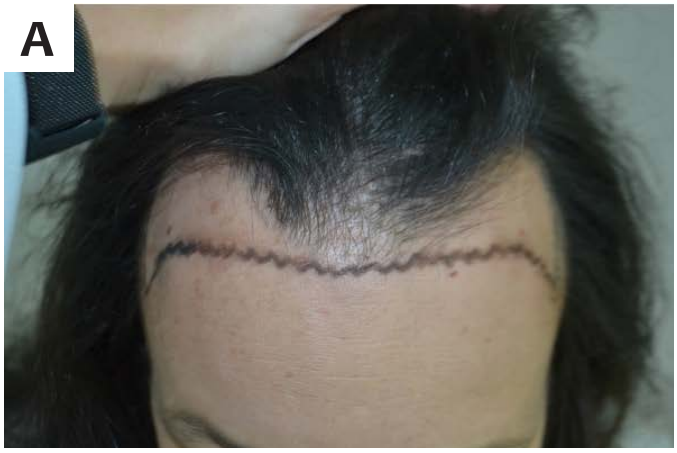


Figure 1: First day after hair transplantation using the Follicular Unit Transplantation (FUT) technique



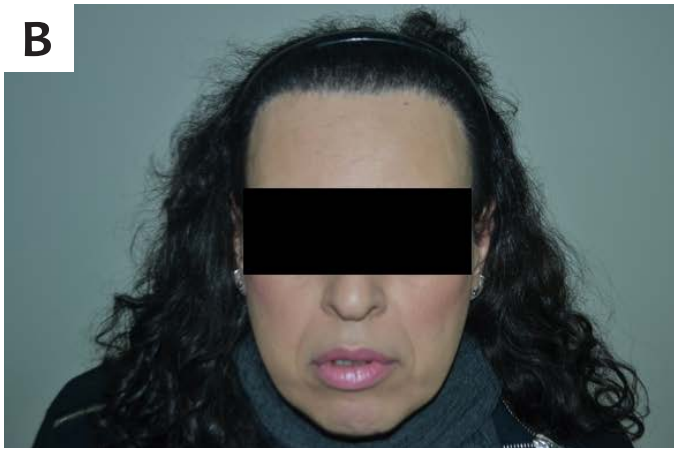


Figure 2: A - Before transplantation; **B -** Final result after one year of hair transplant

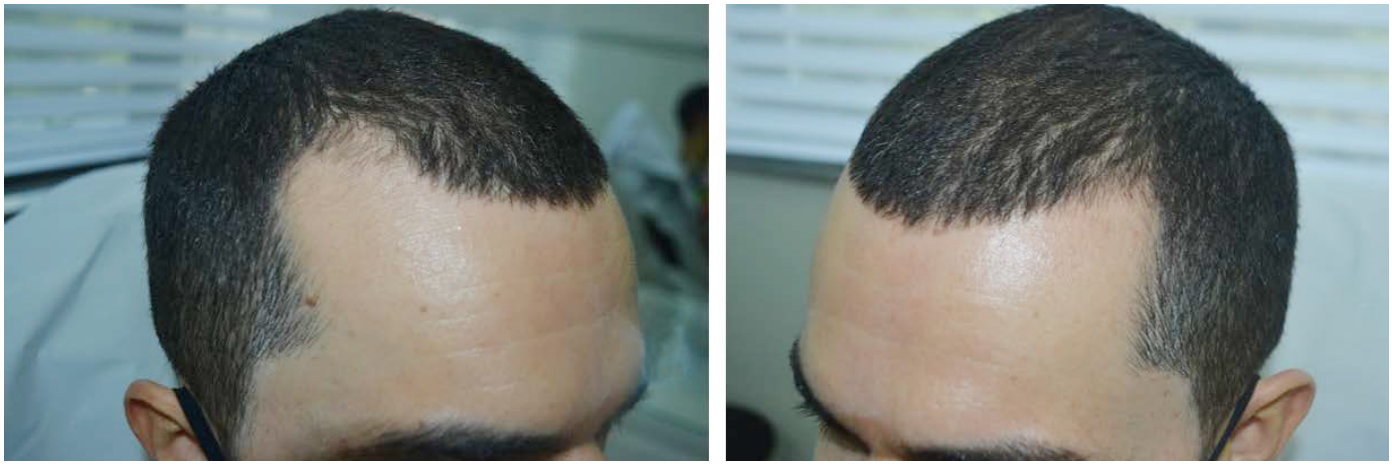


Figure 3: Before hair transplant

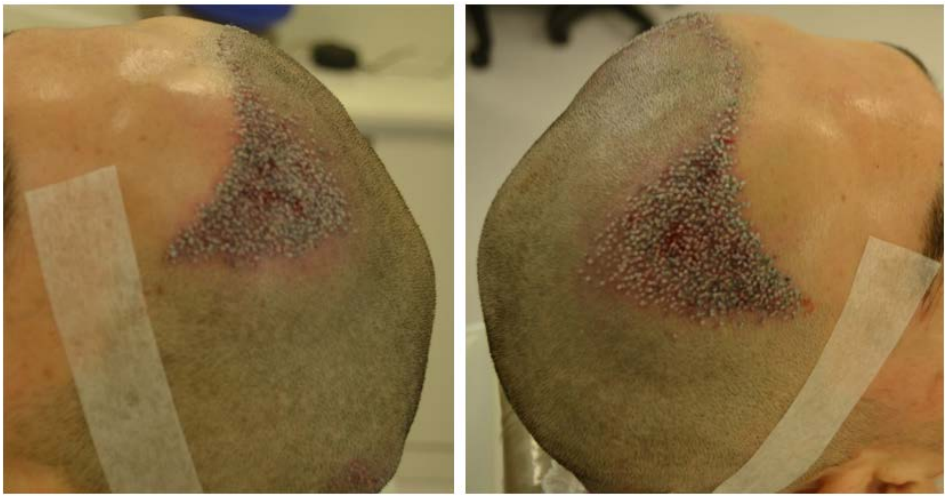


Figure 4: Immediate postoperative period of hair transplantation with the Follicular Unit Extraction (FUE) technique

Figure 5: Result after six months of hair transplant

DISCUSSION

While many transgender people seek medical treatments, such as hormone therapy or plastic surgery, to feel more comfortable in their skin, others are reluctant due to fear, financial reasons, or even bad experiences with prior medical care. Nevertheless, transgender people often undergo hormonal therapy to improve their physical appearance and alleviate gender dysphoria due to the difficulty in both personal and social acceptance, which can lead to social stigma and isolation.

Hormone therapy involves estrogens and/or antiandrogens, such as spironolactone. The role of estrogens in the hair

cycle is still uncertain despite reducing androgen levels.[3] There is evidence of a pro-hair growth effect with an increase in the anagen phase and hair density in pre-menopausal and pregnant women.[4] However, not everyone wants to take gender-affirming hormone therapy.

The recessed anterior hairline design is stigmatized for transgender women, as people see the presence of bitemporal retractions or a more posterior frontal line as a more masculine facial pattern. For those diagnosed with androgenetic alopecia, treatment includes minoxidil antiandrogens and hair transplantation and is influenced by gender-affirming hormonal therapy.[5] There are reports of significant improvement in the pattern of androgenetic alopecia in transgender women with hormonal therapy with estrogen and spironolactone.[6] However, studies also show an inhibitory effect on hair growth.[7] Hair transplantation is an option for those who want a more feminine hair implantation line.

Transgender women seek hair transplantation due to the feminization of the face: the hairline is lower and rounded on the forehead, compared to the M or undefined shape in men, and because it is a less aggressive option than facial feminization surgery. *Capitán et al*. recommend hair transplantation in patients with type II hair implantation lines, i.e., with bitemporal recess and good hair density and without active androgenetic alopecia. Type III patients have an indication for the hairline lowering procedure (reduction of the anterior line), which removes a strip of skin from the forehead, with an advancement of 1-2 cm.[2]

In patients with short hair, the FUE technique is selected, while in long hair with good skin elasticity, the FUT technique is chosen, or even FUE without shaving the hair or FUE in windows. The doctor in agreement with the patient decides on the technique. Although hair transplantation is a popular option for patients suffering from androgenetic alopecia, few studies specifically address the results and effectiveness of the procedure in transgender patients as well as the right timing for surgery, i.e., before or after other procedures such as facial feminization and hormone therapy. More studies are needed to identify improvements in the multidisciplinary and multidisciplinary approach to transgender patients, as well as consider the unique needs and characteristics of these patients. ●

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Perianal extramammary Paget's disease: a rare case report and review of the literature

Doença de Paget extramamária perianal: relato de caso raro e revisão da literatura

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ABSTRACT

Extramammary Paget's disease (EMPD) is a rare malignancy and is quite difficult to diagnose. We report a case of a 51-year-old female patient with perianal EMPD. Because experience with this disease is still very limited, we searched international databases for similar publications. After consultation with an oncologist, the treatment was wide excision without adjuvant therapy. This treatment option was curative.

Keywords: Paget Disease, Extramammary; Surgery, Plastic; Anal Gland Neoplasms.

RESUMO

A doença de Paget extramamária (DPEM) é uma doença maligna rara e bastante difícil de ser diagnosticada. Relatamos o caso de uma paciente de 51 anos com DPEM perianal. Como a experiência com esta doença ainda é muito limitada, pesquisamos artigos similares em bases de dados internacionais. Após consulta com oncologista, o tratamento foi excisão ampla sem terapia adjuvante. Essa opção de tratamento foi curativa.

Palavras-chave: *Doença de Paget Extramamária; Cirurgia Plástica; Neoplasias das Glândulas Anais*

Case report

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INTRODUCTION WITH LITERATURE REVIEW

EMPD is an uncommon intraepithelial malignancy reported in the worldwide medical literature.[1] It is considered a form of adenocarcinoma that can invade the dermis and spread via the lymphatic vessels.[2] EMPD was originally described by Darier and Couillaud in 1893. The first cases were reported in the perianal region (Crocke 1889), vulva (Dubreuilh 1901), and axilla (Satani 1920).[3] Regardless of the similar clinical and histopathologic appearances of Paget's disease of the nipple and the anus, mammary Paget's disease is undoubtedly connected with underlying ductal carcinoma, while perianal Paget's disease may or may not be associated with an underlying malignancy (33%-86% of cases).[4] The most common cancers related to EMPD are colorectal and tubo-ovarian.[5] In the literature, a recent large series reported that perianal EMPD was associated with an adnexal adenocarcinoma in 7% of cases and an internal malignancy in 14%.[6] However, in most cases EMPD arises primarily as an intraepidermal neoplasm,[7] characteristically in skin areas rich in apocrine glands, such as the genital region. Because of its rareness and multicentric nature, diagnosis and treatment represent a major challenge. In this context, the aim of this report is to present the case of a 51-year-old woman admitted to our outpatient clinic and summarize the latest evidence about EMPD.

CASE REPORT AND METHODS

A 51-year-old obese woman presented to our outpatient service with pruritus ani as her sole symptom. She was not taking any medications and had no other comorbidities. There was no associated pain or any other gastrointestinal complaints. Clinical examination revealed a white, moist, raised lesion at the 2 o'clock position of the right gluteus, measuring 3.5×2×0.7cm. Rectal examination and proctosigmoidoscopy were negative. There were no palpably enlarged lymph nodes. The patient had been undiagnosed for 1 year. Prior to surgery, dermatoscopy was made by dermatologist in order to marke the border of tumor, which showed pink structureless area with dotted and short linear vessels. After consultation with a dermatologist and oncologist, a wide excision was performed, encompassing the perianal skin together with the anal mucosa up to the level of the dentate line, preserving the internal sphincter. The surgical defect was successfully closed. Histological examination described squamous epithelium containing nests of atypical mucus-producing Paget cells, with large, pale cytoplasm and hyperchromatic nuclei in hyperplastic epidermis, confirming the diagnosis of EMPD. Resection margins were clear, and there was no evidence of other underlying carcinoma, tumor, or distant metastases. The patient was discharged on the same day. A radiation oncologist confirmed there was no need for adjuvant therapy, only regular follow-up every 3 months during the first year. At the time of writing, the patient has remained disease-free for 1 year after surgical treatment. (Figure 1 and 2).

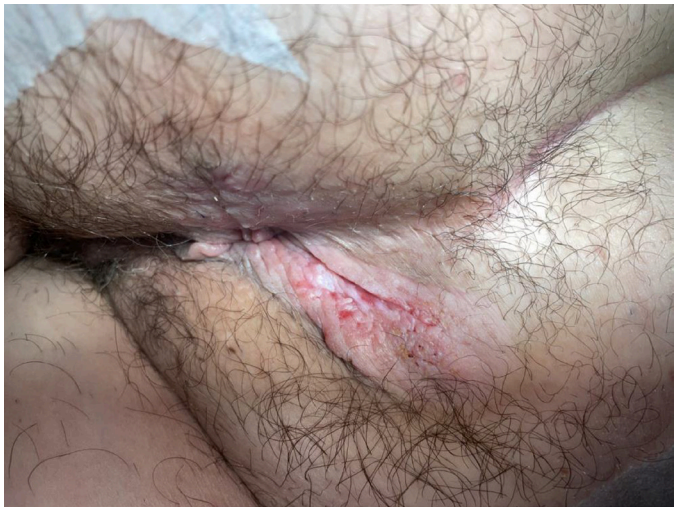

FIGURE 1: Skin lesion in right gluteal region

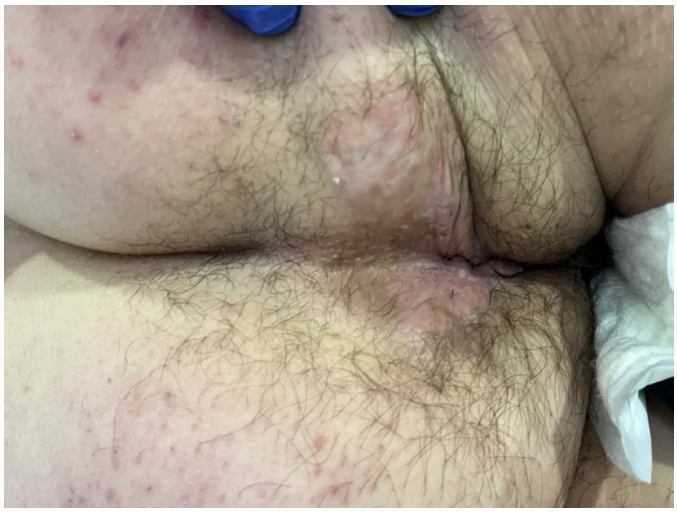

FIGURE 2: Appearance 1 year after surgical treatment, free of tumor

DISCUSSION

We searched major international electronic bibliographic databases for articles related to our topic. The search terms were extramammary Paget's disease and perianal extramammary Paget's disease, excluding other possible locations of extramammary Paget's disease, such as the perineum, vulva, scrotum, and penis. The search was limited to studies published in the English language. In brief, perianal EMPD affects patients between the ages of 50 and 80 years, especially white (Caucasian), peaking at age 65, but the true incidence is difficult to measured due to its rarity.[4,8] Overall, women are more commonly affected (1.4:1 female-to-male ratio). Its pathogenesis is unclear, but most cases are thought to arise as a primary intraepidermal neoplasm of glandular origin.[7,9,10] Clinically, lesions usually present as well-defined, elevated erythematous or white nonhealing plaques, averaging 6-12 cm in diameter, with accompanying irritation and ache.[1,11,12] They may also present as annular or hypopigmented plaques with scales, excoriations, and/

or erosions.[13] Typical presenting symptoms are anal rash and irritation. Anal pain, bleeding, mucoid discharge, lumps, and difficulty defecating may also occur.[14] The most commonly affected sites are vulvar, perineal, perianal, scrotal, and penile skin; rare sites include the thighs, buttocks, axilla, eyelids, and external ear canal. EMPD has also been reported in ovarian teratomas and bronchial epithelium.[15,16,17] The term ectopic EMPD refers to cases affecting areas in which apocrine glands are not usually found, such as the lateral aspect of the back or lower portion of the chest. The differential diagnosis includes many conditions, such as psoriasis, contact dermatitis, fungal infection, lichen sclerosus, histiocytosis, Pagetoid basal cell carcinoma, mycosis fungoides, and hemorrhoids.[18,19] Once a diagnosis of EMPD has been confirmed, the next step is to rule out metastases. In a study by Williams et al., among 7 patients who presented with EMPD, in no one was the correct diagnosis made clinically.[20] When there is a diagnosed underlying malignancy, up to 50% of EMPD cutaneous lesions have already metastasized. In these cases, an average survival is limited to 3 years.[19] Due to that, suitable diagnostic procedures to exclude other underlying carcinomas include: pelvic ultrasound scan, hysteroscopy, laparoscopy, and/or an MRI scan of the pelvis; colonoscopy, sigmoidoscopy, and/or barium enema; cystoscopy and intravenous pyelogram (IVP); mammogram and chest imaging.[21] An ideal modality treatment should offer both minimal tissue destruction and low recurrence rates. This modality must also overcome inconvenient features of EMPD, namely multicentricity and irregular histological margins that extend well beyond the clinically visible lesions. Wide local excision with 2-cm margins or Mohs' micrographic surgery is the favored approach for noninvasive, locally confined disease.[22] Intraoperative frozen sections can be misleading.[23] Furthermore, wide local excision requires four-quadrant biopsies, including grossly normal skin. A study performed at Roswell Park Cancer Institute between 1970 and 1998 concluded that surgery offers a moderate chance of cure in advanced cases; long-term multimodal approaches are still needed.[13] Nevertheless, surgical biopsy is crucial to confirm the right diagnosis.[21] Surgical removal of tumors is considered curative if radical resection with histologically clear margins can be achieved. However, many patients present with advanced primary tumors, so curative surgery is not feasible. Since radical excision usually results in significant tissue loss, the defect frequently needs to be covered with local flaps or skin grafts. When the disease is associated with an underlying anorectal carcinoma, the procedure of choice is abdominoperineal resection with wide excision of the cutaneous lesion.[24] Other treatment methods include radiotherapy, laser therapy, and topical and systemic chemotherapy; photodynamic therapy is most promising among recent options. Besa et al. and Burrows et al. found that radiotherapy might be an treatment modality appropriate for patients with non-invasive EMPD who are not surgical candidates.[26,27] On the other hand, Thirlby showed that radiotherapy alone is not adequate treatment.[23,24,25] In a few cases, only combined chemoradiotherapy was associated with full response on long-term follow-up. Zampogna et al. reported two cases treated with imiquimod cream, which can be used only in a setting of limited primary cutaneous EMPD.[11] Finally, the physician must maintain a high index of suspicion, especially in cases with characteristic lesions unresponsive to conventional dermatologic therapy. In view of the above, treatment of EMPD remains a challenge shared by surgeons, pathologists, and dermatologists. Due to its malignant potential, many studies suggest that EMPD should be grouped with other cutaneous carcinomas. Close follow-up for at least 8 years is mandatory for all patients presenting with this rare disease. Bech et al. suggested a follow-up program which includes at least a complete physical examination, proctosigmoidoscopy, and random biopsy of the perianal region once a year. Colonoscopy should be performed at 2-to-3-yearly intervals.[5]

CONCLUSION

This case report with review of the literature draws attention to a rare condition that should be always kept in the differential diagnosis of perianal disorders. It must be noted that there is usually a delay in establishing the right diagnosis. Treatment and prognosis depend primarily on the presence and type of underlying carcinoma. Therefore, it is crucial to have a group of specialists involved in management, including s dermatologist, surgeon, pathologist, and oncologist. We concluded that, in this case, wide excision was curative. In other, more advanced cases, adjuvant chemo- or radiotherapy would probably be recommended. Adequate evaluation and long-term follow-up are crucial in all patients with EMPD to identify recurrence and potential development of other malignancies.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

All aspects of the work covered in this manuscript have been conducted with the ethical approval of all relevant bodies and such approvals are acknowledged within the manuscript.

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PDO threads for the treatment of abdominal skin laxity: description of the technique

PDO threads for abdominal laxity

Descrição de técnica de aplicação de fios de PDO para tratamento de flacidez cutânea abdominal

Fios de PDO para flacidez abdominal

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ABSTRACT

Polydioxanone (PDO) threads have been used as a non-surgical alternative to treat skin laxity. This article describes the technique of applying mono, twin, and screw PDO threads around the umbilical scar forming a support mesh on the abdominal wall, to pull the skin in this region in the opposite direction to gravity. The authors present the results obtained with the technique one and four months after the procedure, showing the improvement of tissue connection with the repositioning of the abdominal scar and general aesthetic improvement.

Keywords: Scar; Esthetics; Cosmetic Techniques; Skin; Polydioxanone; Methods

RESUMO

A aplicação de fios de polidioxanona (PDO) tem sido utilizada como alternativa não cirúrgica para o tratamento da flacidez cutânea. Este artigo apresenta a descrição da técnica de aplicação de fios de PDO liso, twin e parafuso ao redor da cicatriz umbilical, formando uma malha de sustentação na parede abdominal, a fim de tracionar a pele desta região no sentido oposto ao da gravidade. Os autores apresentam os resultados obtidos com a técnica, um e quatro meses após o procedimento, mostrando a melhora da conexão tecidual, com o reposicionamento da cicatriz abdominal e melhora estética geral.

Palavras-chave: *Cicatriz; Estética; Técnicas Cosméticas; Pele; Polidioxanona; Métodos*

Case Report

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INTRODUCTION

Surgical treatment was the gold standard for many aesthetic aspects of aging for many years. However, the growing demand from patients for aesthetic improvements, with minimal risk and rapid recovery, has encouraged the development of non-surgical rejuvenation techniques.[1] Approximately 10-20% of patients undergoing abdominoplasty suffer local complications, such as seroma, hematoma, infection, necrosis, suture dehiscence, hypertrophic scarring, and asymmetries, and up to 1% of patients suffer systemic complications, such as pulmonary thromboembolism, respiratory depression, and death.[2,3]

Polydioxanone threads (PDO) offer a non-surgical alternative for correcting the umbilical scar descent and stimulating local collagen.[4,5] Polydioxanone is an absorbable synthetic polymer that has low tissue reactivity.[6] The duration in the body is approximately 180 days, but its aesthetic effects last up to two years.[7] The threads are applied using the thread embedding acupuncture (TEA) technique, where the threads are introduced inside a needle, remaining in the superficial subcutaneous tissue after removal of the needle.[8,9]

The surrounding tissue is stimulated as the body absorbs the polydioxanone is absorbed by the body.[4,5,10,11] Histological studies show that, after one month, neocollagenesis is stimulated, with an increase in the number of fibroblasts, myofibroblasts, and blood capillaries. After three months, the collagen fibers become thicker, and there is an improvement in the connection between the dermis and the deep fascia through the strengthening of the connective septa.[7,10] The increased collagen production remains for over a year, even after thread fragmentation.[4,12]

The mechanism of action of PDO threads occurs in several ways, including tissue trauma due to needle insertion; mechanical tension, inducing the myofibroblast differentiation and generating tissue contraction; and chemical stimulus, by generating an inflammatory process by the presence of the implant.[4,13-15]

There are several PDO thread architectures available on the market. The spiculated thread has small barbed spicules, the laser cut 360 degrees around the thread promoting traction and repositioning of the tissues in addition to chemical and mechanical biostimulation, with an elevation of the skin in the anti-gravity direction. Smooth threads can be mono, twin, screw, or twin screw, among others. Twin mono threads are two monofilaments that come out of the same needle, and screw threads are monofilaments twisted inside the needle to increase its diameter and the contact surface with the fabric.

Also, there are several techniques for applying the threads, including parallel, crossed, and V-shaped fan.[14] The crossing of the threads produces a reinforced support mesh, increasing the stimulus of neocollagenesis due to the greater polydioxanone concentration in the treated tissue.

METHODS

We selected a 43-year-old woman with a body mass index (BMI) of 19.9 kg/m^2, two full-term pregnancies, a history of abdominal liposuction 20 years ago, and umbilical hernia correction with complementary flank liposuction two years ago. She had moderate abdominal flaccidity, with dermal-subdermal folding upon movement.

The treatment was concentrated in the upper and central region of the abdomen to promote local collagen stimulation, resulting in traction and aesthetic improvement in the periumbilical area. The authors used mono-twin and screw-type PDO threads (i-THREAD, Hyunday, South Korea) (Figure 1), in a mesh technique, with a distance of 1 cm from each other, forming 5x5 cm squares, as the threads have 5 cm long.

We positioned the patient in the supine position, performed antisepsis on the area to be treated, and applied local anesthesia with topical lidocaine. A vertical line passing through the middle of the umbilical scar and a horizontal line passing over the scar divided the abdominal region. Two lines were then drawn above the umbilical scar, with an interval of 5 cm, and a line 5 cm below the umbilical scar. Two lateral vertical lines to the right of the midline and two to the left were marked at a distance of 5 cm. As a result, we obtained eight 5x5 cm quadrants,

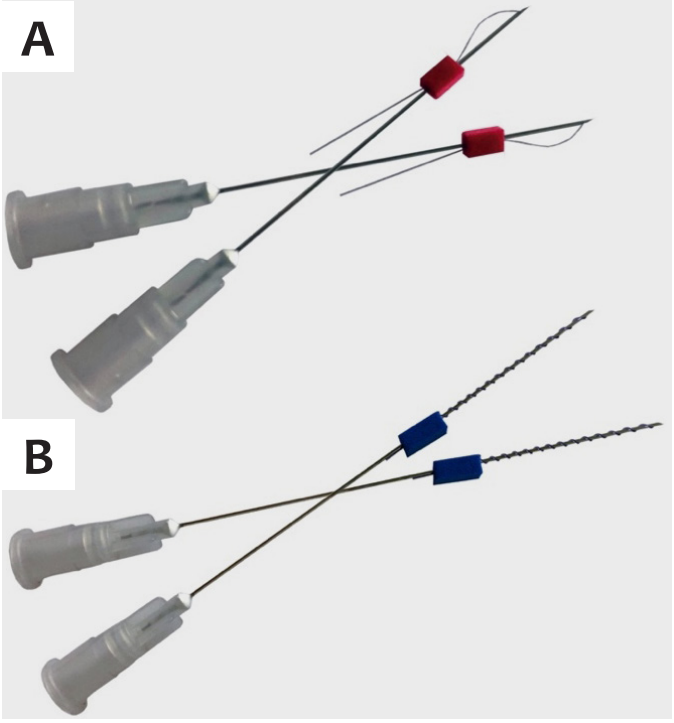

Figure 1: A - Twin mono PDO threads formed by two monofilaments in a single needle. Caliber: 27G; needle: 38 mm; thread length: 50 mm. **B -** PDO screw threads formed by monofilament twisted along the needle. Caliber: 27 G; needle: 38 mm, thread length: 50 mm

which served as the basis for the treatment (Figures 2 and 3). The size of the quadrants is defined according to the size of the needle used to ensure full implantation of the thread and avoid extrusion.

The needles are inserted into the superficial subcutaneous tissue every 1 cm in a crisscross fashion, forming 90º angles, remaining in place until the end of the procedure, when they are removed. Then we introduced 5 cm PDO threads (Figures 2 and 4).

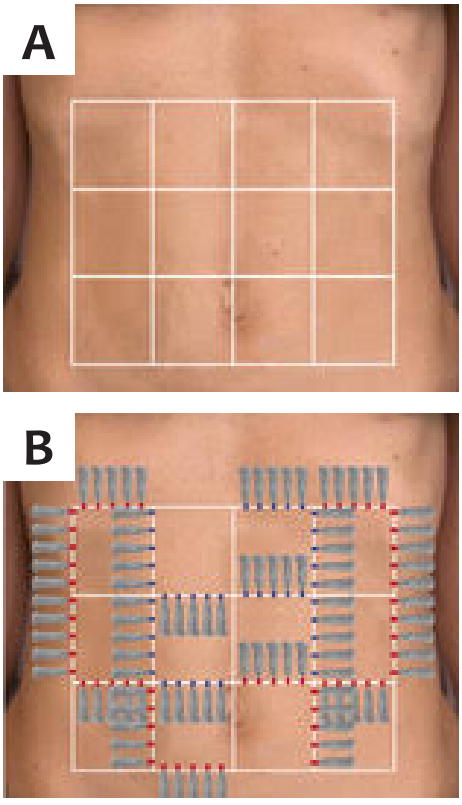

Figure 2: A - Schematic drawing of the mesh technique. 5x5 cm quadrants are designed for the use of 50 mm threads. **B -** Needles are inserted every 1 cm in the horizontal and vertical directions, forming a supportive polydioxanone network in the superficial subcutaneous tissue

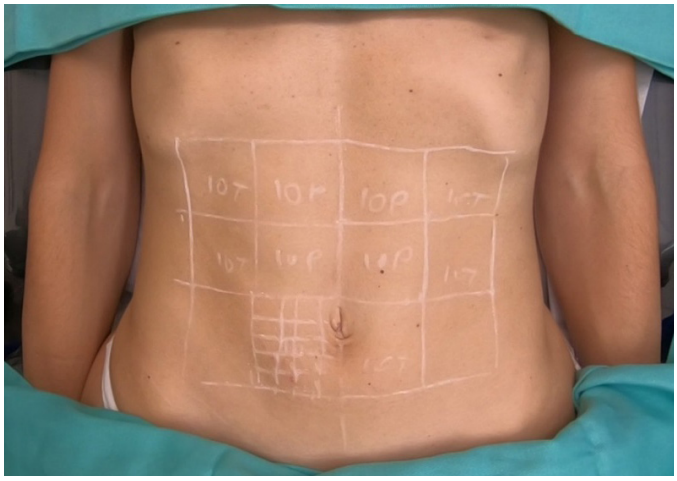

Figure 3: Markings made on the patient before the procedure, as described in Figure 2

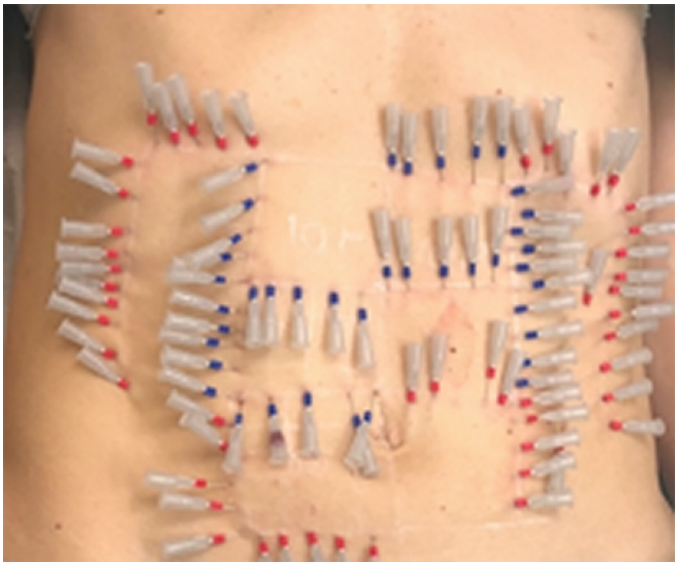

Figure 4: Technique to treat abdominal sagging using 100 PDO threads: 40 screw threads (blue needle barrel) and 60 mono twin threads (red needle barrel). Threads implanted in the superficial subcutaneous tissue

We used 40 screw threads (needle with a blue barrel) to treat the upper-central region of the abdomen, allowing greater collagen stimulation. For the lower-lateral reinforcement, 60 smooth twin threads were used (needle with the red gun).

The needles were removed in a slow, continuous retrograde movement, with compression of the skin with the other hand, minimizing possible bleeding and reducing discomfort. There is no need for bandages, analgesia, or recovery time after the procedure.

RESULTS

We observed significant results after just one session. Figures 5 to 7 show the improvement in sagging after one and four months. Analyzing the photos, a decrease in sagging can be observed when moving and twisting the trunk and the umbilical scar repositioning. The patient had a quick recovery period with an immediate return to usual activities. No complications arose from the procedure. The discomfort reported by the patient was minimal, lasting 48 hours. There was no asymmetry, hematoma, or skin folding.

DISCUSSION

Tissue retraction depends on the endogenous neocollagenesis process and occurs progressively over the subsequent months due to improved dermal-subdermal anchorage.[4,5,7,9-11] The quantity and architecture of PDO threads influence the result as they determine the biostimulation capacity of the thread and its ability to act as a solid filler. The twin or screw thread

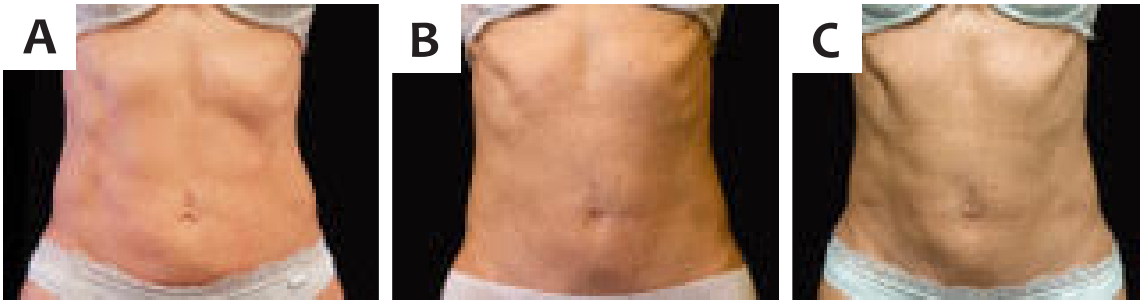

Figure 5: Frontal image of the abdomen in extension. **A -** Before the procedure. **B -** One month after the procedure. **C -** Four months after the procedure: improvement in sagging and tissue contraction with reduced skin folding and repositioning of the umbilical scar

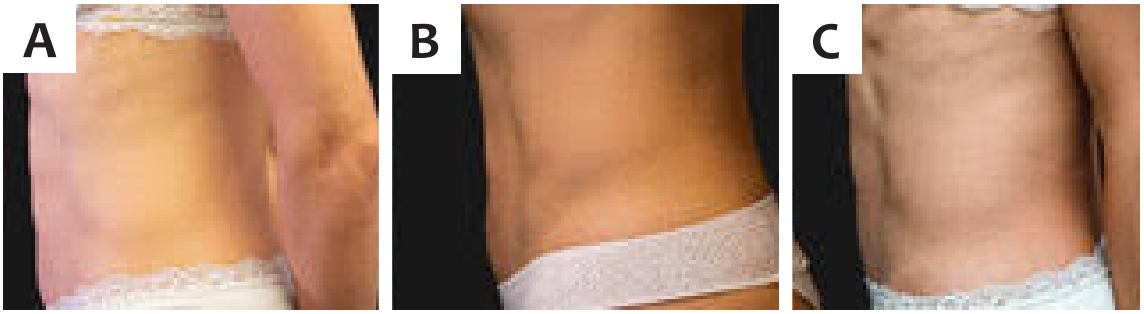

Figure 6: Lateral image of the abdomen in extension. **A -** Before the procedure. **B -** One month after the procedure. **C -** Four months after the procedure: improvement in sagging and tissue contraction with reduced skin folding

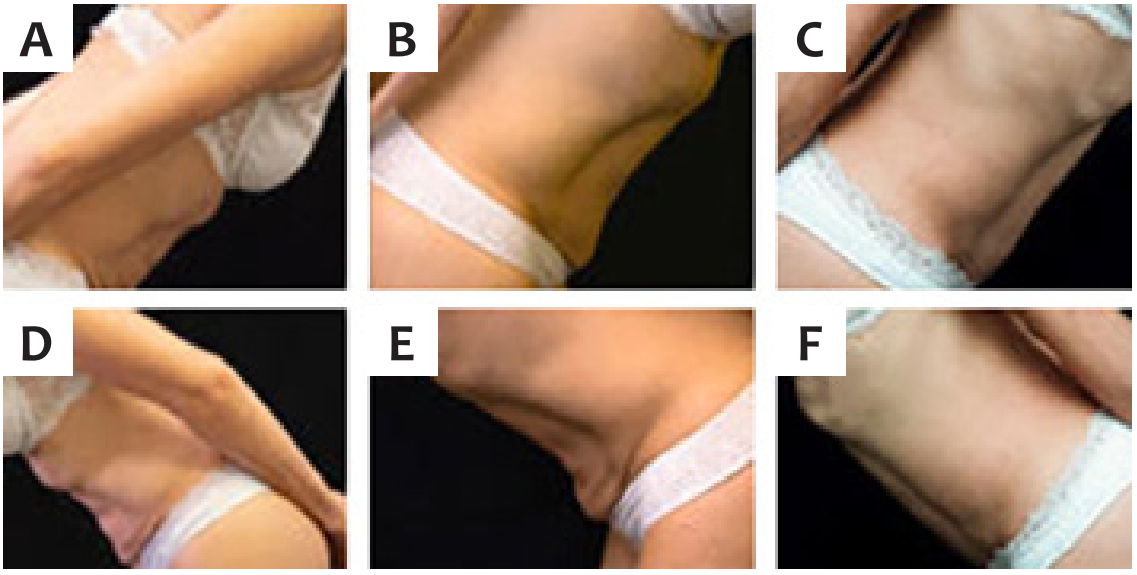

Figure 7: A, B, C, and D - Right and left lateral images of the abdomen in flexion **(A, D)** before the procedure; **(B, D)** one month after the procedure; and **(C, F)** four months after the procedure: improvement in sagging and tissue contraction with reduced skin folding

increases the support and stimulation of the connective tissue, generating an effect similar to a solid filler.

The selection of the patient was based on the analysis of the body constitution and the presence of abdominal skin flaccidity. The correct indication of the procedure is necessary to achieve a good clinical response. Patients with a BMI greater than 25 kg/m^2, with ventral hernias or large abdominal diastasis, are not candidates for treatment with PDO threads. The best

indication for these cases remains abdominal dermolipectomy, whether or not associated with complementary liposuction.[3]

The implantation of PDO threads is a safe medical procedure.[16] PDO threads are absorbable, and their biochemical behavior has been known for over 30 years,[6,17] with application in several body areas.

CONCLUSION

Patients' growing desire for rejuvenation procedures with minimal risk and rapid recovery has led to improved non-surgical technologies. The implantation of PDO threads is a procedure of little technical difficulty and an effective non-surgical alternative to treat abdominal sagging. Its safety and effectiveness depend primarily on the correct indication and precision of planning and marking. It is essential to point out to the patient that the procedure aims to treat sagging skin and not localized fat. ●

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CO2 laser treatment for vulvar syringoma: a case report

Técnica terapêutica com laser de CO2 em siringoma vulvar: relato de caso

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ABSTRACT

Syringoma is a rare benign adnexal tumor of the intraepidermal eccrine duct of unknown etiology. It is typically characterized by multiple, bilateral, yellow-brownish or skin-colored papules measuring 1-5 mm. Syringomas predominantly affect the face but can also be found in gluteal, pubic, vulvar, or thoracic regions. In this article, we report two cases of vulvar papules with a confirmed diagnosis of syringoma by histopathological analysis, which were successfully treated with carbon dioxide (CO_2) laser therapy. The selected treatment approach was easy to implement and resulted in a favorable clinical response, including improvement of itching after the first session.

Keywords: Syringoma; Vulvar Diseases; Pruritus Vulvae; Adenoma; Sweat Gland; Lasers

RESUMO

O siringoma é um tumor benigno raro do ducto sudoríparo écrino intraepidérmico, sem etiologia definida, caracterizado por pápulas geralmente múltiplas, bilaterais e amarelo-acastanhadas ou cor da pele, de 1-5mm. A face é a área mais acometida, mas também é encontrado em tórax, regiões glútea, pubiana ou vulvar. Nesse trabalho, foram acompanhadas duas pacientes com lesões papulosas em vulva, com diagnóstico histopatológico de siringoma, que apresentaram boa resposta ao tratamento com laser de dióxido de carbono (CO_2). O tratamento escolhido foi fácil de implementar e demonstrou boa resposta clínica, incluindo melhora do prurido já após a primeira sessão.

Palavras-Chaves: *Siringoma; Doenças da vulva; Prurido vulvar; Adenoma de glândula sudorípara; Lasers*

Case report

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INTRODUCTION

Syringoma is a rare benign adnexal tumor of the intraepidermal eccrine duct (adenoma). It is characterized by multiple yellow, brown, or skin-toned papules measuring from 1 to 5 mm. The lesions are typically bilateral and symmetrical, but sometimes may be isolated. Syringomas are usually asymptomatic but may be associated with itching.[1-4] Although they are more likely to affect white-skinned women during puberty and tend to occur sporadically,[5,6] there are familial forms with autosomal dominant inheritance affecting both sexes equally and which seem to represent a form of mosaicism.[7-9]

The most commonly affected area is the face, particularly the eyelids and periorbital region, but the chest, neck, buttocks, pubic region, and vulva can also be affected. Vulvar syringoma should be included in the differential diagnosis of vulvar itching.[1,2,10]

Clinical diagnosis is challenging, as syringomas can be mistaken for different dermatitis or allergies. Thus, a definitive diagnosis should be obtained by histopathological analysis.[13] Hematoxylin and eosin-stained sections show multiple small channels and epithelial cords consisting of a double layer of flat cuboidal cells within a fibrous stroma, usually without atypia.[12]

Several therapeutic techniques have been described, such as excision,[13,14] electrocautery and electrodesiccation,[15,16] oral isotretinoin, topical retinoic acid,[13] laser application,[4,17-19] and techniques combining trichloroacetic acid and carbon dioxide (CO_2) laser.[20,21] However, none of these treatments eliminate the risk of syringoma recurrence, often making treatment frustrating.[20]

Lasers have been used to treat several types of skin tumors, such as warts, sebaceous adenomas, and superficial basal cell carcinomas.[15] The energy generated is absorbed by water, resulting in minimal heat conduction and thermal damage to adjacent tissue, allowing for more precision with minimal damage to healthy tissue and little scar formation.[20]

In this context, we report two rare cases of vulvar syringoma treated with CO_2 laser, a method that, due to its advantages, should be more widely disseminated and used.

CASE REPORT

Case 1

A 56-year-old woman who had undergone menopause 3 years earlier complained of intense vulvar itching, especially after showering, with no improvement after treatment with dexamethasone. Recent pap smear and mammography results were normal. Physical examination revealed multiple yellow-brown periocular papules, a hypochromic and scaly plaque on the upper portion of the right inner thigh suggestive of fungal infection, and multiple bilateral yellow-brown papules measuring 1 mm on the labia majora suggestive of syringoma. There was also a clean-based ulcer on the right labium majus measuring approximately 0.5 cm (Figure 1).

The fungal infection was treated with oral ketoconazole.

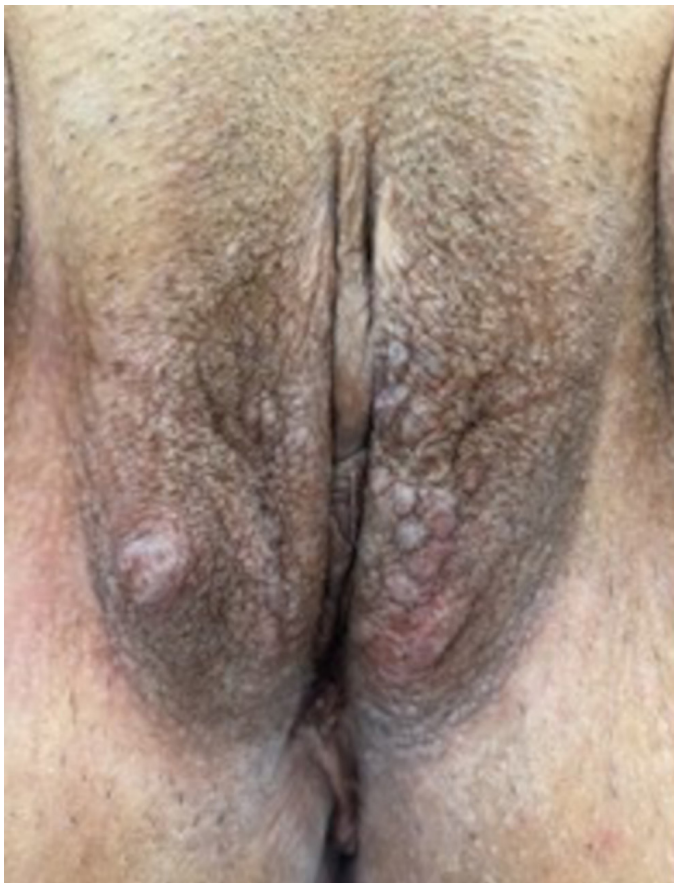

FIGURE 1: First patient before treatment

Pathological examination of a biopsy of a papule on the left labium majus confirmed the diagnosis of syringoma. Treatment with CO_2 laser vaporization was performed. The Smartxide device (Deka, Florence, Italy) was used in continuous mode, at a power of 12 W.

In the first laser session, surgical excision of the ulcer and vaporization of the lesions on the left labium majus were performed (Figure 2). At 15-day follow-up, the patient reported significant improvement in general itching but still complained of symptoms on the right labium majus. A second laser session was performed to treat the remaining lesions. Fifteen days after the second session (Figure 3, first patient 30 days after the first session), the patient reported localized hypopigmentation and mild itching but significant overall improvement. The patient was discharged and instructed to continue treatment for facial lesions on the Dermatology department.

Case 2

A 46-year-old hypertensive woman, living with HIV since 1998, presented with vulvar itching since September 2020.

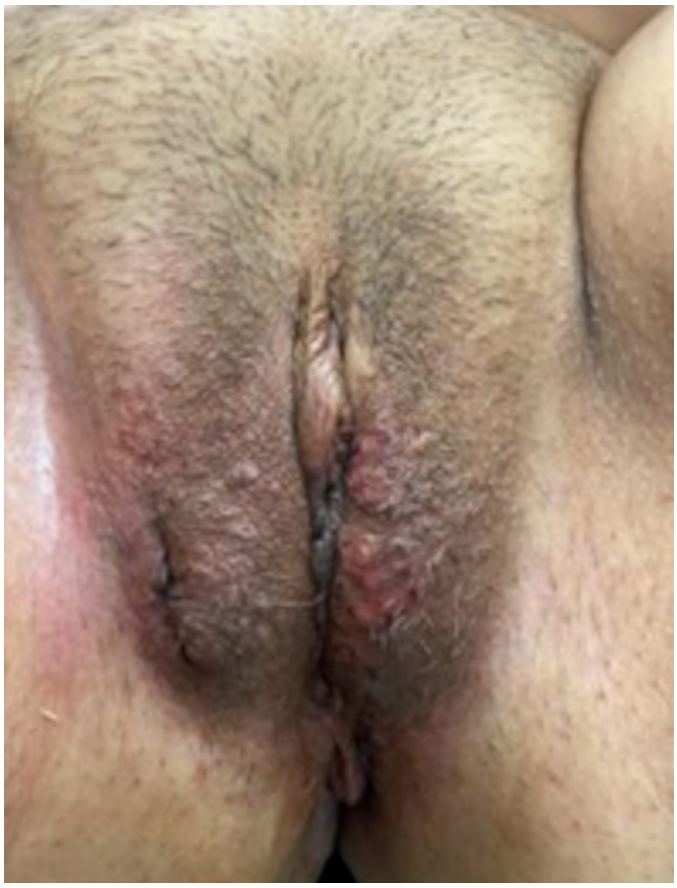

Figure 2: First patient immediately after the first CO2 laser session

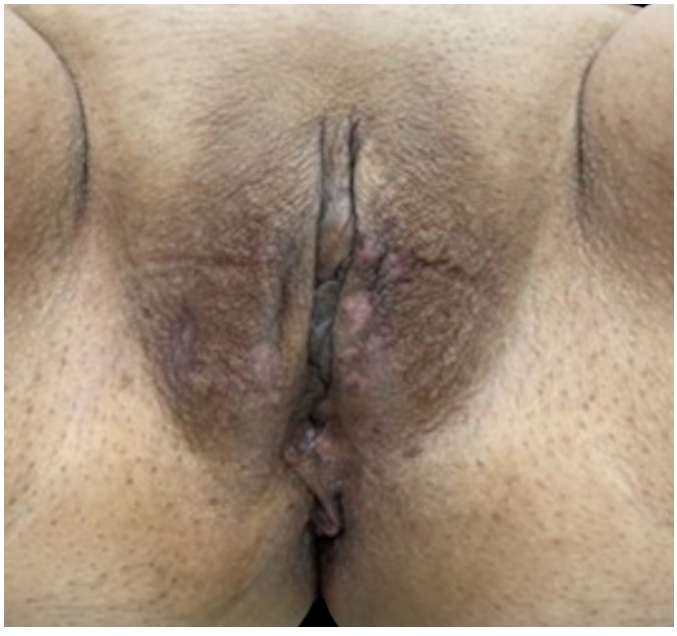

Figure 3: First patient after treatment

She was clinically diagnosed with lichen sclerosus, and histopathology confirmed the diagnosis of vulvar syringoma (the biopsy was performed in December 2019). Initially, topical treatment with 0.1% mometasone furoate ointment and clinical monitoring were prescribed. The patient returned 30 days after the start of treatment with worsening itching. Physical examination revealed a hypochromic plaque on the labia majora and a small hypochromic area in the left perianal region, forming an "8" shape. Multiple syringomas were identified (Figure 4). Treatment with CO_2 laser was performed.

Local anesthetic infiltration with 2% lidocaine with adrenaline was administered, followed by vaporization of the papules using the same device parameters as in the other case. At 30-day follow-up (Figure 5), the patient reported postoperative burning during urination and persistent itching. A second laser session was conducted to treat the remaining lesions at the same visit (Figure 6). There were no complications. The patient returned without complaints, with improved itching.

DISCUSSION

Syringomas are adenomas of sweat glands that affect several locations, most commonly the face. Lesions in the vulvar region are rare.[1-3,17] They are typically asymptomatic and identified during routine examination.[17,22,23] In the cases described in

Figure 4: Second patient before treatment

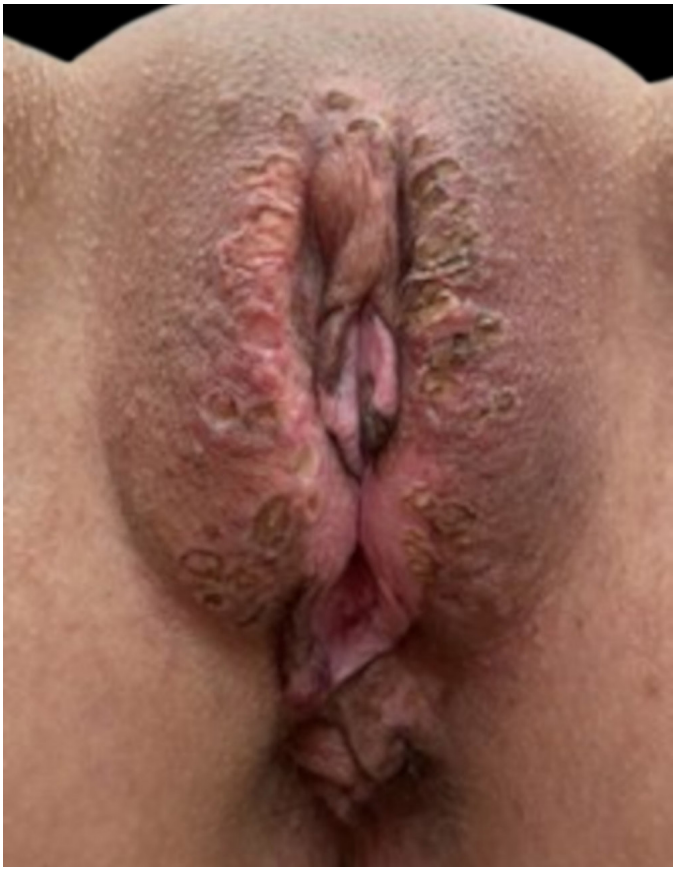

Figure 5: Second patient 30 after the first laser session

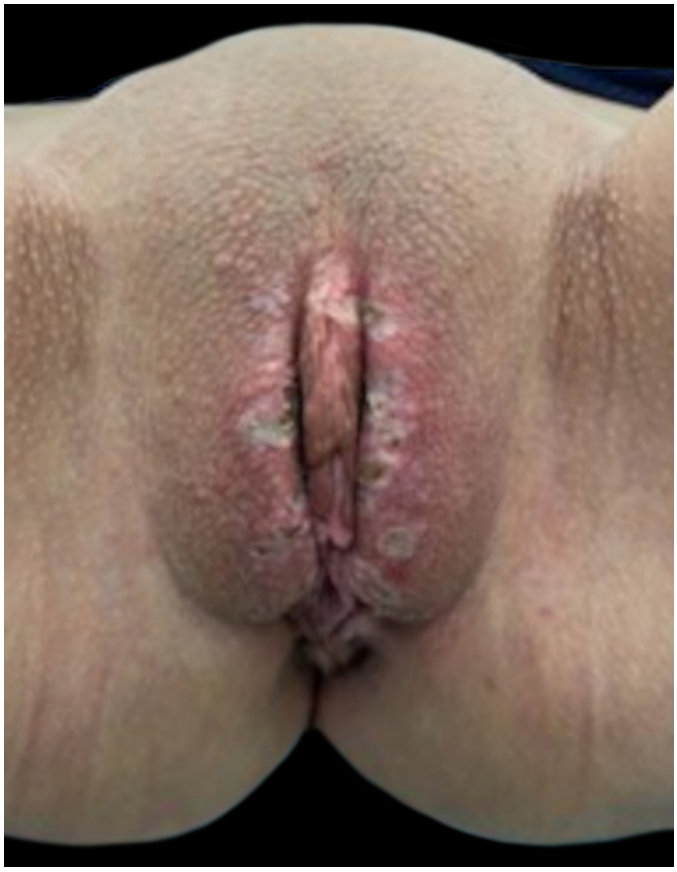

Figure 6: Second patient immediately after the second laser session

this report, both patients had vulvar lesions, and one also presented facial lesions. Intense itching was the main complaint that made them seek medical care. Treatment is usually indicated for aesthetic reasons, especially in visible areas, as these are benign, nonprogressive, and usually asymptomatic lesions.[19,20,24]

Although these lesions typically develop during puberty,[5,6] our patients were diagnosed in adulthood, and one of them was already post-menopausal.

Syringomas pose a diagnostic challenge for gynecologists and dermatologists and should be considered in the differential diagnosis of vulvar papular lesions, itching, and vulvar pain; histopathological diagnosis is essential.[16,22] Syringomas can be associated with other causes of vulvar itching, such as lichen.

Medical treatment is little effective, often requiring some form of surgical intervention.[22,25] Surgery is commonly associated with hyperpigmentation, scar formation, and recurrence[17,19]; however, lasers provide better aesthetic results,[20] as seen in these cases, with only slight hypopigmentation in one patient.

Lasers are a more costly method compared with others[15] and are unavailable in many public services in Brazil. However, laser therapy has the advantage of being performed in an outpatient setting, with only local anesthesia, and requiring a few sessions. The availability of the equipment at our service allowed and facilitated early treatment.

CONCLUSION

There are several treatments for syringoma, including topical medications, surgery, and lasers, but few studies report the use of lasers on the vulva and postoperative follow-up results. In this study, CO_2 laser vaporization was a good treatment option due to its ease of execution in an outpatient setting, patient satisfaction regarding aesthetic results, itching improvement, and no need for multiple sessions. Patients had good pain tolerance even though the procedure was performed only with local anesthesia, and there were no severe complications resulting from the treatment. ●

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Treatment of a rare case of nodular cutaneous amyloidosis in the nose: a case report

Tratamento de raro caso de amiloidose cutânea nodular no nariz: um relato de caso

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ABSTRACT

Although primary cutaneous amyloidosis (PCA) is prevalent worldwide, it is underdiagnosed. Among the subtypes, nodular amyloidosis (NA) is the rarest. There is no consensus in the literature; treatment is challenging, and no therapy has been proven effective. The authors report the case of a patient with a nodule in the nose, whose anatomopathological examination was compatible with amyloidosis, with no evidence of systemic disease. It was then classified as nodular PCA. The lesion was excised satisfactorily. It was concluded that surgical removal is an effective therapy for the treatment of NA.

Keywords: Amyloidosis; Amyloid; Congo Red

RESUMO

A amiloidose cutânea primária (ACP) tem prevalência mundial, entretanto é subdiagnosticada. Dentre os subtipos, a amiloidose nodular (AN) é o mais raro. Seu tratamento é desafiador, não há consenso na literatura e nenhuma terapêutica mostrou-se efetiva. Os autores relatam o caso de um paciente com nodulação no nariz, apresentando exame anatomopatológico compatível com amiloidose, sem evidências de doença sistêmica, classificado, então, como ACP nodular. Foi realizada excisão da lesão, com resultado satisfatório. Concluiu-se que a remoção cirúrgica é uma terapêutica eficaz para o tratamento de AN.

Palavras-chave: *Amiloidose; Amiloide; Vermelho Congo*

Case Report

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INTRODUCTION

Amyloidosis is a heterogeneous group of conditions characterized by extracellular deposition of amyloid material.[1] In the primary cutaneous form, deposition is restricted to the skin, with no systemic repercussions.[2] Nodular primary cutaneous amyloidosis (PCA) or nodular amyloidosis (NA) is the rarest form, with few cases reported in recent years; it has particular characteristics, as up to 7% of cases can progress to systemic amyloidosis.[1] There is still no effective treatment for removing amyloid deposits, but there is a wide range of therapies to improve aesthetics. Not all treatments, however, are effective.[1]

CASE REPORT

A 32-year-old male patient referred to the Dermatology Department complaining of an eight-month-old single lesion on his nose, initially a papule, which grew slowly and progressively. He denied any local symptoms and reported only aesthetic discomfort.

He reported sporadic smoking and alcohol consumption, tension headaches, and was taking sertraline 50mg/day. No family history was reported.

Dermatological examination revealed an erythematous nodule measuring approximately 3 × 2cm, with a fibroelastic consistency, in the transition between the dorsum of the nose and the right nasal wall (Figure 1).

Diagnostic hypotheses of cutaneous lymphocytoma, dermatofibrosarcoma protuberans, nodular cutaneous amyloidosis, and facial granuloma were initially considered. A biopsy of the lesion was requested for anatomopathological analysis.

Histopathology revealed a deposit of amorphous and hyaline material in the reticular, perivascular, and perianexial dermis, which turned reddish when stained with Congo red and greenish under polarized light, thus characterizing amyloid material (Figures 2 and 3).

Screening for systemic disease with imaging tests (computed tomography of the skull, chest, and abdomen) and laboratory tests (blood count, complement system, serum, and urine protein electrophoresis) were performed, with no alterations, and the diagnosis of nodular PCA was confirmed.

The patient's wishes were met with an explanation of the available and possible therapeutic options. We decided to perform surgical excision of the lesion, with subsequent skin grafting, using a graft from the suprascapular region. A satisfactory aesthetic result was achieved and the patient has had no signs of recurrence for a year (Figure 4).

DISCUSSION

Amyloidosis can be divided into primary and secondary, systemic or localized, based on historical classification.[7] Although cutaneous amyloidosis is prevalent worldwide, it is

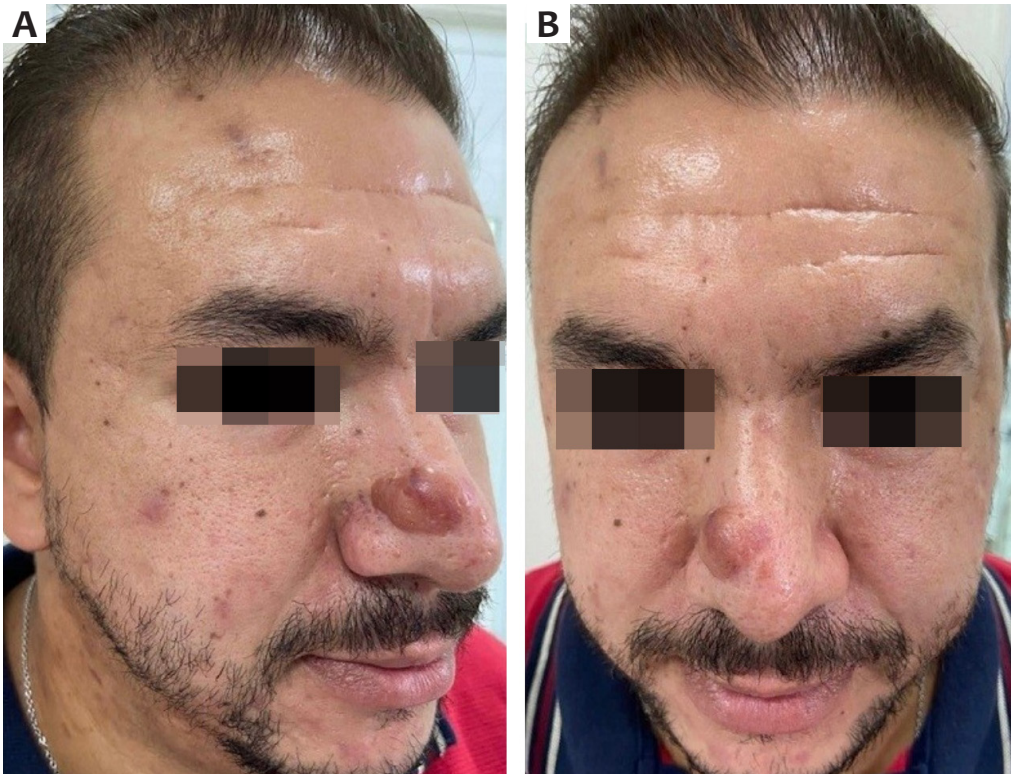

FIGURE 1: (**A** and **B**) - Cutaneous amyloidosis lesion in the right nasal ala, preoperative treatment

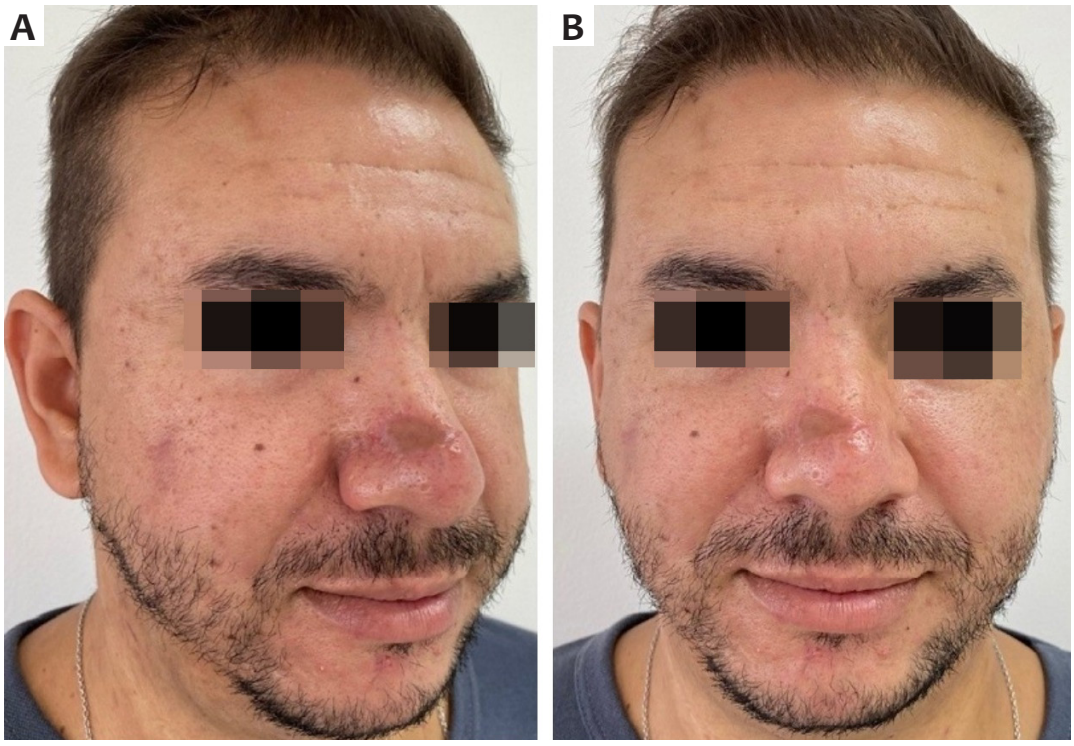

Figure 2: (**A** and **B**) - Lesion after surgical treatment with skin graft

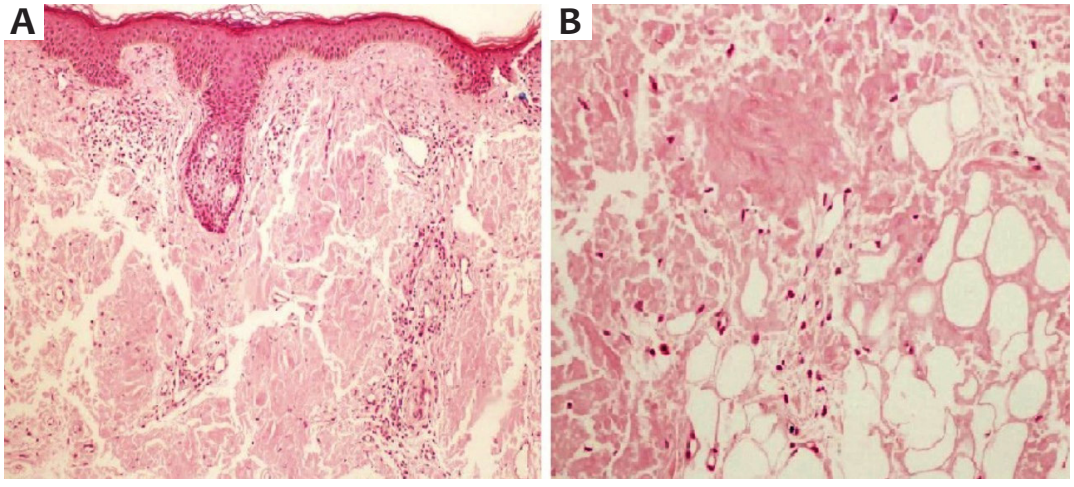

Figure 3: A - Hematoxylin & eosin anatomopathology, 10x magnification, showing amorphous and hyaline material in the reticular, perianexial and perivascular dermis. **B -** Hematoxylin & eosin, 40x magnification

still underdiagnosed. It is not associated with systemic diseases. It occurs due to abnormal extracellular protein deposition in the dermis by aggregation, polymerization, and formation of fibrils. These are deposited, becoming insoluble and resistant to proteolysis.[5] The pathogenesis is still unknown, but it is attributed to the death of keratinocytes as a result of a preexisting dermatosis.[5]

PCA is subdivided into macular, lichen amyloid, nodular, and biphasic. The nodular form is the rarest and its pathology differs from the others in that the amyloid material stems from the deposition of light chain immunoglobulin produced locally by monoclonal plasma cells, and not from degenerated keratinocytes.[4,5] These deposits are not restricted to the dermis, but also include vessels and appendages.[8] Histopathology shows deposits of amorphous and eosinophilic material in the superficial dermis and around vessels and appendages, stained with Congo red. Under polarized light, these deposits show a birefringent green color.[2]

Clinically, NA presents as single or multiple nodules, pre-

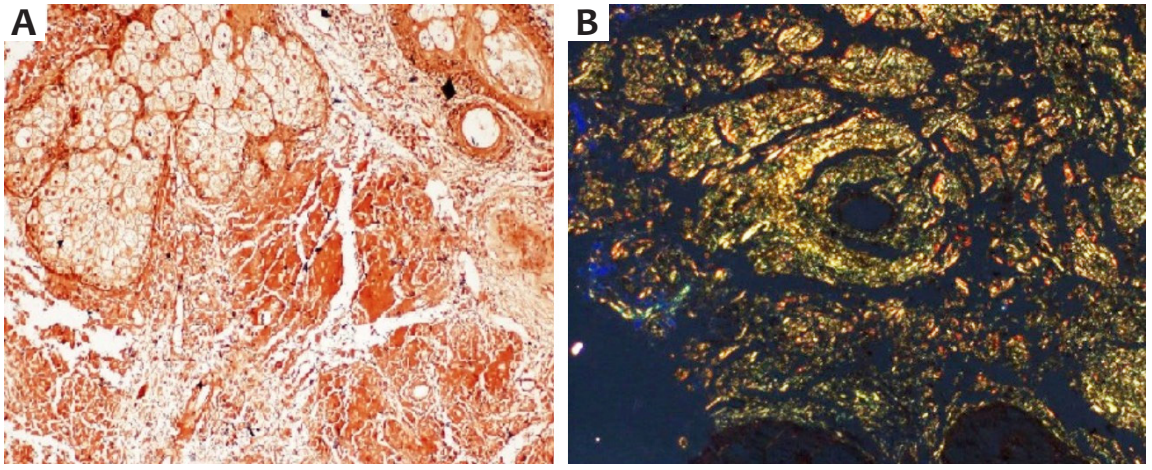

FIGURE 4:
A - Amyloid material stained with Congo red.
B - Amyloid material with birefringence under polarized light

dominantly on the face, extremities, and scalp.[7] It grows insidiously and is sometimes asymptomatic, which can lead to late diagnosis or underdiagnosis. However, regular follow-up is extremely important given the 7% risk of progression to systemic amyloidosis.[5,7,8] Furthermore, the possible association with systemic sclerosis and Sjogren's syndrome is well established in the literature.[8]

Various therapeutic options have been described in the literature, but none have proven to be effective in completely removing the amyloid material or preventing the progression of the deposits, which leads to a common local recurrence.[1,9,3] Some therapies have been responsible for accelerating or deepening these deposits.[3] Well-established options include the use of occlusive or intralesional topical corticosteroids, although some studies have associated these drugs with the acceleration of deposits, dermabrasion, surgical excision, and technologies such as the CO2 laser.[3,7,9]

This report aimed to portray a case of NA effectively treated with surgical excision, corroborating it as a good option for treatment, both in terms of aesthetic appearance and easy accessibility. However, more studies with robust evidence are needed to establish therapies and protocols.

CONCLUSION

Given that it can present as an insidious and asymptomatic lesion, the diagnosis of NA can be delayed or even missed, thus leading to underdiagnoses. However, due to the importance of its association with systemic diseases and the possibility of progression to systemic amyloidosis, NA should be part of the dermatologist's diagnostic scope for nodular lesions. Once the diagnosis has been established, the patient should be followed up regularly. Treatment will depend on the patient's complaint or request, always in agreement with their doctor about accessible and available therapies, considering possible recurrence. ●

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Hypersensitivity reaction to hyaluronic acid dermal filler concomitant with coronavirus infection - case report

Reação de hipersensibilidade ao preenchimento com ácido hialurônico, concomitante a infecção pelo coronavírus - relato de caso

Case Report

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ABSTRACT
The incidence of hypersensitivity reactions to dermal fillers with hyaluronic acid is between 0.3 and 4.5% being mediated by T lymphocyte. Influenza-like illnesses can trigger immunological reactions at the site of the filler. The authors report a case of a patient who presented a hypersensitivity reaction to the filler concomitant with a SARS-COV-2 infection. With the large-scale growth of procedures with fillers, there has been an increase in allergic reactions, making their identification essential for adequate treatment, minimizing the deleterious consequences to the patient.
Keywords: Hypersensitivity; Hyaluronic Acid; Coronavirus.

RESUMO
A incidência de reações de hipersensibilidade aos preenchedores dérmicos, com ácido hialurônico, está entre 0.3 a 4.5%, mediada por linfócitos T. Doenças semelhantes à gripe podem desencadear reações imunológicas no local do preenchimento. Os autores reportam um caso de uma paciente que apresentou reação de hipersensibilidade ao preenchedor, concomitante à infecção pelo SARS-COV-2. Com o crescimento, em larga escala, dos procedimentos com preenchedores houve um aumento das reações alérgicas, tornando-se essencial a sua identificação, para o tratamento adequado, minimizando as consequências deletérias ao paciente.
Palavras-chave: *Hipersensibilidade; Ácido Hialurônico; Coronavirus.*

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INTRODUCTION

In 2019 there was a 15.7% growth in the number of procedures performed with dermal filler, hyaluronic acid (HA), compared to the previous year. The increase in the number of cases of patients with COVID-19, who presented adverse events resulting from the application of hyaluronic acid, drew the attention of the international scientific community to an alarming trend of the amplification of hypersensitivity reactions [1,2]. Adverse effects of treatments with fillers are often classified into two types, depending on the onset of symptoms. Type 1 hypersensitivity reactions are IgE-mediated, occur minutes to hours after the procedure, and may result in clinical pictures of angioedema and anaphylaxis. Delayed-type hypersensitivity reactions are rare, occurring between 24 hours to weeks or months after the process. These reactions are T-lymphocyte mediated and present clinically with a picture of edema, erythema, and local pain [4].

The exact mechanism of late-onset reactions is not fully understood. However, factors such as infection, filler properties, trauma, injection technique, and influenza-like illnesses contribute to the increased incidence, triggering activation of the immune system against the injected product [5].

CASE REPORT

A 47-year-old woman underwent a procedure with hyaluronic acid (Juvederm Ultra Plus XC with lidocaine - Allergan) to fill the nasolabial fold. We perform the approach using a 27G 1/2 needle without any intercurrence. After 24 hours, the patient started presenting intense edema at the application site, mild pruritus, and local pain. Treatment with prednisone 40 mg and loratadine 10 mg was initiated, with regression of the edema a few hours later. On the third day after the procedure, the patient presented flu-like symptoms. The corticosteroid was then suspended due to the hypothesis of coronavirus infection, and the antihistamine was maintained.

The patient performed a self-test, which was positive for COVID-19. The respiratory symptoms were mild, presenting with coryza and cough, which improved after ten days. Loratadine was maintained for seven days. On the 15th day after the filling, the patient was examined, did not presenting anyedema at the site, and was satisfied with the result of the filling in the nasolabial fold. As per the patient's personal history, she had never had a procedure with hyaluronic acid and presented an urticarial picture after the ingestion of contrast in an exam performed three years ago (Figure 1).

DISCUSSION

The exact pathophysiological mechanism of late-type hypersensitivity reactions, which occur after the filling, is not fully understood. However, it is believed that the triggering of these reactions may be related to the pattern of the patient's immune response to an infectious condition, similar to what occurs with the influenza virus, but in this case, SARS-COV-2. This response is initiated by the activation of T lymphocytes via CD44 and mediated by CD4+ cells associated with macrophage memory consolidation.[2,6]

Hyaluronic acid (HA) is a naturally occurring, non-sulfated glycosaminoglycan with a high molecular weight of 4,000 to 20,000,000 daltons. Its structure consists of polyanionic disaccharide units of glucuronic acid and N-acetylglucosamine connected by alternating b1-3 and b1-4 bonds. It is a linear polysaccharide of the extracellular matrix of connective tissue, synovial fluid, embryonic mesenchyme, vitreous humor, skin, and many other organs and tissues. HA has essential immunological functions, acting as the major ligand for CD44, a glycoprotein expressed in mammalian cells involved in lymphocyte recruitment and targeting.[2] HA occupies several roles in cell signaling, depending on its molecular weight. High molecular weight (HMW) HA is known to have anti-inflammatory effects, while low molecular weight (LMW) HA, less than 500 kDa, is pro-inflammatory. LMW HA activates dendritic cells and macrophages, providing stimulatory co-signals to T cells via CD44 cell surface receptors that alter HA production or degradation via synthetases or hyaluronidase, respectively.[3]

Dermal fillers with hyaluronic acid can introduce two types of LMW HA: during product degradation and as cross-linking agents. Beleznay et al. (2015) suggested that systemic inflammatory responses, similar to those occurring in flu-like conditions, may trigger accelerated degradation of the HA dermal filler due to free radical production, resulting in LMW HA fragments lea-

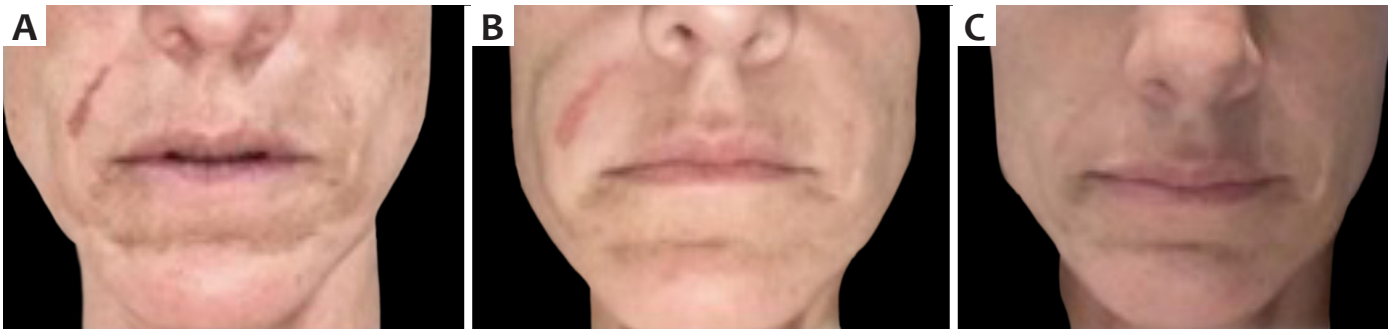

Figura 1: A - 24 hours after the hyaluronic acid injection procedure, edema is observed in the nasolabial fold. B - 3 hours after the hyaluronic acid injection procedure, intense edema at the application site. **C -** 15 days after the procedure

ding to prolonged irregular CD44-HA signaling, thus resembling the pathophysiology described in the reported case.

Another consequence of LMW HA production is the recruitment of lymphocytes to the filling site where there is the highest concentration of HA. Therefore, HA dermal filler is a risk factor in the development of hypersensitivity reactions in the presence of systemic infection, and this is the likely cause of edema in HA dermal filler after SARS-COV2 infection. Without modification, the half-life of HA in tissues is 24-48 hours, making it unsuitable as a dermal filler. Cross-linking agents are used to produce a viscoelastic, stable gel for cosmetic use to overcome this, the exact technology of which often remains undisclosed by dermal filler manufacturers. It is believed that these cross-linking agents can also activate the immune system.[7] Bitterman-Deutsch et al. (2015)[9] report that glycosaminoglycans such as HA can act as a superantigen and directly trigger an immune response, unlike the other theories that suggest the degradation of HA into low molecular weight fragments resulting in molecules with pro-inflammatory activity.

Turkmani et al. (2019)[6] highlight that influenza infection or the use of medications such as antibiotics, non-steroidal anti--inflammatory drugs, and antipyretics, counteracting infectious agents, could instigate delayed hypersensitivity reactions by activation of lymphocytes through CD4+ cells.

Injection of HA fillers causes erythema, edema, bruising, pain, and itching due to disruptions in the vasculature and dermal structures, as well as excessive water retention due to the hydrophilic nature of HA.

A mild inflammatory reaction is normal, characterized by infiltration of resident macrophages and activation of fibroblasts leading to collagen production that anchors the gel to the tissue. These events usually resolve within a few days. However, with the exponential increase in the use of fillers, it has been shown that HA compounds can trigger acute local hypersensitivity reactions early and late, with the overall incidence rate being 0.8%. More recently, the incidence of late-onset nodules using fillers with VYcross technology has been reported, ranging from 0.5% to 4.25%. Rohrich et al. (2007)[3] proposed the most relevant classifications of these hypersensitivity reactions, suggesting that complications should be named as early, late, and delayed (less than 14 days, 14 days to one year, and more than one year, respectively). However, this classification encompasses all types of adverse effects and fillers, and with time, the need for new algorithms emerged. Mikkilineni et al. (2020)[4] proposed a new classification scheme that correlates the timing of the inflammatory process for hyaluronic acid only. During the inflammatory process, neutrophils and monocytes are predominant during the first week. Then, between the first and fourth week, the inflammatory response is mild, and the monocytes differentiate into macrophages that activate and interact with T lymphocytes, most of them CD4+ and, to a lesser extent, CD8+ and B lymphocytes, followed by macrophages that engulf particles of the injected material. Subsequently, macrophage-dependent fibroblast infiltration leads to chronic perpetuation and collagen deposition. Thus, adverse hypersensitivity events can be early (up to one week), intermediate (one week to one month), and late (one month to years).[9,10] Determining the exact cause of the pathophysiology of the SARS-COV-2 virus with the hypersensitivity process requires further investigation. Several hypotheses collectively determine a broad combination of immunoregulatory properties of HA associated with susceptible host genetic background. Other factors, such as depolymerization of high molecular weight fragments to low molecular weight fragments by enzymatic degradation, cause biological effects that induce immune activation in a local microenvironment depending on host genetics in the case.[10]

CONCLUSION

With the increasing use of filler treatments, the incidence of hypersensitivity reactions will consequently increase as well. Recognizing, classifying, and treating hypersensitivity reactions is fundamental, requiring the physician to have an accurate pathophysiological and biochemical understanding of this procedure. Thus, he can identify the patient's predisposition to hypersensitivity reactions by recording the clinical history, preventing and promoting the best prognosis. Improving the infiltration technique and early recognition of complications, as well as mastering the management, are essential for all who perform the procedure, thus reducing the deleterious consequences for the patient. ●

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Pseudoaneurisma de artérias supratrocleares: rara complicação após retalho cutâneo

Supratrochlear artery pseudoaneurysm: A rare complication of skin flap surgery

Case Report

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ABSTRACT
Arterial pseudoaneurysm is a rare complication caused by damage to the arterial wall, resulting in a locally confined hematoma connected to the lumen of the artery. We report the case of a patient on anticoagulants who developed nodules at the surgical wound site after Mohs micrographic surgery for basal cell carcinoma. The initial clinical suspicion was the formation of a simple hematoma. However, Doppler ultrasound examination revealed the presence of pseudoaneurysms in the bilateral supratrochlear arteries. We believe this is the first reported case of supratrochlear artery pseudoaneurysm following dermatologic surgery.
Keywords: Aneurysm, False; Carcinoma; Basal Cell; Ultrasonography, Doppler, Color

RESUMO
O pseudoaneurisma arterial é uma complicação rara causada por dano à parede arterial, resultando em um hematoma localmente confinado conectado ao lúmen da artéria. Relatamos o caso de um paciente em uso de anticoagulantes que desenvolveu nódulos no local da ferida cirúrgica após cirurgia micrográfica para carcinoma basocelular. A suspeita clínica inicial foi a formação de um hematoma simples. No entanto, o exame de ultrassom Doppler revelou a presença de pseudoaneurismas nas artérias supratrocleares bilaterais. Acreditamos que este seja o primeiro caso relatado de pseudoaneurisma da artéria supratroclear após cirurgia dermatológica.
Palavras-chave: *Falso Aneurisma; Carcinoma Basocelular; Ultrassonografia Doppler em Cores*

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INTRODUCTION

Pseudoaneurysms are rare complications caused by damage to the arterial wall resulting in incomplete hemostasis and the formation of a locally confined hematoma. Once a hematoma reaches a certain size, it may not resolve spontaneously, resulting in the formation of a pseudomembrane of coagulation cascade products with turbulent blood flow within.[1] The most common presentation of a pseudoaneurysm occurs in the femoral artery following vascular surgery. However, rarer cases include visceral pseudoaneurysms due to chronic pancreatitis and traumatic pseudoaneurysms of the superficial temporal artery.[1,2] Doppler ultrasound is the gold standard for diagnosis, allowing assessment of size, location, and contact with adjacent structures to guide treatment.[3]

CASE REPORT

An 84-year-old male patient was diagnosed with an infiltrative basal cell carcinoma (BCC) on the nasal dorsum near the glabellar region (Figure 1). He had a history of chronic atrial fibrillation and was on regular apixaban therapy. The patient underwent Mohs micrographic surgery using the Munich method to treat the BCC, resulting in a 2.6-cm surgical defect after tumor removal and a final 6.5-cm surgical defect. Wound was then closed using the glabellar advancement flap technique (Figure 2). There were no complications or abnormal bleeding during surgery or in the immediate postoperative period.

To prevent hemorrhagic complications, anticoagulation was discontinued five days prior to surgery. As there was no bleeding within the first 48 hours postoperatively and the patient needed to resume apixaban, medication was resumed 72 hours after surgery. On the fourth postoperative day, the patient developed extensive facial ecchymosis. Medication was continued, and the patient was closely monitored. Ecchymosis gradually improved, but on postoperative day 10, two erythematous-violaceous nodules appeared, measuring 2.2 cm in the right glabellar region and 2.4 cm in the left glabellar region. The leading diagnostic hypothesis was the formation of a seroma or hematoma, so bilateral puncture and aspiration of the nodule contents was performed by using a 10ml syringe and a 21G needle, draining a total of 10ml of blood. Lesions were reduced in size after surgery and a compressive dressing was applied.

Anticoagulant was therefore discontinued. Patient was re-evaluated 14 days after the procedure and the nodules had increased in size (Figure 3). At that time, he was referred for ultrasound to confirm the diagnosis. A color Doppler ultrasound (Logiq E, GE Medical System CO. LTD.) was performed with a 12 MHz linear multifrequency transducer and showed two hypoechoic nodules in the bilateral frontal region without flow consistent with hematoma (Figure 4).

The right-sided hematoma had a heterogeneous echo texture and measured 2.9 × 1.4 × 2.2 cm. Within this nodu-

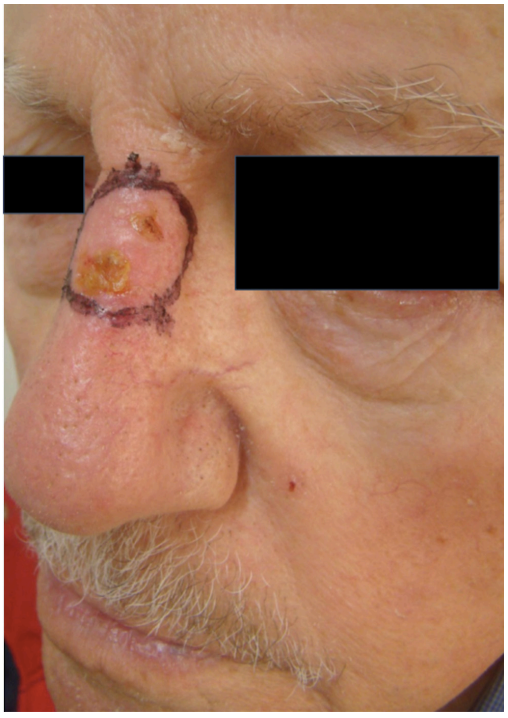

Figure 1: Infiltrative basal cell carcinoma on the nasal dorsum

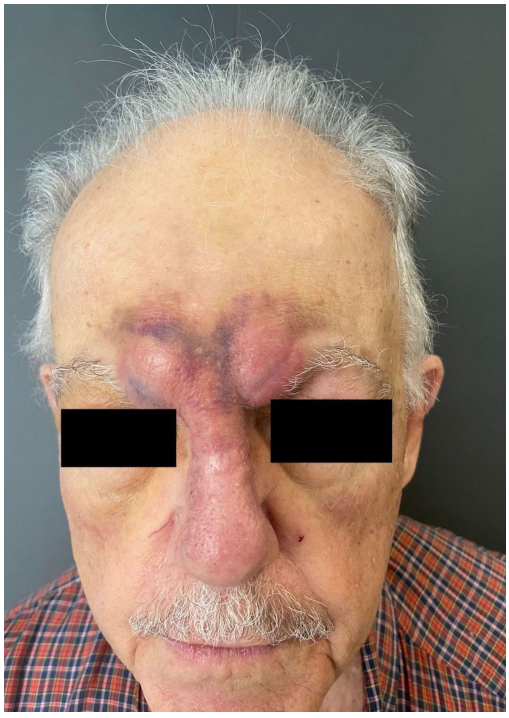

Figure 2: Nodules in the frontal region corresponding to the clinical lesions of pseudoaneurysms of the supratrochlear arteries

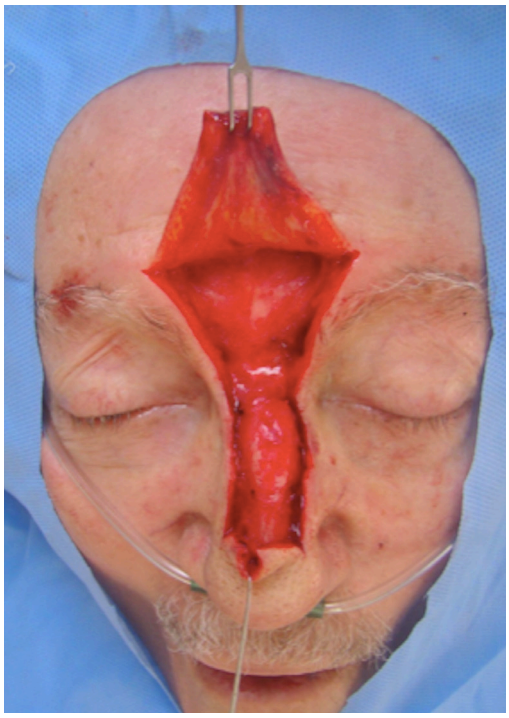

Figure 3: Final surgical defect. Reconstruction with an advancement flap in the glabellar region

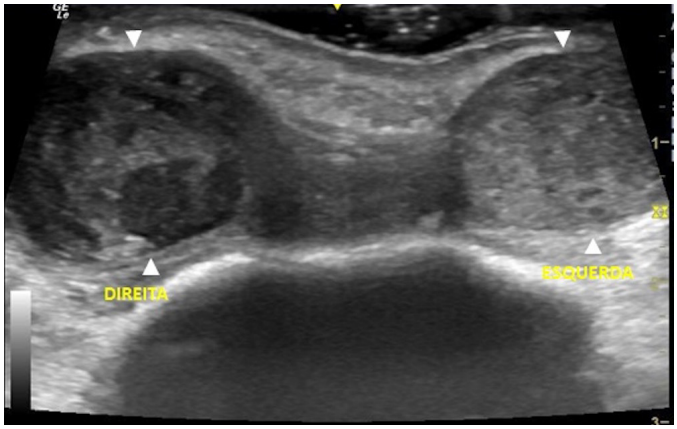

Figure 4: Transverse section of the frontal region: right and left hematomas marked by white arrowheads

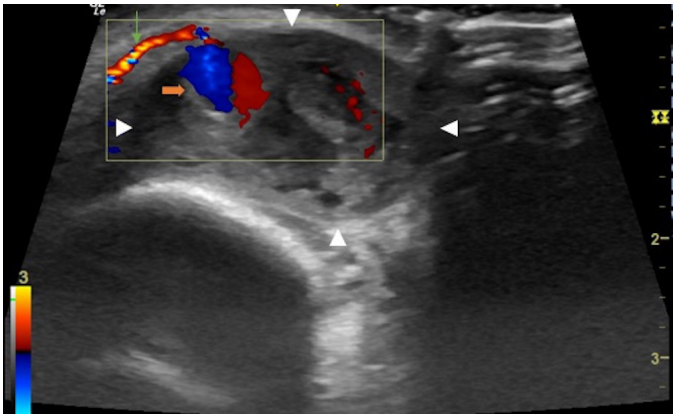

Figure 5: Longitudinal section of the right frontal region: right frontal hematoma marked by white arrowheads, right supratrochlear artery indicated by the green arrow, and the pseudoaneurysm indicated by the orange arrow

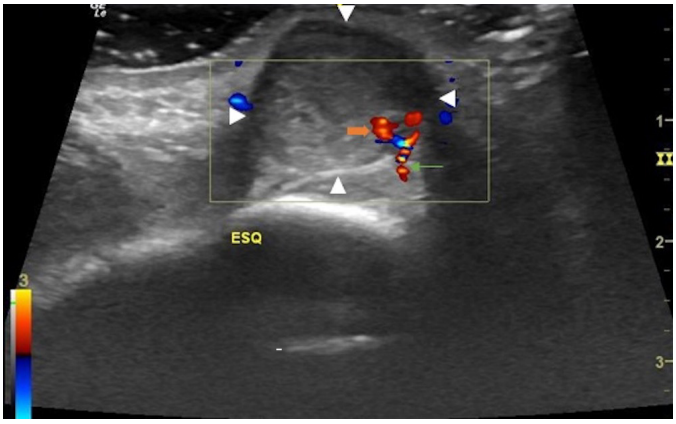

Figure 6: Transverse section of the left frontal region: left frontal hematoma marked by white arrowheads, left supratrochlear artery indicated by the green arrow, and the pseudoaneurysm indicated by the orange arrow

le, another well-defined anechoic nodule was observed, measuring 0.7 × 0.7 cm, with bidirectional flow on color Doppler examination, fed by the right supratrochlear artery located superficially at the periphery of the hematoma (0.3 cm from the epidermis) (Figure 5). The left-sided hematoma, measuring 2.2 × 1.3 × 1.8 cm, had a more homogeneous echo texture than the right-sided one. Left supratrochlear artery was located deeper (approximately 1.0 cm from the epidermis) at the periphery of the hematoma.

A small nodule measuring 0.2 × 0.2 cm was observed adjacent to the left supratrochlear artery and showed bidirectional flow on color Doppler examination (Figure 6). Visualization of the nodular images along the arteries, combined with the presence of bidirectional color flow on Doppler (yin-yang sign), led to the diagnosis of supratrochlear artery pseudoaneurysm.

After the diagnosis of supratrochlear artery pseudoaneurysm, patient was referred to vascular surgery and underwent ligation of supratrochlear arteries 7 days after the ultra-

sound with excellent results. Thirty days after the procedure, the patient showed complete resolution of lesions.

DISCUSSION

Hematomas and seromas are complications that can be expected after dermatologic surgery. These complications should be suspected when patients develop swelling or nodules over the postoperative wound days or weeks after the procedure. However, pseudoaneurysm has never been reported as a complication of dermatologic surgery.

Pseudoaneurysms are caused by a localized rupture of the arterial wall, which may occur because of vascular trauma, resulting in a contained hematoma that maintains a persistent connection to lumen of the arteria.[1,2] They can be classified as iatrogenic or noniatrogenic. Iatrogenic pseudoaneurysms are the most common and typically occur after arterial access in endovascular procedures or after surgical vascular anastomoses. Noniatrogenic causes include trauma, infection, and chronic pancreatitis.[1]

Facial artery pseudoaneurysms are rare. There are a few reports in the literature of pseudoaneurysms of the internal carotid, maxillary, and superficial temporal arteries after cranioencephalic trauma.[4-9]

Intraoperative bleeding and hematoma formation are well-documented adverse effects in patients taking anticoagulants, including factor Xa inhibitors, such as apixaban.[10,11] There is also an increased risk of pseudoaneurysm in patients on anticoagulants and dual antiplatelet therapy.[2] Since pseudoaneurysms form due to damage to the arterial wall, we believe that extensive and deep surgical defects near larger vessels are more prone to complications such as pseudoaneurysms in dermatologic surgery.

In the case described, we believe that the use of anticoagulants, together with the trauma caused by the puncture and aspiration of the hematoma, may have contributed to the formation of pseudoaneurysm. The possibility of a pseudoaneurysm should be considered in cases of persistent hematomas, some of which may be pulsatile and painful.

Doppler ultrasound has a sensitivity of 94-99% and a specificity of 94-97% for the diagnosis of pseudoaneurysm, making it the diagnostic tool of choice.[12] in-yang sign, created by the inflow and outflow of blood during systole and diastole, is used to differentiate pseudoaneurysms from hematomas and true aneurysms.[13] Besides, ultrasound helps to determine size, location, and contact with underlying structures, aiding in therapeutic planning.[12]

Small pseudoaneurysms may resolve spontaneously after compression with bandages. However, pseudoaneurysms larger than 2 cm, those that are growing, or those with large adjacent hematomas should be treated. Therapeutic options include ultrasound-guided compression, ultrasound-guided thrombin injection, and surgical correction.[14]

CONCLUSION

Pseudoaneurysm is an extremely rare vascular complication. We believe this is the first reported case involving the supratrochlear artery after dermatologic surgery. The use of anticoagulants is a risk factor for hematoma and pseudoaneurysm formation, and their temporary suspension should be evaluated on a case-by-case basis. In the reported case, the patient developed associated complications even after suspension of the medication according to current guidelines. In this case, Doppler ultrasound was the gold standard test for diagnosis and surgical planning. ●

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Intense pulsed light therapy for the treatment of facial erythema and hypertrophic scar after phenol peeling

Terapia de luz intensa pulsada para tratamento de eritema facial e cicatriz hipertrófica pós-peeling de fenol

Case Report

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ABSTRACT
Facial erythema after phenol peeling is one of the expected effects of the healing process and collagen formation. Intense Pulsed Light (IPL) therapy is one of the forms used as a treatment accelerating recovery, reducing redness, inflammation, and itching symptoms that may occur after peeling. IPLT can also be used to treat hypertrophic scars, which is also one of the adverse events that can happen with deep peeling. We report a successful case of IPLT treatment in a patient who presented facial erythema and hypertrophic scarring after undergoing phenol peeling.
Keywords: Phenol; IPL treatment; Hypertrophic Scar.

RESUMO
O eritema facial pós-peeling de fenol é um dos efeitos esperados do processo de cicatrização e formação de colágeno. A terapia de luz intensa pulsada (LIP) é uma das formas utilizadas como tratamento, acelerando a recuperação, reduzindo a vermelhidão, a inflamação e os sintomas de prurido que podem ocorrer após o peeling. A LIP também pode ser utilizada para tratar cicatrizes hipertróficas, um dos efeitos adversos que pode acontecer com o peeling profundo. Relata-se um caso bem-sucedido de tratamento com LIP em paciente que apresentou eritema facial e cicatriz hipertrófica após ter realizado o peeling de fenol.
Palavras-chave: *Fenol; Terapia de Luz Pulsada Intensa; Cicatriz Hipertrófica.*

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INTRODUCTION

Facial erythema is one of the most common outpatient complaints in Dermatology. There are several causes of facial erythema, which can be physiological and transient or occur in diseases such as rosacea, lupus erythematosus, and dermatomyositis.[1] Facial erythema can also occur as an adverse event after phenol peeling, currently used to treat deep wrinkles and severe acne scars. Phenol is a deep peeling that immediately coagulates superficial epidermal and dermal proteins with a histological increase in collagen and elastic fibers.[2]

Prolonged post-phenol peel erythema is benign. It begins during the first week and peaks in the second week after the procedure. Erythema is a normal part of the healing process and is a sign of reticular dermal collagen formation. Patients typically present this condition within three to six months and up to a year during exercise.[3] The formation of hypertrophic scars can occur in specific areas, such as the zygomatic arch, pre-auricular region, medial upper eyelids, lower eyelids, and neck, where the peeling should be less vigorous.[3]

Intense Pulsed Light (IPL) therapy is a light device commonly used to treat these conditions of facial erythema and hypertrophic scars.[1,4] This light emits wavelengths between 420 nm to 1400 nm. It emits the wavelength needed to target specific chromophores and improve penetration by using filters, thus minimizing energy absorption by other chromophores. Advantages of the IPL system include lower cost, versatility to target multiple chromophores, flexible parameters with less complexity, and fewer adverse events.[5] Incorrect patient selection, i.e., skin color or ethnicity, is a significant cause of burn injury as there are variations in melanin content in different people.[1]

METHODS

A 52-year-old woman, Fitzpatrick skin phototype II, presented facial erythema and hypertrophic scar after undergoing phenol peeling with Hett formula 1.2% to treat photoaging and periocular wrinkles. Three IPL sessions were performed on the entire face at monthly intervals, one month after the deep peeling, using parameters as shown in table 1 and photographic monitoring before and after each procedure (Figure 1).

During the laser sessions, the patient developed a hypertrophic scar in the mandibular region bilaterally, one of the most

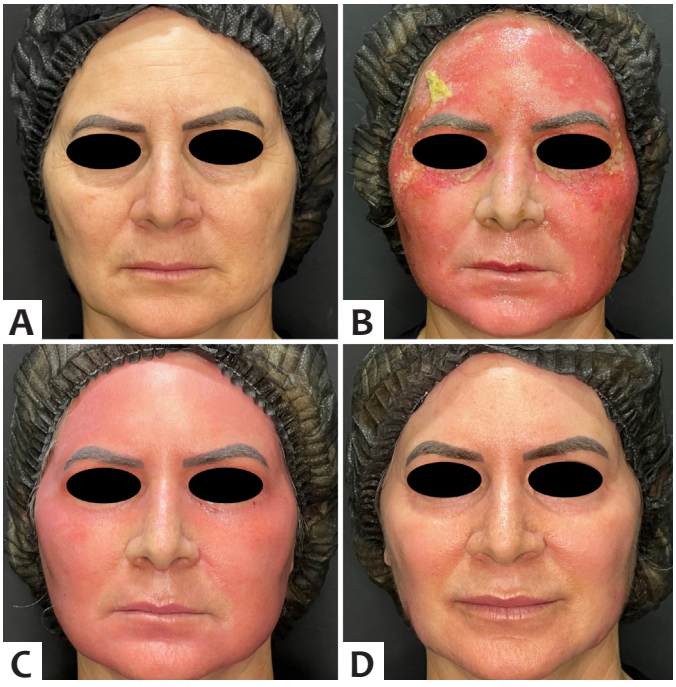

FIGURE 1: Skin recovery after phenol *peeling*. **A -** Before peeling; **B -** Seven days post-peeling; **C -** 30 days post-*peeling* and before performing the first IPL session; **D -** After completing three IPL sessions

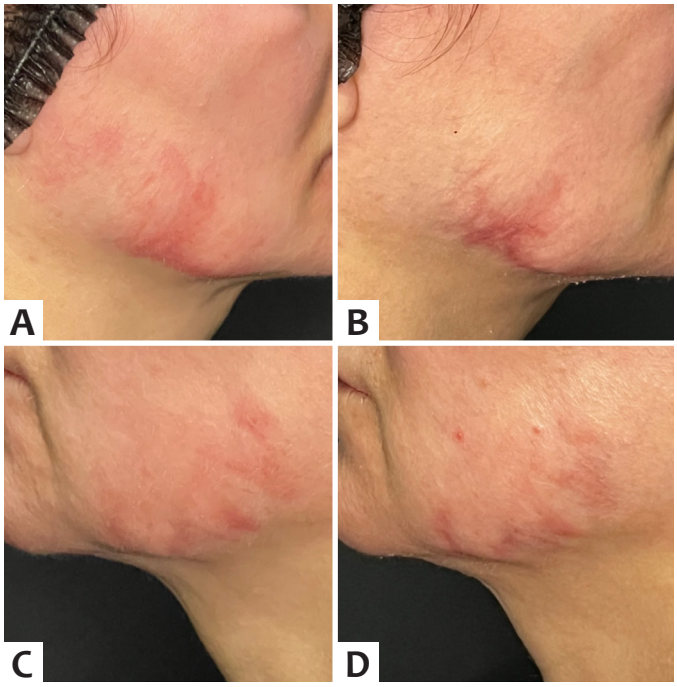

Figure 2: A - and **C -** Lateral photo of the face *showing* the appearance of the hypertrophic scar after 70 days of phenol peeling; **B -** and **D -** Lateral photo of the scar after two sessions of infiltration with 10% kenalog diluted with 0.9% SS in a 1:4 ratio, respectively, at fortnightly intervals, followed by three sessions of IPL, showing an improvement in the erythema and telangiectasias

Table 1. Full face intense pulsed light therapy for erythema + infiltration (INF) in hypertrophic scar in the right and left mandibular region

Session	Filter	J/cm	ms	Hz	Cooling
1st IPL	540 nm	13	15	0.50	maximum
1st INF	Kenalog 10% diluted with 0.9% SS in a 1:8 ratio, respectively				
2nd IPL	540 nm	15	15	0.50	maximum
2nd INF	Kenalog 10% diluted with 0.9% SS in a 1:8 ratio, respectively				
3rd IPL	540 nm	18	15	0.50	maximum

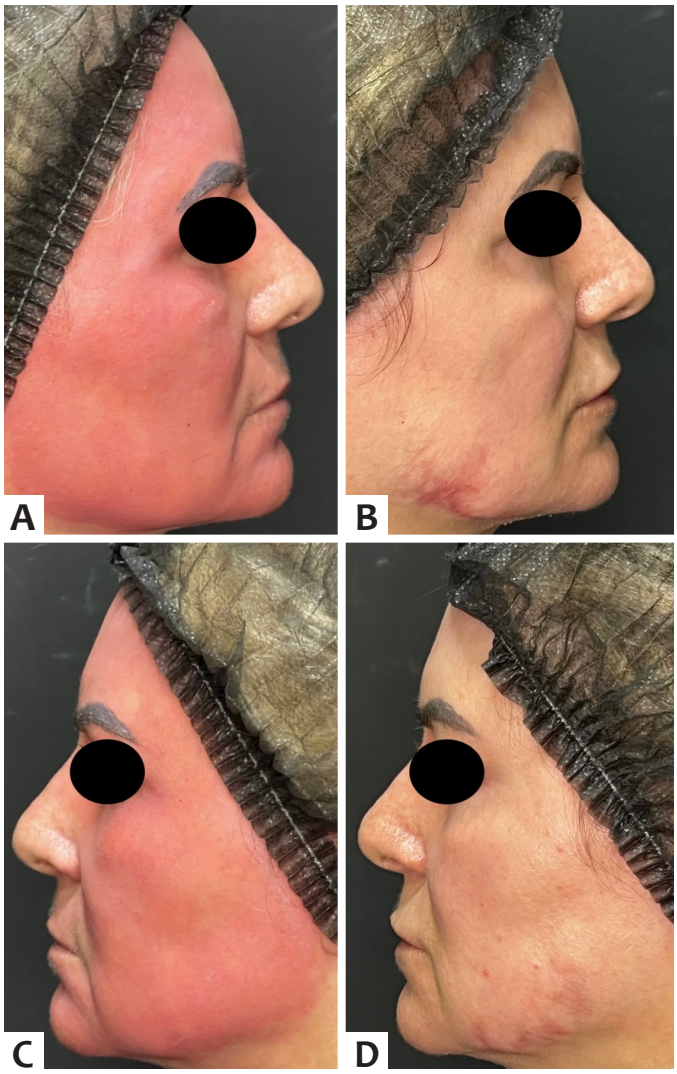

Figure 3: A - Right side photo of the face before performing IPL therapy; **B -** Right side photo after completing three IPL sessions; **C -** Left lateral photo before performing IPL therapy; **D -** Left side photo after completing three IPL sessions

feared complications of phenol peeling. Between IPL sessions we conducted two infiltrations using 10% kenalog diluted with 0.9% saline solution (SS) in a 1:8 ratio, respectively, with fortnightly intervals, always one week before the IPL sessions, resulting in improvement of erythema and telangiectasias (Figure 2).

RESULTS

After the three IPL sessions, we observed a reduction in facial erythema and an improvement in the appearance and symptoms of itching in the hypertrophic scar in the mandibular region on both sides of the face through the photographic comparison. Although the patient had post-peeling adverse events, she obtained the desired improvement in her deep periorbital wrinkles, reporting that she was satisfied with the result after all the procedures (Figure 3 to 6).

DISCUSSION

Phenol has been used as a deep peeling both alone and in association with other components that act as penetration and permeation promoters. These products result in an intense cell renewal process, normalizing skin pigmentation, reducing marks, and minimizing wrinkles.[6] Prolonged erythema may persist for a period ranging from three to six months after the deep peeling.[3] Furthermore, IPL can treat telangiectasias resulting from the dilation of capillary microvessels. In this case, its mechanism of action is based on photothermolysis, or thermal damage to the vessels, which induces intravascular coagulation.[7]

Scars can occur after peeling and can be permanent. They generally appear in regions such as lips, eyelids, and jaw.[6] The mechanism of action of IPL in hypertrophic scars is not fully understood, but it probably targets vascular proliferation essential for excessive collagen production. Wavelengths from 400 nm to 600 nm impact the vasculature directly, reducing its thickness and inhibiting its growth. It also heats the dermal collagen fibers, promoting their contraction and improving the texture of scars.[7]

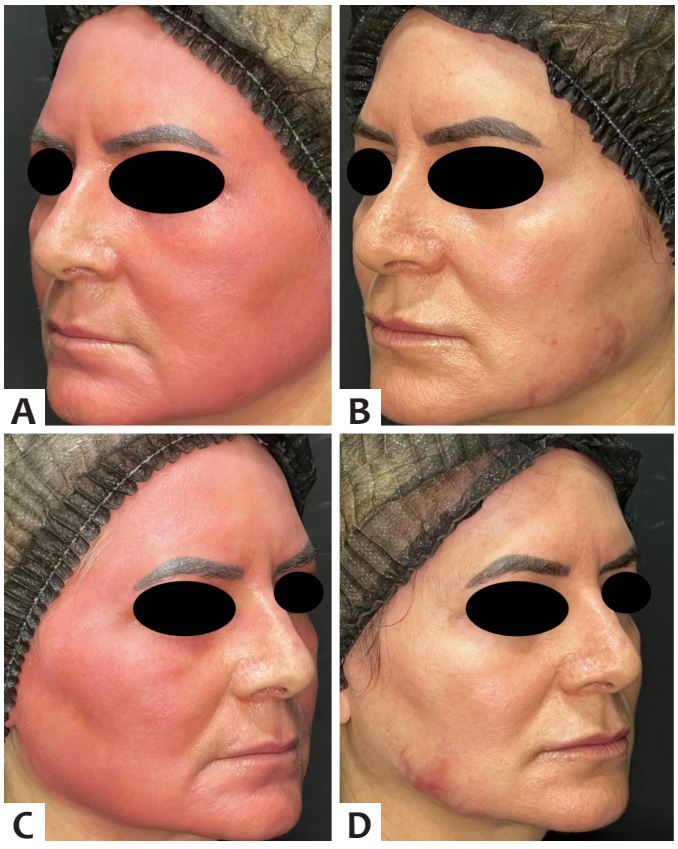

Figure 4: A - Right diagonal photo of the face before performing IPL therapy; **B -** Right diagonal photo after completing three IPL sessions; **C -** Left diagonal photo before performing IPL therapy; **D -** Left diagonal photo after completing three IPL sessions

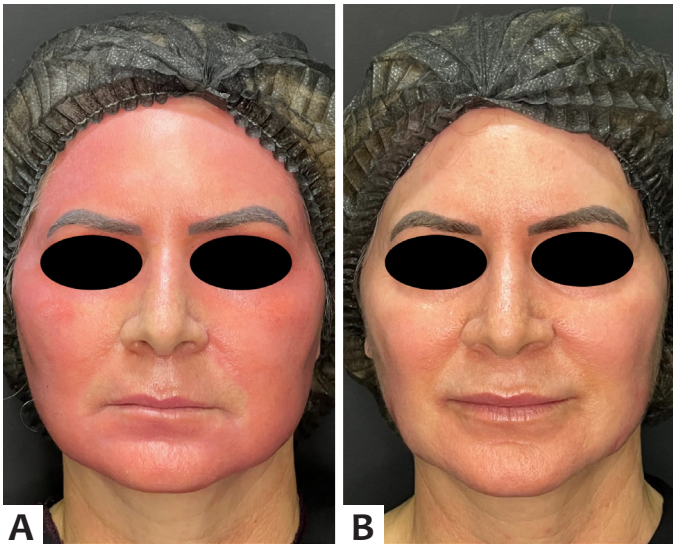

Figure 5: A - Photo of the frontal position of the face before performing IPL therapy; **B -** After completing three IPL sessions

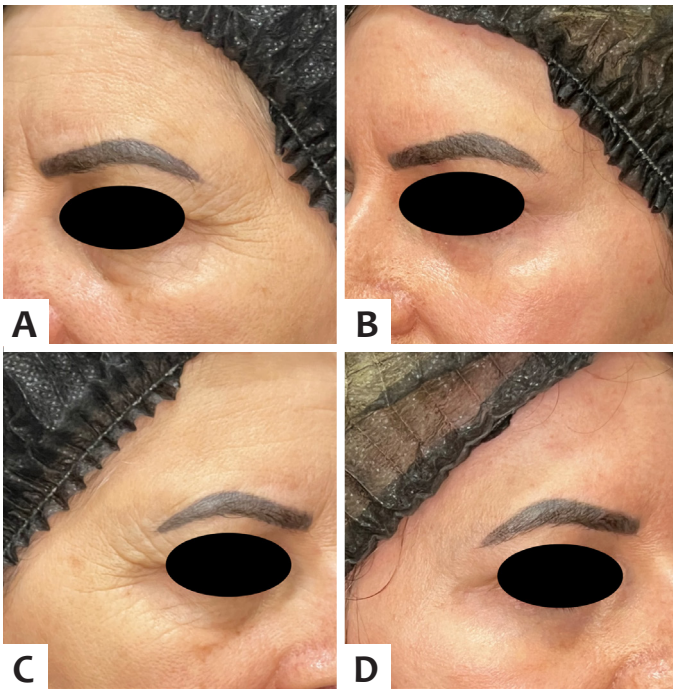

Figure 6: A - Right diagonal photo of the face before phenol peeling; **B -** Right diagonal photo after peeling; **C -** Left diagonal photo before phenol peeling; **D -** Left diagonal photo after peeling, showing an improvement in fine and deep wrinkles

In 2014, Meymand assessed the use of IPL associated with intralesional corticosteroids in the treatment of 86 patients with hypertrophic scars and keloids. The study held eight sessions every three weeks. According to the paper, the association between treatments accelerated results without presenting significant adverse events, with a degree of clinical improvement considered excellent in 73% of cases.[7]

CONCLUSION

Complications from phenol peeling are a challenge for dermatologists, and it is necessary not only to identify them early but also to know how and when to intervene. Intense pulsed light (IPL) therapy is a proven effective technique to treat facial erythema and hypertrophic scars. Therefore, it is critical to deepening the knowledge of IPL to optimize the application techniques, keeping in mind that combining techniques results in greater comfort and requires a smaller number of sessions.[7]

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Interpolation flap on the posterior surface of the ear

Retalho de interpolação na face posterior da orelha

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ABSTRACT

The posterior surface of the ear is an uncommon site for skin cancer. It has anatomical and cutaneous characteristics that make local reconstruction difficult using standard surgical techniques. We present a case of reconstruction of a defect on the posterior surface of the ear secondary to excision of a basosquamous carcinoma, using an interpolation flap.

Keywords: Carcinoma, Basosquamous; Ear; Surgical Flaps

RESUMO

A região posterior da orelha é um local incomum de câncer de pele. Ela tem características anatômicas e cutâneas que dificultam a reconstrução local por meio de técnicas cirúrgicas habituais. Apresentamos um caso de reconstrução de um defeito em face posterior de orelha, secundário à exérese de um carcinoma basoescamoso, utilizando-se um retalho de interpolação.

Palavras-chave: *Carcinoma Basoescamoso; Orelha; Retalhos Cirúrgicos*

Report Case

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INTRODUCTION

The skin is the most common organ affected by cancer, which occurs in places where there is more sun exposure, such as face and neck.[1] Depending on the size and site of the tumor, a graft or flap needs to be made to reconstruct the defect resulting from the excision.[2]

The posterior surface of the ear has curves and ridges, with skin that has little mobility for a simple flap; it is difficult to fix compressive dressings in the case of grafting, which can pose a challenge in reconstructing the site with no anatomical distortions.[3]

An interpolation flap (IF) consists of using tissue from a site not immediately adjacent to the defect, maintaining a vascular pedicle to supply the flap until neovascularization is established between the flap and the recipient bed, and only after integration of these two sites (recipient and flap) the pedicle is sectioned.[4]

We report a reconstruction of a defect on the posterior surface of the ear, following excision of a basosquamous carcinoma, in which we used an IF, with good aesthetic and functional results.

METHODS

We treated a patient with a basosquamous carcinoma on the posterior surface of the left ear:

An 83-year-old male patient presented with an erythematous vegetating plaque on the posterior surface of his left ear, measuring 37 × 23mm, whose incisional biopsy confirmed a basosquamous carcinoma, which underwent surgical excision, with margins of 4mm, with a resulting defect measuring 41 × 27mm (Figure 1A). We decided to reconstruct it with an IF.

Description of the technique:

Patient in horizontal dorsal decubitus;

The lesion was marked with methylene blue or a surgical pen with a 4mm margin (Figure 1A). The donor area was marked, starting in the retroauricular area, at the lower margin and parallel to the defect, extending caudally through the posterior cervical area up to 2cm below the earlobe (Figure 1B);

Antisepsis with topical 10% polyvinyl-iodine;

Placement of surgical drapes:

Infiltrative anesthesia with 2% lidocaine with vasoconstrictor;

Incision of the lesion with a 15 blade and en bloc excision of the piece up to the subcutaneous tissue;

Hemostasis;

Incision of the flap, as previously marked. Detachment of the flap and its positioning and suturing at the defect site, maintaining the vascular pedicle (Figure 2);

Detachment of the edges of the donor site with curved Metzenbaum scissors;

Primary suturing of the donor site (Figures 2 and 3);

After three weeks (Figure 4), sectioning and repositioning of the pedicle (Figure 5).

RESULTS

The patient showed good integration between the flap and the recipient area postoperatively. Figure 6 compares the images preoperatively and two weeks following the second stage of the surgery.

DISCUSSION

Large surgical wounds resulting from excisions of cutaneous neoplasms in the auricular area are challenging for the dermatological surgeon.[3] Satisfactory results depend on the technique used and the training to perform it, and the patient's health conditions.[4]

The posterior surface of the ear is an uncommon site for skin cancer, generally serving more as a donor area because it is less photoexposed.[5] For reconstruction of this site, an ideal flap should be thin and flexible, match the color of the recipient area and not have an obvious scar on the donor site.[6]

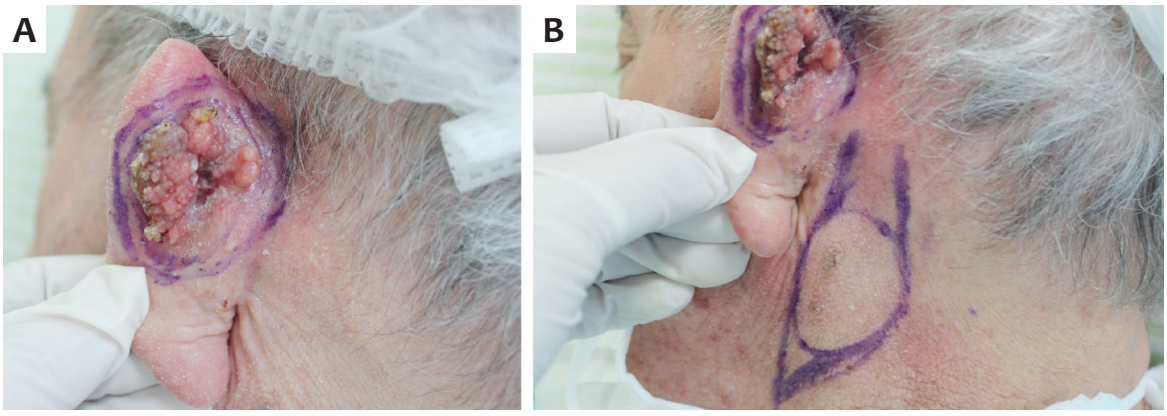

FIGURE 1: A - Erythematous vegetating plaque on the back surface of the left ear. **B -** Drawing of the flap

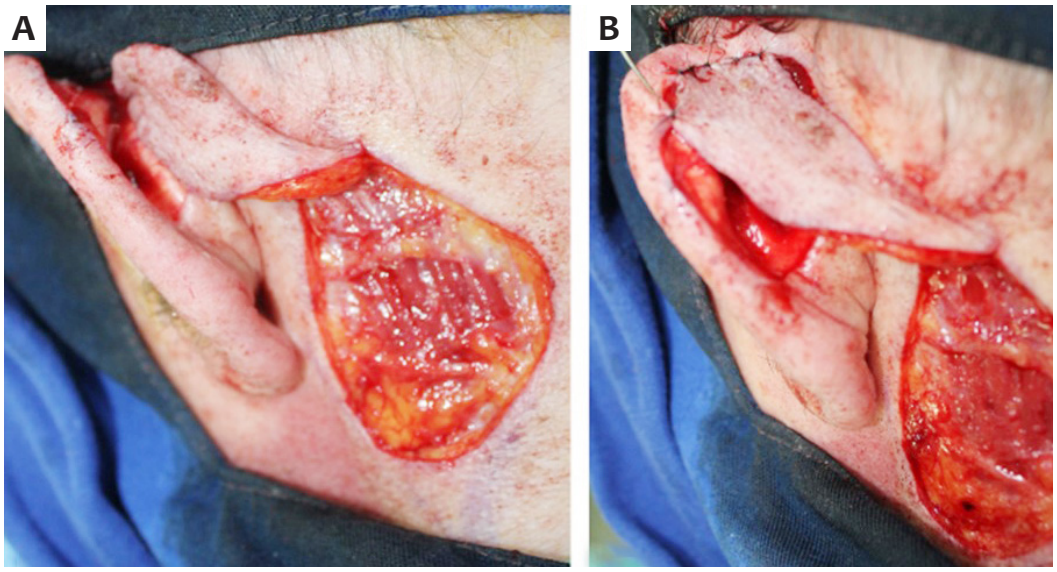

Figure 2: A - Erythematous vegetating plaque on the back surface of the left ear. **B -** Drawing of the flap

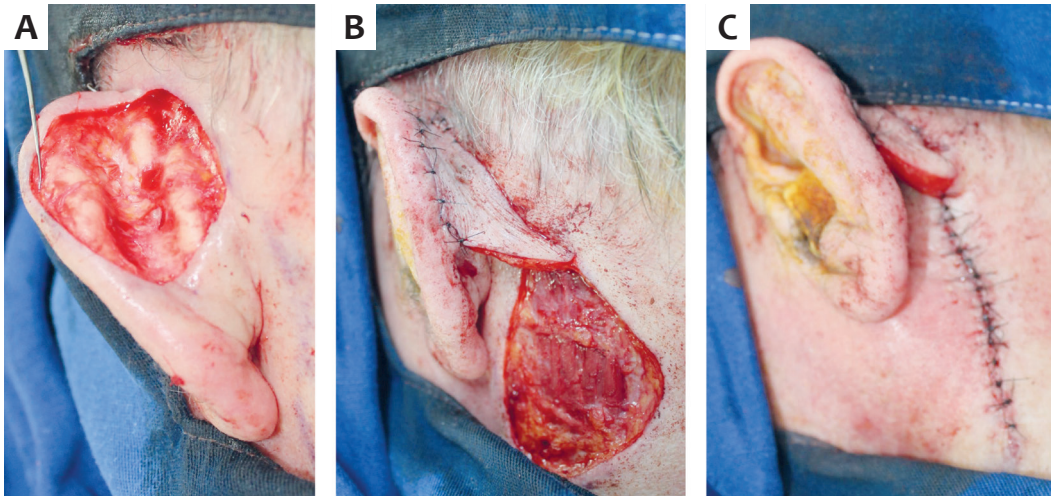

Figure 3: A - Defect following excision of the lesion. **B -** Positioning the flap in the recipient area. **C -** Donor area sutured

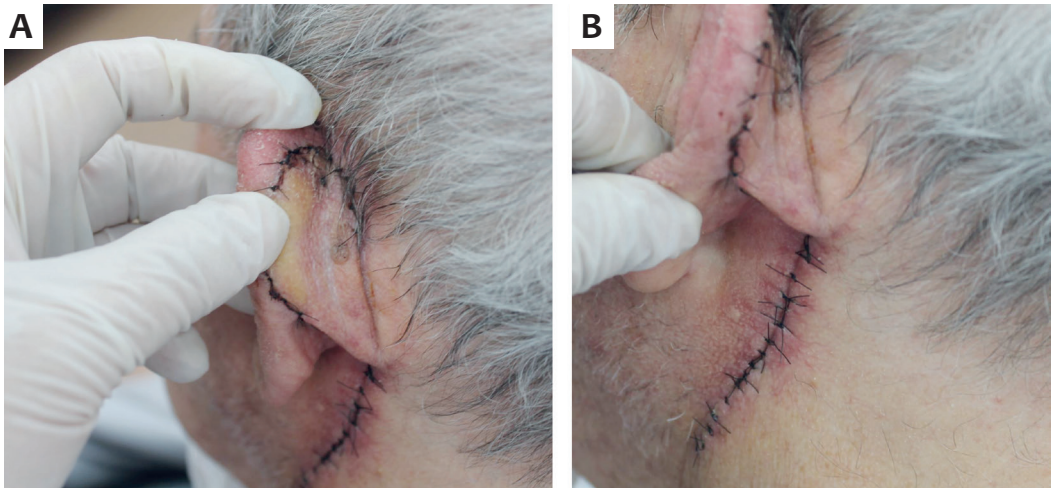

Figure 4: A - Three weeks following surgery. Good integrity of the recipient and donor areas. **B -** Detail of the pedicle

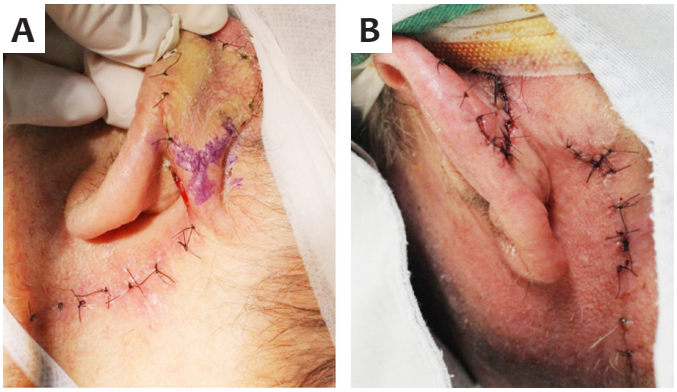

Figure 5: A - Before sectioning the pedicle. **B -** After sectioning the pedicle and repositioning in the donor area

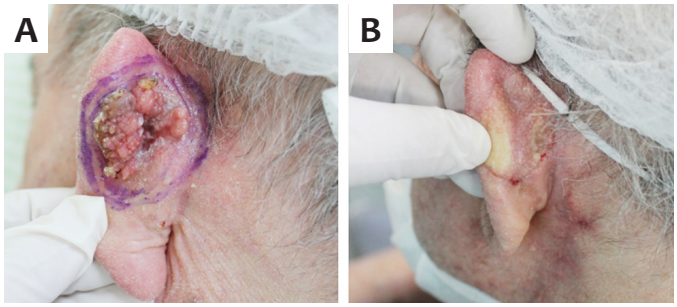

Figure 6: A - Pre-operative. **B -** Two weeks after sectioning and repositioning the pedicle

Although thick flaps can cause trap doors, which is elevation at the recipient site, the important thing is to maintain the functionality of the ear in the final result, as it supports glasses and hearing aids.[7]

An IF uses tissue from an area not contiguous to the defect, maintaining a vascular pedicle to supply the flap until neovascularization occurs between the flap and the recipient bed. The disadvantage is that it requires a second stage, after three weeks, when the pedicle will be sectioned after the integration of the two areas (recipient and flap).[4] Our patient had a good evolution, maintaining the flexibility of the ear, without a trapdoor, preserving local anatomy and functionality (support for glasses, hearing aid, and protective mask), with the scar hidden in the posterior cervical area.

CONCLUSION

An IF is a good option for reconstructing defects on the posterior surface of the ear, with good aesthetic and functional results. ●

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Fibromyxosarcoma mimicking a benign cystic lesion: a case report of a high-grade mesenchymal tumor in an atypical site

Fibromixossarcoma mimetizando lesão benigna cística: relato de caso de tumor mesenquimal de alto grau em localização atípica

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.2024160305

ABSTRACT

Fibromyxosarcoma is a rare subtype of soft tissue sarcoma characterized by the presence of spindle cells and myxoid matrix. We report the case of an older patient who presented with progressive growth of a nodule in the interscapular region, and further investigation confirmed the diagnosis of high-grade fibromyxosarcoma. Notably, this neoplasm more commonly occurs in the lower limbs and may exhibit recurrence associated with increased histological grade. Therefore, early diagnosis and treatment are crucial for mitigating morbidity and mortality. We emphasize the significance of diagnosing an atypical case and providing timely therapeutic intervention, contributing to the optimization of clinical outcomes.

Keywords: *Sarcoma; Neoplasms, Connective and Soft Tissue; Solitary Fibrous Tumors*

RESUMO

O fibromixossarcoma é um subtipo raro de sarcoma de partes moles, caracterizado pela presença de células fusiformes e matriz mixoide. Relatamos o caso de uma paciente idosa que apresentou crescimento progressivo de um nódulo interescapular, cuja investigação confirmou o diagnóstico de fibromixossarcoma de alto grau. É notório que esta neoplasia ocorre mais comumente nos membros inferiores e pode exibir recorrência associada ao aumento do grau histológico. Por isso, diagnóstico e tratamento precoces são fundamentais na mitigação da morbimortalidade. Enfatizamos a relevância do diagnóstico de um caso atípico e da intervenção terapêutica oportuna, contribuindo para a otimização dos desfechos clínicos.

Palavras-chave: *Sarcoma; Neoplasias de Tecido Conjuntivo e de Tecidos Moles; Tumores Fibrosos Solitários*

Case Report

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INTRODUCTION

Fibromyxosarcoma is a rare subtype of soft tissue sarcoma, composed of spindle cells and myxoid stroma. It is the most common mesenchymal neoplasm in older patients, presenting as painless, slow-progressing nodules, common in the lower extremities.[1] Histologically, according to cellularity and atypia, they can be classified as low, intermediate, or high grade. This classification has no correlation with the high risk of recurrence (between 50-60% for all subtypes), but it is a predictor of metastases, which are present in 20-35% of intermediate and high grades, and are uncommon in low-grade sarcomas.[2] Unlike other sarcomas, myxofibrosarcomas tend to gradually present with a higher histological grade with each recurrence.[3] This highlights the importance of early diagnosis, staging, and treatment, with a view to lower morbidity and mortality. We report the case of an older patient with high-grade myxofibrosarcoma in the interscapular region.

CASE REPORT

A 68-year-old female patient presented with a one-year--old, painless nodular lesion in the interscapular region. The initial dermatological physical examination revealed a painless, mobile nodular lesion measuring 6 × 4cm. She had a previous soft tissue USG at the beginning of the condition, compatible with an epidermal cyst with free muscle planes (Figures 1A-1B). As the clinical picture was not consistent with the imaging exam, a CT scan was requested, which showed that it was a 7 × 3cm cystic lesion, and excision was scheduled. Following incision, amorphous, gelatinous, blackened tissue could be seen, not corresponding to the initial hypothesis (Figures 1C-1D). A deep biopsy of the lesion was then performed, with histopathological results showing a high-grade myxofibrosarcoma (Figure 2). Magnetic resonance imaging of the spine was requested, showing the presence of an expansive lesion measuring 10.1 × 8.8 × 4.0cm, invading the muscle bulge of the underlying trapezius, with no signs of invasion of other muscle planes or adjacent bone structures (Figure 3). For staging, a PET-CT scan was performed, which showed hypermetabolism in bilateral axillary lymph nodes, suggestive of metastases, not confirmed through biopsy of the hypercapturing lymph nodes (Figure 4). The patient was referred to the Orthopedics team and the lesion was excised with wide margins. The patient was then referred to Oncology for clinical follow-up, and no adjuvant treatments were indicated. The patient is being followed up by a multidisciplinary team six months after excision, with no recurrence (Figure 5).

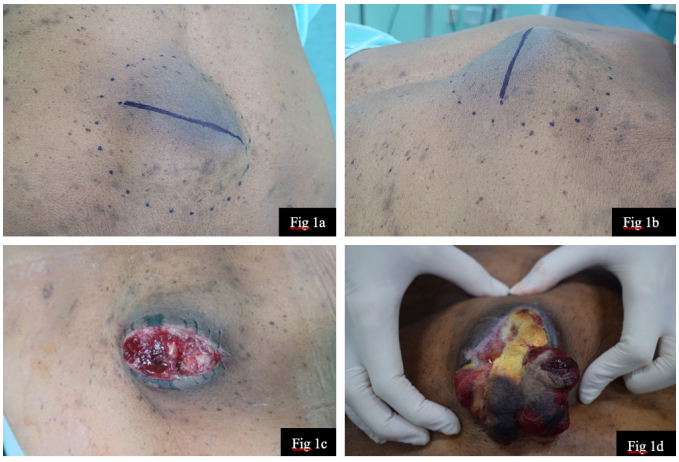

Figure 1: A-B - Nodular lesion in the interscapular area prior to biopsy. C: Appearance of the lesion after the biopsy, showing dehiscence of the sutures. D: Exuberant exophytic growth of the tumor mass can be seen, and also the infiltrative aspect of the muscle planes

DISCUSSION

Fibromyxosarcoma is a rare subtype of soft tissue sarcoma, first described by Enzinger and Weiss in 1977.[1] Previously called malignant fibrous histiocytoma myxoid variant, it has a mesenchymal origin and is composed of spindle cells and myxoid stroma. It is the most common malignant mesenchymal neoplasm in older patients, predominantly affecting males in the 50s to 70s.[1-3]

The most common site is the lower limbs, with lesions rarely occurring in the trunk, upper limbs, or cephalic segment.

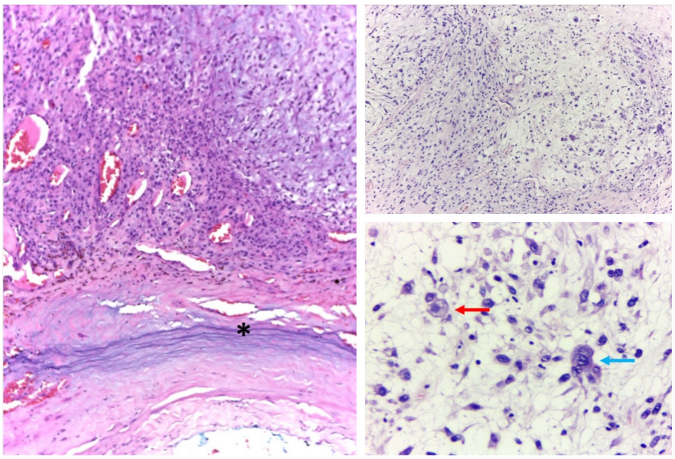

Figure 2: Neoplasm showing tissue with atypical and pleomorphic fibroblastic proliferation, sometimes containing binucleation or multinucleation, hyperchromatism, cytoplasm varying from slightly acidophilic to more abundant and foamy, also called pseudolipoblasts (red arrow). Note the presence of atypical mitotic figures (blue arrow). The stroma consists of abundant and richly vascularized myxoid tissue, with delicate, curved vessels. Note the relationship between the tumor and the muscular fascia (*).

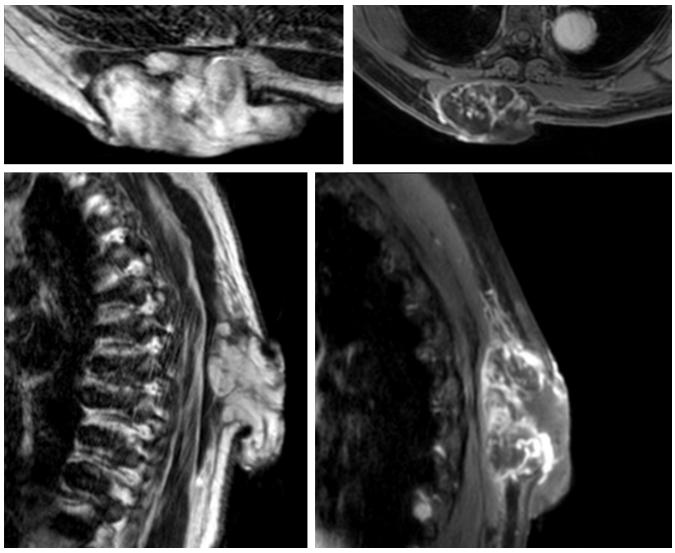

Figure 3: MRI: Expansive lesion, measuring 10.1 × 8.8 × 4.0cm, with invasion of the underlying trapezius muscle bulge

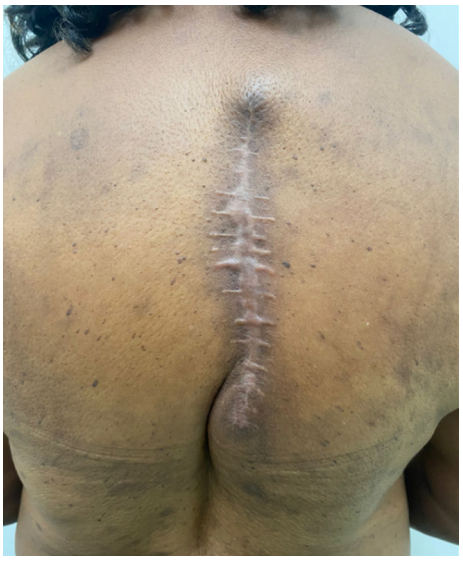

Figure 5: Scar appearance six months after surgical excision

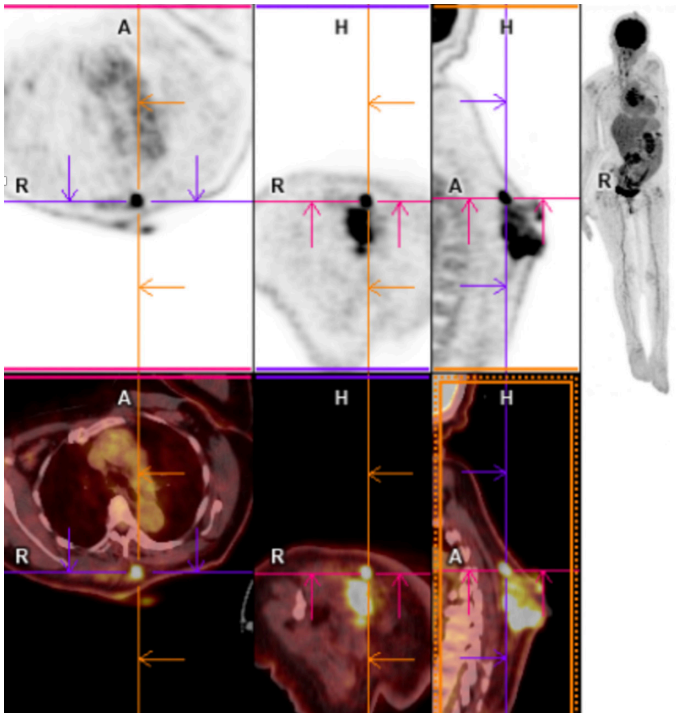

Figure 4: PET-CT scan: Heterogeneous interscapular mass, compatible with primary neoplasm. Hyper-uptake of axillary lymph node level I on the left and level V bilaterally

In general, it presents as painless, slow-progressing, normochromic, or slightly erythematous nodules or tumors. It occurs more frequently in subcutaneous soft tissues than in deep tissues.[1,4,5]

Histopathological examination is the gold standard for diagnosing the disease. The sample must be deep to guarantee a reliable assessment of the material. Superficial biopsies can show benign characteristics or even subclassify a high-grade tumor.[6] Histologically, it is classified as low, intermediate, or high grade, according to cellularity and atypia. Immunohistochemistry shows low specificity in myxofibrosarcoma and is generally positive for vimentin and rarely for smooth muscle actin, S100, and desmin.[6,7]

The treatment of choice is excision of the lesion with wide margins. Local recurrence occurs in 50-60% of cases, and this risk is apparently not related to the depth of the lesions or the histological grade.[8] However, there is a tendency for the myxofibrosarcoma to gradually become more cellular, more pleomorphic, more mitotically active, and thus have a higher histological grade with each recurrence. This characteristic is not observed in other sarcomas. Metastases are rare in low histological grade tumors, but occur in 20-35% of intermediate and high grade tumors, especially to the lungs and bones. The differential diagnosis includes other myxoid tumors.[1,2,8]

The ability of the tumor to present high rates of recurrence and advance in histological grade supports the need for early diagnosis and treatment, so as to reduce morbidity and mortality. ●

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Electrosurgery in rhinophyma: report of two cases

Eletrocirurgia em rinofima: relato de dois casos

Case report

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ABSTRACT

Rhinophyma is characterized by chronic inflammation of the tissues of the nose, resulting in irregular exophytic growth and telangiectasias. The disease progresses with hyperplasia and hypertrophy of the nasal sebaceous glands, associated with fibrosis and dilation of local blood vessels and connective tissue. These changes can lead to complete nose deformity and compromise the patients' quality of life. There are different treatment methods, such as laser, microdermabrasion, chemical exfoliation, cryosurgery, surgery with skin graft, and electrosurgery, with varying results and costs. We report two cases of rhinophyma treated with electrosurgery with very satisfactory results.

Keywords: Rhinophyma; Electrosurgery; Case Reports; Acquired Nasal Deformities.

RESUMO

Rinofima caracteriza-se por inflamação crônica dos tecidos do nariz resultando em crescimento exofítico irregular e presença de telangiectasias. A doença evolui com hiperplasia e hipertrofia das glândulas sebáceas nasais, associadas a fibrose e dilatação dos vasos sanguíneos e do tecido conjuntivo locais. Essas alterações podem levar à deformidade completa do nariz e comprometer a qualidade de vida do paciente. Há diferentes métodos de tratamento, como laser, microdermoabrasão, exfoliação química, criocirurgia, cirurgia com enxerto e eletrocirurgia. Todos esses procedimentos apresentam resultados e custos variados. Relatamos dois casos de rinofima tratados com eletrocirurgia e resultados bastante satisfatórios.

Palavras-chave: *Rinofima; Eletrocirurgia; Relatos de Casos; Deformidades Adquiridas Nasais.*

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INTRODUCTION

Rhinophyma, also called alcoholic nose and nasal elephantiasis, among others, is characterized by chronic inflammation of the nose tissues with changes in texture, color, and vascularization, resulting in irregular exophytic growth and telangiectasias.[1,2] This clinical condition has a strong association with alcoholism and rosacea, and some authors consider it the final stage of the latter.[2] It can be classified as simple hypertrophic when it evolves with hyperplasia and hypertrophy of the nasal sebaceous glands or fibroangiomatotic when associated with fibrosis and dilation of blood vessels and local connective tissue.[1] These changes are responsible for giving the region a tuberous appearance and darker color and can lead to complete deformity of the nose.[1]

The prevalence of rhinophyma is 5% to 10% in the general population, and it is observed frequently in middle-aged and elderly men.[3,4] Some studies have demonstrated ratios of 12 men to one woman.[2] Other associated factors include a positive family history of rhinophyma, excess sun exposure, and high consumption of spicy foods and caffeine – all of these cause facial flushing and rosacea, predisposing factors to the appearance of the lesion.[1,2]

In addition to being an aesthetic problem as it is located in the central region of the face, exophytic growth can hide a basal cell carcinoma (BCC).[5,6] The literature cites several treatments with varying results and costs.[4,5] We report two cases of rhinophyma without association with skin neoplasms, treated with electrosurgery, a low-cost method with very satisfactory results.

METHODS

Two patients with fibroangiomatotic rhinophyma underwent surgical procedures:

PATIENT 1: A 46-year-old man was referred to the Dermatology Service to treat a tumor on his nose, which had been growing progressively for four years. The patient was diagnosed with hepatitis B, untreated at the time, had systemic arterial hypertension, and a history of smoking and daily sun exposure without photoprotection. He was taking ramipril 10 mg a day. Examination demonstrated increased nasal volume, erythema, telangiectasias, nodules, and skin thickening, compatible with rhinophyma. The patient denied prior treatment for the condition. The surgical approach was indicated (Figure 1).

PATIENT 2: A 71-year-old man attended the Dermatology Service due to complaints of increased nasal volume for 20 years, with significant worsening for three years. He had systemic arterial hypertension as a comorbidity and denied alcohol consumption or smoking. He was taking atenolol 25 mg a day. A dermatological examination showed a nose with skin thickening, nodules, and erythema. Surgical treatment was indicated (Figure 2).

Description of the technique:

Patient in horizontal supine position;

Antisepsis with topical 10% polyvinyl iodine;

Placement of surgical drapes;

Infiltrative anesthesia using 2% lidocaine with vasoconstrictor. Wait two minutes for the procedure;

Electrocoagulator in cutting mode and power 20 (Wavetronic® 5000 Digital) and introduction of the loop electrode (Figure 3A), cutting the skin at a depth of 2 mm to 3 mm and sculpting the spare parts;

Electrocoagulator in coagulation mode to achieve local hemostasis. Depending on the need to remodel the nose, it is possible to return to the cutting mode to excise excess skin, and hemostasis is completed again in the coagulation mode;

Once the electrocoagulated nasal tissue is standardized and hemostasis is complete, local cleaning is performed with saline solution (Figure 3B and 3C);

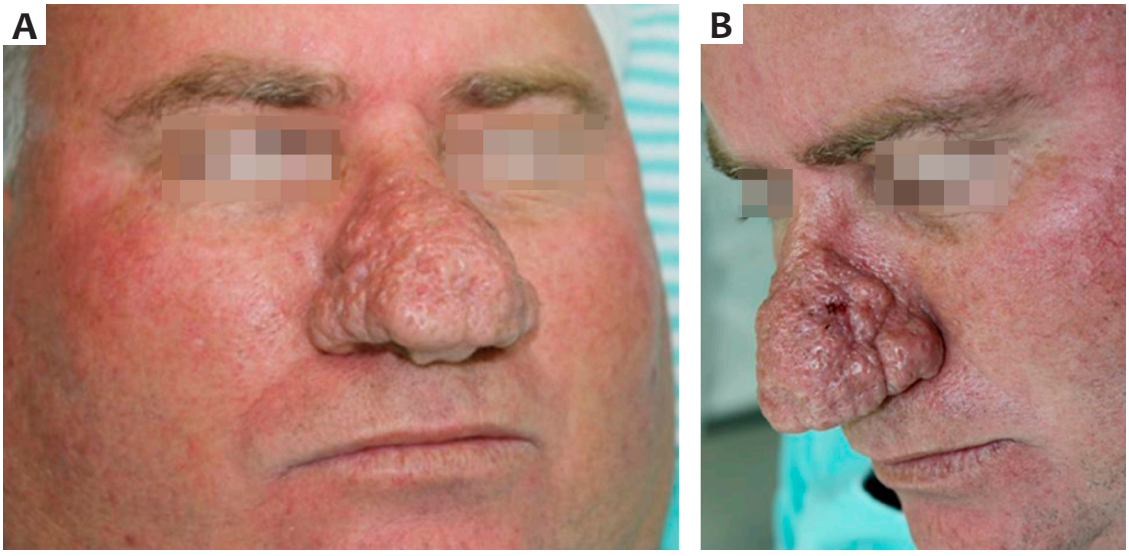

FIGURE 1: Patient 1 with nasal exophytic plaque. **A -** Front view. **B -** Side view

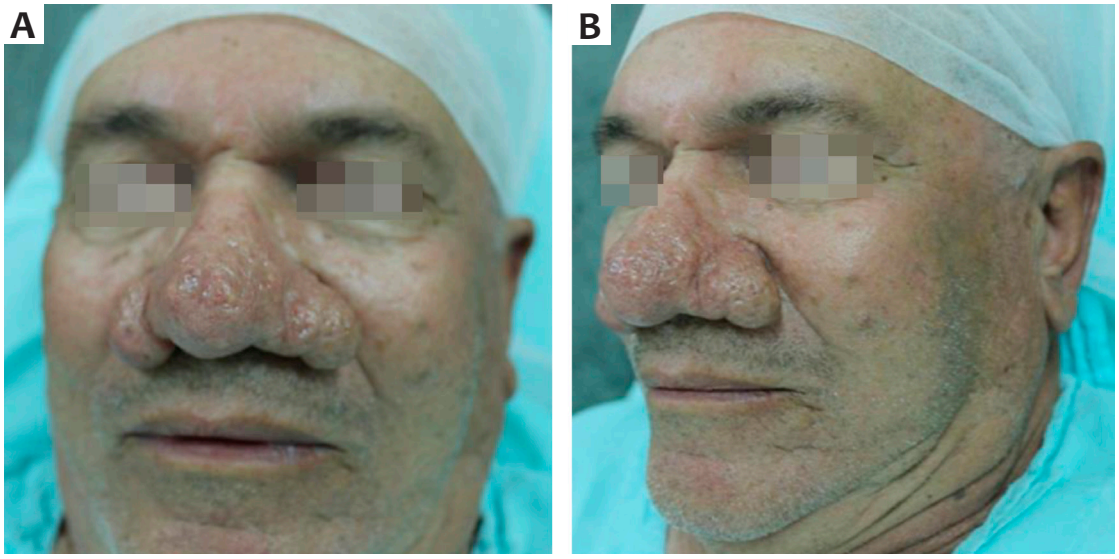

Figure 2: Patient 2 with nasal exophytic plaque. **A -** Front view. **B -** Side view

The procedure is completed with an occlusive dressing with gauze and neomycin ointment. The dressing is fixed with hypoallergenic tape.

The return is made after 24 hours to remove the first dressing, with instructions for occlusive dressings (once daily) with collagenase ointment 0.6 U/g with chloramphenicol 0.01 g/g and reassessment in seven days. After this return, only collagenase ointment (without chloramphenicol) is recommended, keeping the surgical wound without occlusion and weekly visits until completing one month.

RESULTS

Both patients evolved without hemorrhage in the immediate postoperative period, presenting total epithelialization of the surface of the nose, without unsightly scars, preserving the nasal shape (Figures 4 and 5). Patients reported great satisfaction with the result.

DISCUSSION

Hebrea, in 1845, replaced names such as "cauliflower" or "alcoholic" nose with the term rhinophyma. This nomenclature is accepted worldwide and derives from the Greek rhino (nose) and phyma (growth). It is a disease that is not only disfiguring but can also negatively impact respiratory function, causing nasal obstruction.[1]

El-Azhary ***et al.*** (1991) classified rhinophyma into three forms: minor, moderate, or major. The minor form is when the patient presents telangiectasias accompanied by mild skin thickening. The moderate type is when lobes accompany the skin thickening. Lastly, the major form is when there are prominent

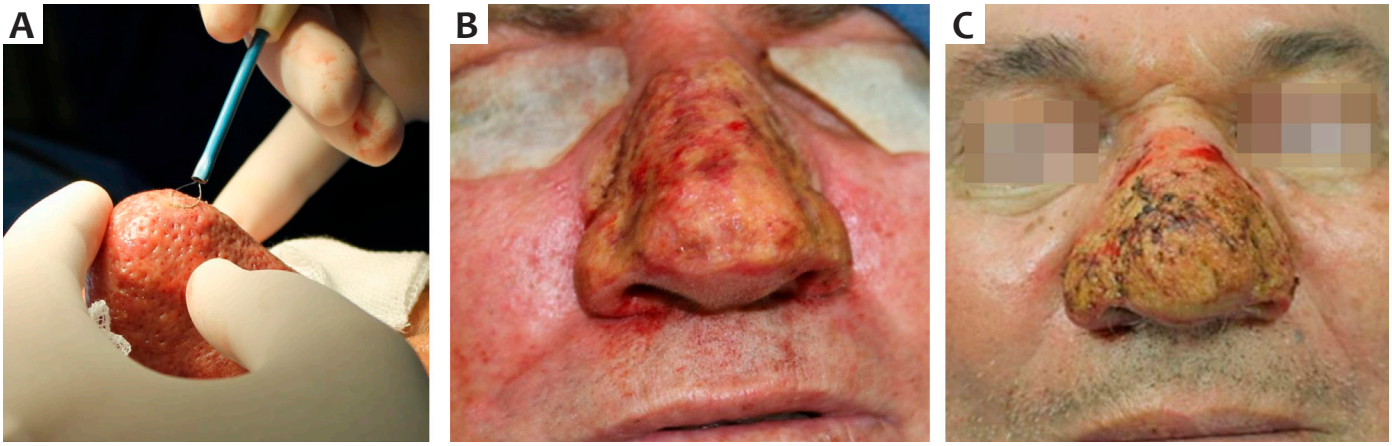

Figure 3: A - Loop-shaped electrode for shaving and electrocoagulation. **B -** Immediate postoperative appearance of patient 1. **C -** Immediate postoperative appearance of patient 2

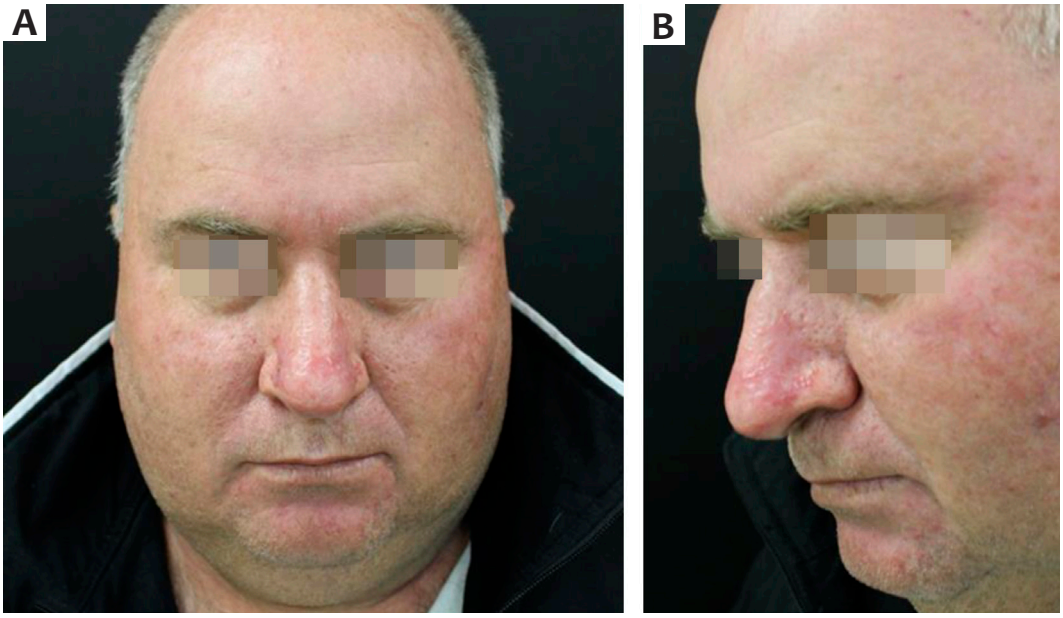

Figure 4: Patient 1, six months after surgery.
A. Front view.
B. Side view

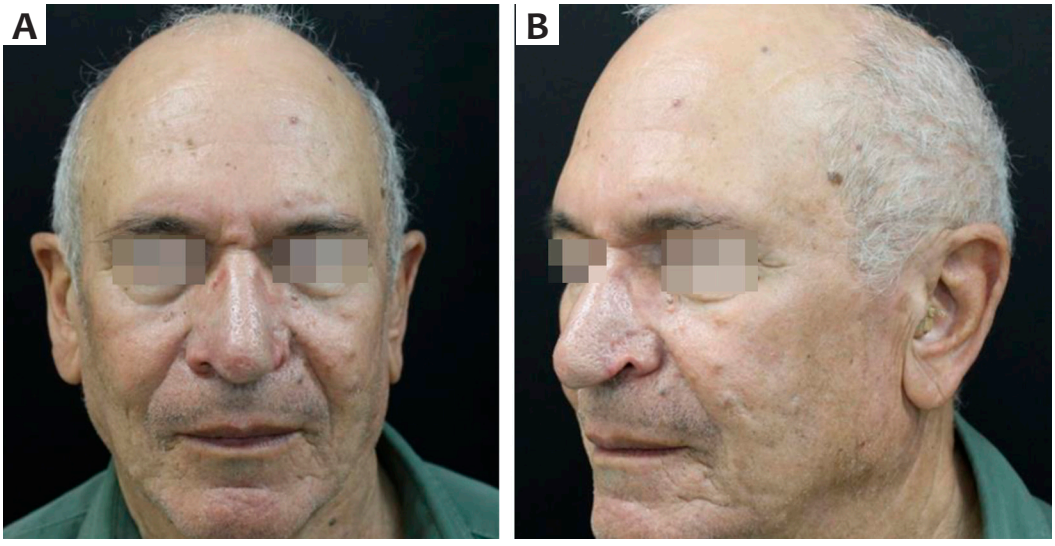

Figure 5: Patient 2, six months after surgery.
A. Front view.
B. Side view

nodules and nasal hypertrophy.[7]

There are several approaches varying according to the rhinophyma classification. The most frequently cited methods are YAG/CO_2 laser, surgical microdermabrasion, electrosurgery (electrocoagulation), cryosurgery, high-frequency equipment (radiofrequency), and total excision with a cold blade and grafting. There is no method of choice in the literature, as costs and results vary, and there is a surgeon-dependent factor.[3]

The YAG/CO_2 laser has a good response but is expensive. Microdermabrasion may require several sessions. Cryosurgery can leave residual post-inflammatory hypochromia, especially in patients with higher skin phototypes. The aesthetic result with grafting is generally unsatisfactory, but it can be used for reconstruction when there is associated BCC.[3,5]

Electrosurgery (ELC), on the other hand, is a simple technique with a low cost of materials. The disadvantages are the difficulty in delimiting the tissue to be excised (surgeon-dependent) and the risk of leaving a scar when going too deep into the skin to be removed.[5]

A vasoconstrictor associated with the anesthetic and manual compression or using the blend mode (mixture of 50% cutting and 50% coagulation) at the time of surgery can reduce

bleeding, another ELC complication.

Our described cases agree with the literature and corroborate the good results obtained with the technique.[4,5]

CONCLUSION

Rhinophyma treatment can be conducted using several methods, with their risks and surgeon-dependent factors. Among them, electrosurgery presents a low cost and shows satisfactory results, as in the cases presented. ●

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Schwannoma of the upper lip in an adolescent: report of a rare case

Schwannoma no lábio superior em adolescente: relato de caso raro

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.2024160313

ABSTRACT

Schwannomas are benign nerve sheath tumors derived from Schwann cells. The sites most often involved are the head and neck (25-48%), with only 1% occurring in the oral cavity. Most schwannomas occur in adult individuals between the third and fifth decades of life. Lip involvement is extremely rare during childhood and adolescence, with few reports in the literature. The prognosis is favorable and surgical excision is the treatment of choice. We report an interesting case of upper lip schwannoma in an adolescent with successful surgical treatment and no evidence of recurrence after 4 years.

Keywords: Neurilemmoma; Lip; Neoplasms; Schwann Cells.

RESUMO

Schwannomas são tumores benignos derivados das células de Schwann da bainha dos nervos. Os locais mais frequentemente envolvidos são a cabeça e o pescoço (25-48%), com apenas 1% dos schwannomas ocorrendo na cavidade oral. A maioria dos schwannomas acomete indivíduos adultos entre a terceira e a quinta década de vida. Acometimento dos lábios é extremamente raro durante a infância e adolescência, com poucos relatos na literatura. O prognóstico é favorável, e a excisão cirúrgica é o tratamento de escolha. Apresentamos um caso interessante de schwannoma no lábio superior em paciente adolescente, com tratamento cirúrgico bem-sucedido e sem sinais de recidiva após quatro anos.

Palavras-chave: *Neurilemoma; Lábio; Neoplasias; Células de Schwann.*

Case report

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INTRODUCTION

Schwannoma or neurilemmoma is a benign neoplasm that arises from Schwann cells in the sheath of peripheral or cranial nerves. The vestibulocochlear nerve is most commonly involved, but any myelinated nerve fiber can be affected, with the exception of the olfactory and optic nerves.[1]

The etiology of these tumors is not fully understood. Evidence suggests that tumor transformation of Schwann cells is caused by loss-of-function mutations of the NF2 tumor suppressor gene and suggests that these tumors have a predilection for locations prone to neural injury due to compression or physical trauma.[2] Approximately 25-48% of schwannomas occur in the head and neck region. Schwannomas account for just over 1% of benign tumors reported in the oral cavity, with the tongue being the most common site.[3] These tumors only rarely appear on the lips, with few cases reported in the literature.[3]

As a rule, schwannoma is a solitary tumor, only occasionally presenting as multiple lesions. Clinically, it appears as an encapsulated, slow-growing nodule.[4] When small, most schwannomas are asymptomatic, but pain, whether localized to the tumor or radiating along the nerve of origin, may be present.[5] Differential diagnoses of schwannoma in the oral region include neurofibroma, granular cell tumor, fibroma, leiomyoma, hemangioma, lymphangioma, lipoma, pyogenic granuloma, and benign salivary gland tumors.[1] Excisional biopsy and histopathological examination are indicated to establish the diagnosis.[4] Histologically, in addition to the classic schwannoma, there are cellular, epithelioid, glandular, and plexiform variants.[5]

Conservative surgical excision is the approach of choice, with a favorable prognosis and low recurrence rates as long as complete removal of the tumor is achieved.[6] Malignant transformation is rare, and wide margins are not recommended.[4] In this report, we present a case of classic schwannoma in an unusual location and age range.

CASE REPORT

A 16-year-old male presented with a painless nodule on his upper lip that had been growing slowly for 2 years. Dermatological examination revealed a fibroelastic nodule of the same color as the adjacent mucosa, 1.5 × 1.0 cm in size (Figure 1). There was no cervical lymphadenopathy. The patient's past medical history was notable for sporadic local trauma.

Despite the likely benign nature of the lesion and absence of local pain, the patient and his legal guardians were anxious to obtain a definitive diagnosis. It was therefore decided to excise the lesion. An infraorbital nerve block was performed and a longitudinal incision was made over the lesion, which was then enucleated. The surrounding nervous structure, motor function and local sensitivity were preserved intact (Figure 2).

Histopathological examination revealed an encapsulated schwannoma, exhibiting the classic Antoni A (with Verocay bodies) and Antoni B areas (Figure 3). There was no evidence of mitosis or necrosis. Immunohistochemical examination showed a positive reaction to anti-SOX10 antibody in the nuclei of neural fibers (Figure 4).

No recurrence has been observed over 4 years of follow-up. Furthermore, a good cosmetic outcome was obtained without compromising local function or sensitivity.

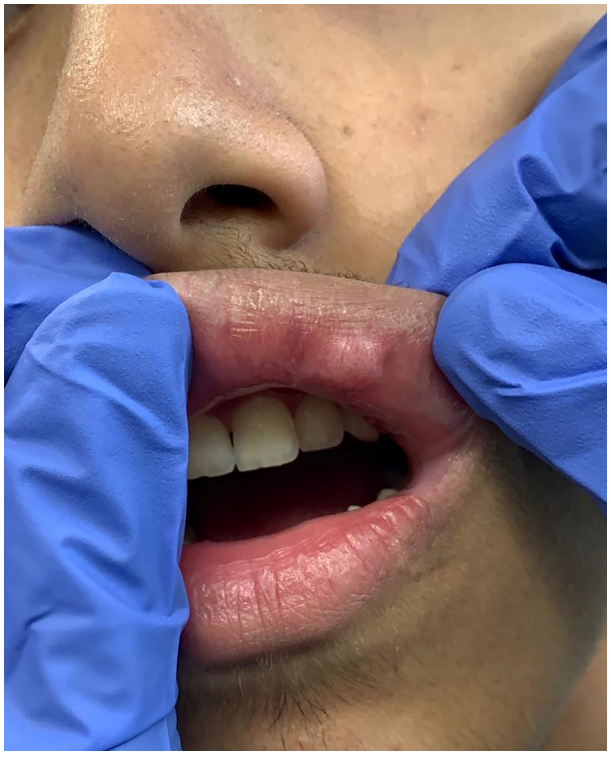

FIGURE 1: Schwannoma. Asymptomatic nodule on the upper lip

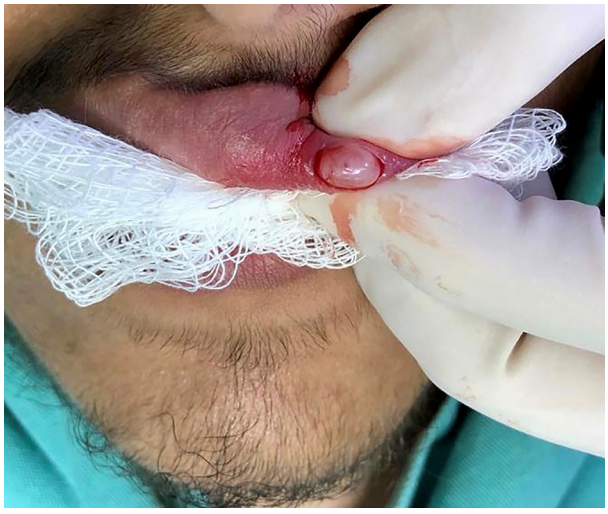

FIGURE 2: Schwannoma. Encapsulated mass observed intraoperatively

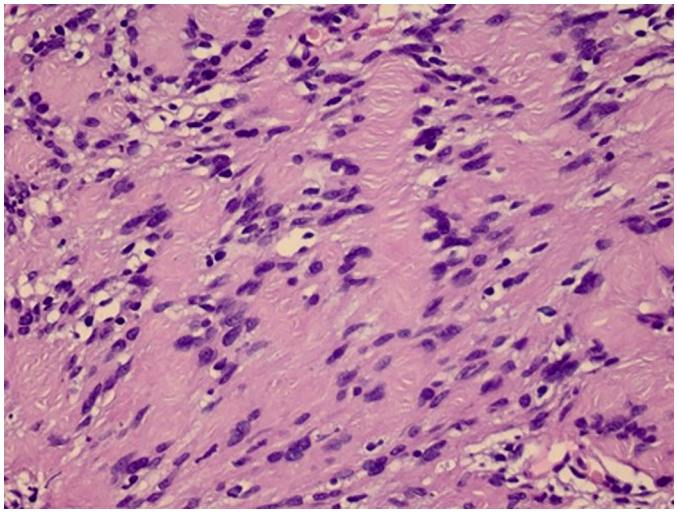

Figure 3: Schwannoma. Benign, encapsulated mesenchymal neoplasm consisting of proliferating neural fibers, which are arranged into several fields with nuclei side by side (nuclear palisading) and cytoplasm in the center, forming Verocay bodies (Antoni A area). Hematoxylin and eosin (H&E) stain, 400× magnification

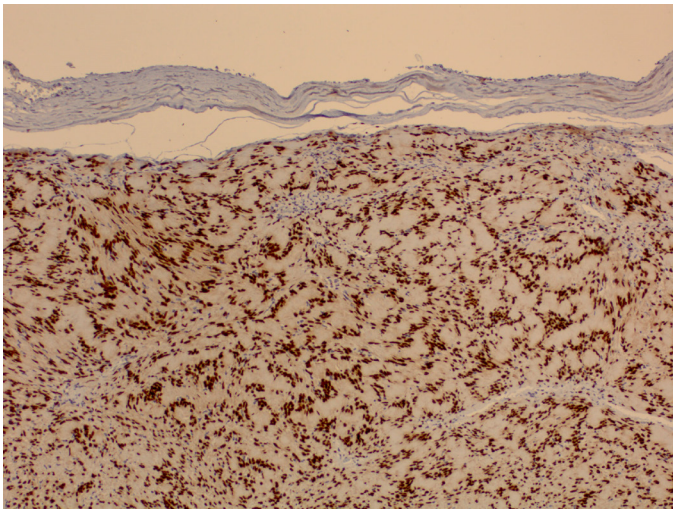

Figure 4: Schwannoma. Immunohistochemical examination showing strong anti-SOX10 antibody positivity in the nuclei of neural fibers (100× magnification)

DISCUSSION

Schwannomas are benign, slow-growing, encapsulated, generally solitary tumors. Although the etiology of neurilemmomas remains unknown, these lesions are believed to originate as a result of proliferating Schwann cells, which can compress and displace the surrounding nerve.[7]

The majority of reported cases occur in the head and neck. Although the oral region is highly innervated, only 1% of these tumors arise from peripheral nerves in the oral cavity.[4] The upper lip is one of the least likely sites, with very few documented cases.[1] Neurilemmomas may occur at any age but are most common between the third and fourth decades of life; in contrast, our patient was much younger. The diagnosis of schwannoma is based on its histological features.[8] In this case, the histological presentation was characteristic and easily distinguishable from that of other lesions composed of spindle cells, such as neurofibroma or leiomyoma. The features of the tumor reported herein meet all histological criteria for a classic schwannoma. Typically, Antoni A type tissue is observed, which consists of spindle cells aligned in a characteristic "nuclear palisade" arrangement. Between two neighboring palisades are small eosinophilic masses known as Verocay bodies, formed by a combination of Schwann-cell cytoplasm and associated reticular fibers. Antoni B areas comprise a smaller number of spindle cells arranged randomly within a loose myxomatous stroma.[5] The nuclear palisade distribution typical of a schwannoma[8] was easily identifiable in this case.

Complementary immunohistochemical analysis showed diffuse anti-SOX10 antibody positive in the nuclei of nerve fibers. The most commonly used immunohistochemical markers for the diagnosis of schwannoma are currently S100 and SOX10.[9]

The prognosis in schwannoma is favorable. Conservative surgical excision is facilitated by the capsule, which provides a safe natural plane of dissection. As a rule, there is no recurrence after complete excision.[6] If the lesion does recur, one must consider whether complete enucleation was indeed achieved or whether malignant transformation has occurred. Malignant transformation is exceedingly rare overall, but is significantly more common in lip schwannomas than in those occurring elsewhere (9.47% versus 0.001%).[4]

Despite their rarity, schwannomas should be considered in the differential diagnosis of labial nodules due to the abundant innervation of the lip.[1] Early diagnosis of these lesions while they are still small increases the odds of a successful surgical outcome, as resection can be particularly complex due to the extensive network of nerves that supply the lips.[4] This patient had an excellent postoperative course, with no evidence of recurrence and no sensory impairment at 4 years of follow-up.

CONCLUSION

Although schwannomas of the upper lip are extremely rare, this diagnosis should be contemplated by dermatologists when evaluating lesions on the lips. Awareness of the histological and immunohistochemical hallmarks of schwannoma is essential to prevent diagnostic error and ensure a satisfactory surgical outcome. Enucleation is an appropriate technique for resection of these encapsulated tumors in the lip region, as it produces a cosmetically acceptable scar while preserving peripheral nerve integrity. ●

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Improvement of abdominal laxity with combined use of calcium hydroxylapatite and radiofrequency microneedling

Melhora da flacidez abdominal com uso combinado de hidroxiapatita de cálcio e microagulhamento com radiofrequência

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.2024160315

ABSTRACT

In clinical practice, not all patients seem to benefit from treatment with calcium hydroxyapatite, often due to the improper indication of this procedure for patients who may require an associated surgical approach. In this context, our objective was to describe a practical method for evaluating and selecting the ideal patient for a non-surgical approach to abdominal skin laxity, along with presenting clinical cases treated with the combined use of calcium hydroxylapatite (CaHA) and microneedling with radiofrequency.

Keywords: Durapatite; Radiofrequency Therapy; Abdomen.

RESUMO

Na prática clínica, nem todos os pacientes com flacidez cutânea se beneficiam do tratamento com hidroxiapatita de cálcio (CaHA), principalmente pela indicação equivocada desse procedimento para pacientes que possivelmente necessitariam de alguma abordagem cirúrgica associada. Nesse contexto, nosso objetivo foi descrever um método prático para a avaliação e seleção do paciente ideal para a abordagem não cirúrgica da flacidez cutânea abdominal. Além disso, apresentamos casos clínicos tratados com a combinação de CaHA e microagulhamento com radiofrequência.

Palavras-chave: *Durapatita; Terapia por Radiofrequência; Abdome.*

Case report

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Conflict of interest: Dr. di Sessa has been a speaker for Merz Pharmaceuticals.

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INTRODUCTION

Calcium hydroxylapatite (CaHA) is a biodegradable, resorbable injectable filler, with a well-established safety profile. CaHA is known to induce collagen, proteoglycan and elastin synthesis and promote remodeling of all aspects of the entire extracellular matrix.[1]

Although CaHA injections have been reported to improve abdominal skin laxity,[2] not all patients with this condition appear to benefit from the procedure in the clinical practice. Accurate assessment of abdominal skin laxity is critical to achieving optimal results. Thus, we aim to describe a practical approach to assessing skin laxity and to present clinical cases using a combination of CaHA and radiofrequency microneedling to improve treatment outcomes.

METHODS

All procedures involving human patients described in this report were conducted in accordance with the ethical standards of our institutional human research ethics committee and with the 1964 Declaration of Helsinki declaration and its subsequent amendments or equivalent ethical standards.

Ethics approval

This study was approved by our centralized institutional human research ethics committee (protocol number 67754022.0.0000.5493). Written informed consent was obtained from all the patients to allow the publication of their case details and any accompanying images published.

Eligible patients were men and women over 18 years of age with mild abdominal skin laxity and/or atrophy who agreed to participate in the study. Exclusion criteria included the presence of active skin lesions in the abdominal area, a history of autoimmune disease, use of anticoagulants, body mass index (BMI) greater than 25, or excess skin. Standardized photographs were taken at the following time points: pre-injection, 30 days, and again at 30 and 90 days after the last injection, using consistent lighting, distance, and frontal, oblique, and lateral views.

Patient evaluation

A thorough evaluation of the abdominal area is essential, considering the presence or absence of the following factors: localized subcutaneous fat accumulation, skin laxity, excess skin, and/or skin atrophy. The most important criteria to consider are the presence or absence of fat and excess skin. If the patient presents with localized fat alone, fat and excess skin, or excessive skin, laxity combined with skin atrophy, (possibly in combination with a non-invasive energy-based procedure) may be recommended (Figure 1).

Excess skin can be identified by signs such as a sad umbilicus,[3] a supraumbilical fold along the linea alba that can occur after pregnancy or due to aging, sagging skin, or excess skin

	Fat	Laxity	Excessive Skin	Skin Atrophy	CaHA injection	Associated Treatment	CaHA Dilutions	n. of session /n. ser per session
	✗	✗	✗	✗	Preventive	None	1:4	1/2
Fat	✓	✗	✗	✗	After treatment	Liposuction	1:4	1-2/2
	✓	✓	✗	✗	After treatment	Liposuction	1:1 1:2	1-2/2
	✓	✓	✓	✗	After treatment	Liposuction/ Tummy tuck Devices	1:2	1-2/2
	✓	✓	✓	✓	After treatment	Liposuction/ Tummy tucky/ Devices	1:2	3/2
No Fat	✗	✓	✗	✗	First treatment	None	1:2	3/2
	✗	✓	✓	✗	Upper OR lower abs(First treatment); Both (Associated treatment)	None/Devices	1:1 1:2	3/2
	✗	✓	✓	✓	After treatment	Mini Tummy tuck/Tummy tuck Reverse Tummy tuck	1:1 1:2	3/2
	✗	✗	✗	✓	First treatment	None/Devices	1:2	3/2

FIGURE 1: Abdominal laxity evaluation and potential treatment approaches. If the subject presents with localized fat alone, fat combined with excessive skin, or excessive skin, laxity associated with skin atrophy, an associated surgical treatment is indicated (with or without the addition of a non-invasive energy-based device)

after liposuction. Other indicators include the presence of an infra-umbilical semilunar line and/or a suprapubic fold. Conversely, patients with skin laxity, but without excessive skin to warrant excisional surgery, or those without localized fat who may benefit from soft tissue contraction after liposuction, are ideal candidates for the combined technique described herein (Figures 2-4).

Treatment plan

Anesthesia was administered using a combination of with topical 2% lidocaine, subcutaneous infiltration of a solution containing lidocaine, epinephrine, and saline, along with 70% nitrous oxide inhalation. Radiofrequency (RF) microneedling was applied to the treatment area in four passes: first, in fixed mode (7mm, 30J), followed by cycle mode (6mm, 50-60J), burst mode (7-5-3mm, 30J), and burst mode again (6-4-2mm, 30J). CaHA (Radiesse®; Merz Pharmaceuticals GmbH, Frankfurt, Germany) was injected immediately after the RF microneedling in the same session. The treatment session was repeated after a 30-day interval for a total of three sessions. Two syringes per session of CaHA, diluted 1:2, were injected per session into the subdermal plane using a 22G 70mm cannula with a fanning technique. The total volume was evenly distributed among six entry points (three in the upper abdomen and three in the lower abdomen), with five radial vectors each, injecting 1.5ml per point and 0.3ml per vector. A post-injection massage was performed immediately following the injections. Hydration was recommended as part of the post-procedure care.

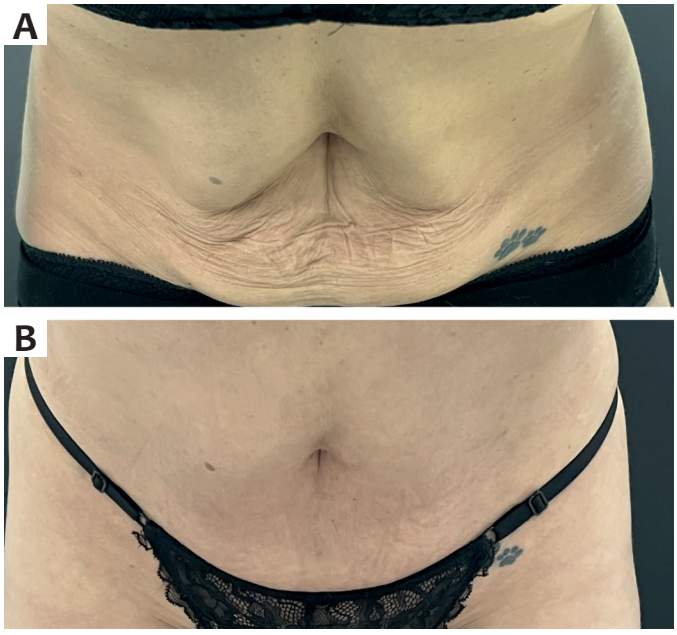

Figure 2: Pre-treatment (**A**) and 30 days after the third session of the combination treatment (**B**)

Results Demography

We report on 10 female patients between the ages of 35 and 45, all with no relevant medical history (e.g., no use of medications that cause bleeding, no active infections or other inflammatory processes in the treatment area, and no history of autoimmune diseases). All patients showed improvement in abdominal skin laxity, as evaluated by both the subjects and the investigator. No major adverse events were reported.

DISCUSSION

RF microneedling has been reported as an effective and safe intervention when used safely in combination with other treatment modalities. RF uses low-frequency electromagnetic waves (ranging from 100 kHz to 5 MHz) to generate an electromagnetic field within the skin.[4] When skin surface temperatures reach 40° to 45°C, this controlled thermal damage to the reticular dermis stimulates a healing response, promoting neocollagenesis, elastin formation, and angiogenesis, which clinically results in skin tightening and improved skin quality.[5] Combining microneedling with RF allows for the delivery of heat at varying depths (from 0.5 to 4 mm), expanding the range of anatomical locations and tissue types that can be effectively treated.[4] Addi-

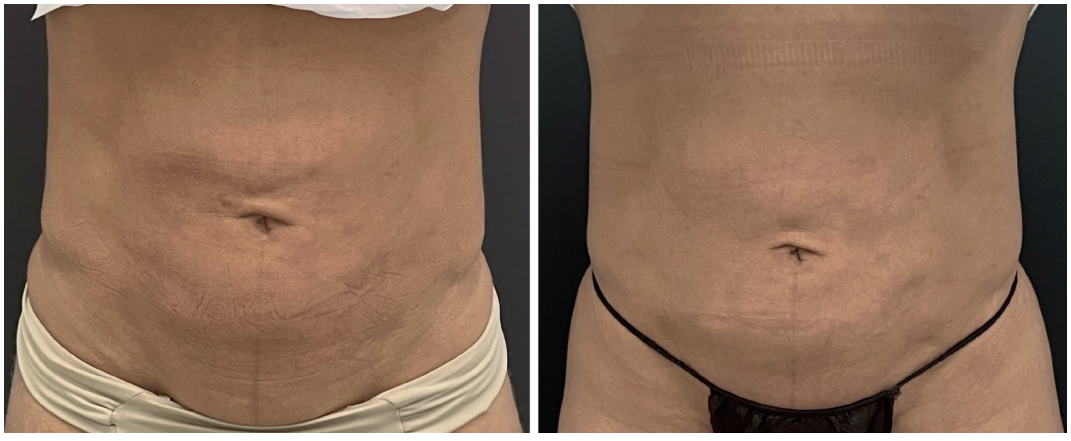

Figure 3: Pre-treatment (**A**) and 30 days after the third session of the combination treatment (**B**)

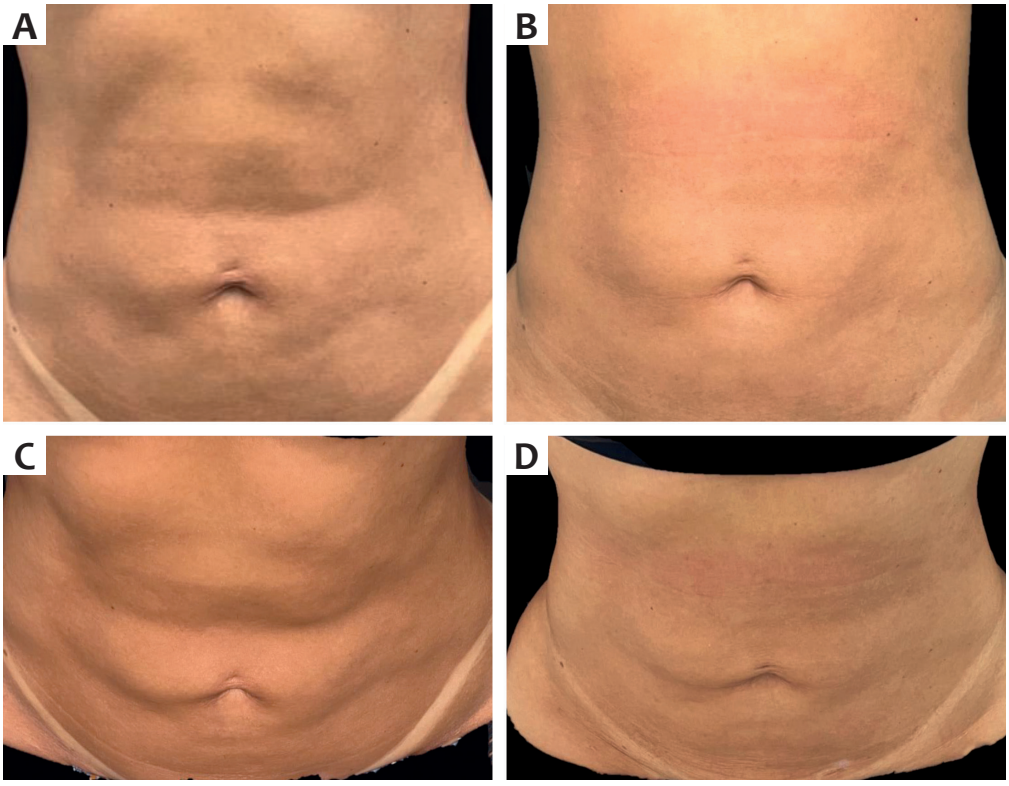

FIGURE 4: Pre-treatment (**A**) and 30 days after the third session of the combination treatment (**B**) in an upright position.
Pre-treatment (**C**) and 30 days after the third session of the combination treatment (**D**) with the body bent at 60 degrees

tionally, fractional RF microneedling leaves portions of the skin untreated, which reduces healing.[4] In an animal model, RF microneedling demonstrated increased levels of tissue remodeling markers, including collagen I and III, compared to microneedling alone group after a single treatment session.[6] The Morpheus[8] device (InMode Aesthetic Solutions), a fractional RF system with programmable penetration depth and energy delivery, features 24 coated needles that coagulate fat while contracting the reticular dermis and surrounding connective tissue.[7] CaHA is a versatile filler, with a well-established safety profile that promotes long-term collagen stimulation, primarily by inducing type 1 collagen deposition. This leads to improved mechanical properties of the skin, unlike type 3 collagen, which is often associated with fibrotic processes.[8] Even in high dilutions (1:2 to 1:6), CaHA has been shown to increase type 1 collagen and elastin production up to 7 months after injection in areas such as the neck and décolletage.[9] In patients with HIV-related lipoatrophy, a 50% increase in skin thickness was observed 3 months after CaHA application, with 91% of patients maintaining this improvement over an 18-month evaluation period.[10] Wasylkowski reported improved skin laxity and dermal thickness in the abdominal region, arms, and thighs, as measured by a skin cutometer and ultrasound, as early as 5 weeks after treatment.[2] The abdomen showed the most significant improvement in skin density, with 88% of cases showing improvement compared to baseline. The combination of two well-established non-invasive methods for collagen stimulation, as presented in this preliminary report, improved skin laxity in all patients. This approach offers a promising treatment option for patients with abdominal skin laxity, particularly those with skin atrophy or laxity who prefer to avoid surgery (Figures 2-4). Further studies with blinded evaluations and randomized designs are necessary to validate these findings. ●

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Approval of the final version of the manuscript, study conception and planning, data collection, analysis, and interpretation, active participation in research supervision, intellectual contribution to the diagnostic and/or therapeutic management of the cases studied, critical review of the manuscript.

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Sulco da alça do sutiã: relato de caso de nova proposta terapêutica com ácido hialurônico injetável

A new therapeutic proposal for brassiere strap groove correction with injectable hyaluronic acid: a case report

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.2024160317

ABSTRACT

Brassiere strap groove is a common aesthetic deformity in women with breast hypertrophy, resulting from chronic pressure exerted by brassiere straps on the soft tissues over the trapezius muscle, causing local tissue depression. This condition is typically treated with fat grafting, often performed simultaneously with breast reduction surgery or lipoabdominoplasty. We report the case of a patient with recurrent brassiere strap groove following prior fat grafting, successfully corrected with hyaluronic acid filler.

Keywords: Hyaluronic Acid; Dermal Fillers; Dermatology.

RESUMO

O sulco da alça do sutiã é uma alteração estética comum em mulheres com mamas hipertrofiadas e de grande volume, causado pela pressão crônica da alça do sutiã nos tecidos moles na região acima do músculo trapézio, causando deformidade com depressão local. É comumente tratado com enxerto de gordura, no mesmo tempo cirúrgico da redução mamária ou lipoabdominoplastia. Relatamos aqui um caso de preenchimento com ácido hialurônico no sulco da alça do sutiã que havia recidivado após tratamento prévio com lipoenxertia.

Palavras-chave: *Ácido Hialurônico; Preenchedores Dérmicos; Dermatologia.*

Case report

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INTRODUCTION

Large breasts can cause postural changes, back and neck pain, stretch marks, intertrigo, and even psychological discomfort.[1] In addition, the weight of the breasts is supported by brassiere straps, creating constant pressure on the shoulders. Over time, this chronic force exerted by the straps on the shoulders, especially in women with breast hyperplasia, may lead to the development of "brassiere strap groove," an evident depression in the soft tissues above the trapezius muscle, where the bra straps rest.[2] In more severe cases, it may cause aesthetic discomfort. This condition is typically corrected with autologous fat grafting, often performed simultaneously with breast reduction surgery or lipoabdominoplasty. In this report, we describe the case of a patient with recurrent brassiere strap groove following prior fat grafting, successfully corrected with hyaluronic acid filler.

METHODS AND RESULTS

Before starting the treatment, the patient signed an informed consent form and was photographed (Figures 1 and 2). A topical anesthetic (4% lidocaine cream) was applied to the treatment area, followed by antisepsis with 2% alcohol chlorhexidine. The bra strap groove defect on each side was marked, and small incisions were made to introduce an 18 G x 70 mm cannula (at the dorsal region, central but external to the marked area). High G-prime hyaluronic acid (Sofiderm® Derm Sub-skin 10 mL, Aeskins Pharmaceauticals, Santana de Parnaíba, SP, Brazil) was injected, 5 mL per side, starting with a small bolus in the center and followed by retrograde injections in a fan-shaped pattern. Manual molding was then performed to ensure even distribution of the product. The procedure was quick, without complications, and the results were immediately visible (Figure 3).

DISCUSSION

Brassiere strap groove is a contour deformity between the neck and shoulder caused by chronic pressure from brassiere straps. Although it is more common in women with large and heavy breasts, it can occur in anyone who wears a bra. This deformity may also present unilaterally in cases of unilateral mastectomy. The contour between the neck and shoulder starts at the neck-body junction, continues downward and laterally, and ends at the shoulder. Under normal conditions, there are no depressions along this contour. However, in women with breast hypertrophy who wear ill-fitting brassieres (eg, with thin straps), a brassiere strap groove may develop. Anatomically, the brassiere strap groove is delimited by the skin (superiorly), scapular spine (inferoposteriorly), clavicle (inferoanteriorly), deltoid muscle (anteriorly), acromioclavicular junction (laterally), transverse part of the trapezius muscle (posteromedially), and deltoid muscle (posterolaterally). Between the insertion lines of the trapezius and deltoid muscles, an imaginary line crosses the scapular spine and clavicle. Brassiere strap grooves occur medially to this imaginary line in women with breast hypertrophy.[1]

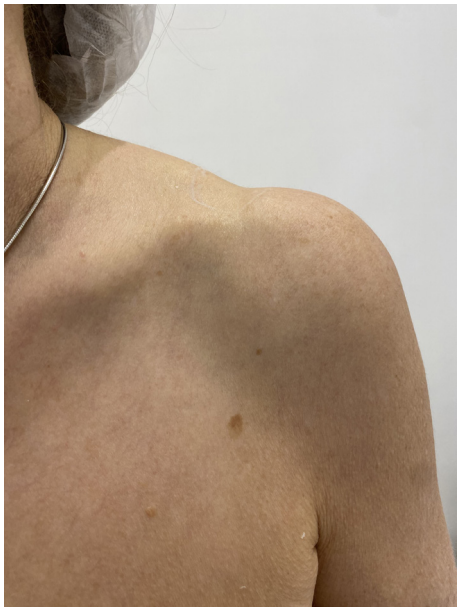

FIGURE 1: Left side, pretreatment

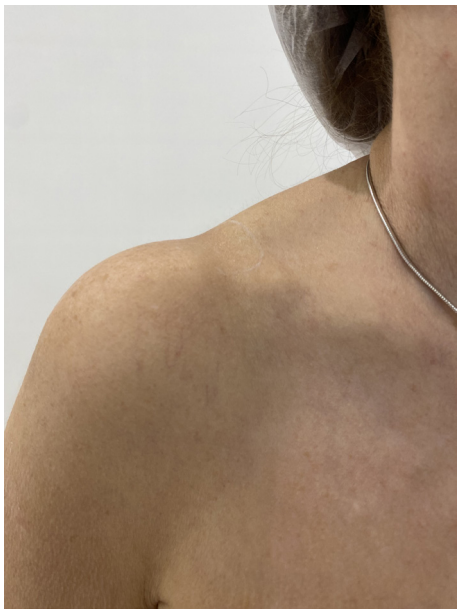

FIGURE 2: Right side, pretreatment

In 2014, Ergün et al. classified brassiere strap grooves into three types. In type 1, or mild deformity, there is a minimal indentation that is mostly perceived by the physician than the patient. In type 2, or moderate deformity, the contour irregularity is more noticeable, as the depth of the depression can measure up to 0.5 cm below the imaginary line, with a width of up to 2 cm. In type 3, or severe deformity, the depression is very evident, with a depth of up to 1 cm and a width of up to 4 cm.[1] Brassiere strap grooves can be prevented by wearing properly fitting bras with wide, padded straps, but for cases of breast hyper-

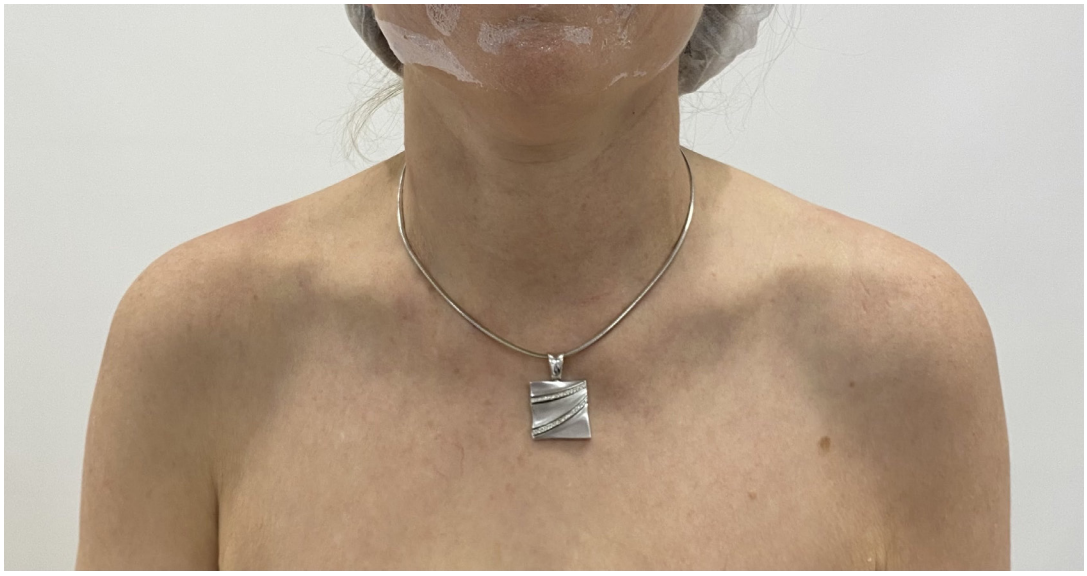

Figure 3: Immediately after surgery

trophy, breast reduction is the primary treatment. Although surgery alleviates back, neck, and shoulder pain, it does not correct shoulder grooves. Traditionally, brassiere strap grooves have been corrected with fat grafting, using approximately 25 to 40 mL of lipoaspirate, with overcorrection necessary due to necrosis and partial resorption of the graft tissue.[3,4]

The use of hyaluronic acid for body shaping has been gaining popularity, particularly for gluteal and breast augmentation. It is a minimally invasive procedure that does not require general anesthesia or hospitalization, allowing for fast recovery and posing a low risk of severe infections due to limited tissue exposure. Considering that patients seek this procedure for aesthetic reasons, avoiding a hospital setting is desirable. Moreover, hyaluronic acid fillers offer the advantage of predictable outcomes, have reproducible techniques, and can be dissolved with hyaluronidase if necessary.[5] Another advantage of injectable hyaluronic acid is that it can be performed in the initial stages of the shoulder groove. It may be used as a first-line treatment depending on the case and the patient's comorbidities, or as an alternative in cases of recurrence after fat grafting, as in the case described in this report. Given the anatomy of the treated region and the injection plane, there is minimal risk of severe complications such as arterial occlusion or nerve damage.

Depending on the classification of the groove, a large amount of injected product may be required. To prevent product migration, we recommend that patients wear strapless bras and avoid carrying heavy bags for a month. This treatment can be combined with other procedures for aesthetic enhancement of the neck and breast region, such as pre and postaxillary fat reduction and collagen stimulation. To our knowledge, this is the first reported case of brassiere strap groove correction using hyaluronic acid filler.

CONCLUSION

Minimally invasive and safe aesthetic procedures that offer quick results are becoming more popular among both physicians and patients. Hyaluronic acid filler for brassiere strap groove correction is another technique that can be refined for broader use in cosmetic treatments. ●

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Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; collecting, analyzing and interpreting data; critical review of the literature; critical review of the manuscript.

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Author's contribution: Approval of the final version of the manuscript; study design and planning; effective participation in research guidance; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical review of the manuscript.
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Cylindroma: a rare tumor in a typical site

Cilindroma: um raro tumor em localização típica

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ABSTRACT

Cylindroma is a rare benign neoplasm of probable origin in the eccrine sweat glands and is characterized by papular and nodular, painless, slow-growing lesions, generally located on the head, neck and scalp. When multiple, they can be part of hereditary syndromes. The authors report the case of a patient with a solitary nodulation on the scalp, presenting pathological examination compatible with cylindroma. The lesion was excised, with satisfactory results and no recurrence.

Keywords: Sweat Gland Neoplasms; Skin Neoplasms; Deubiquitinating Enzyme CYLD.

RESUMO

O cilindroma é uma neoplasia benigna rara, com provável origem nas glândulas sudoríparas écrinas, e caracteriza-se por lesões papulosas e nodulares, indolores, de crescimento lento, em geral localizadas em cabeça, pescoço e couro cabeludo. Quando múltiplas, podem fazer parte de síndromes hereditárias. Os autores relatam o caso de uma paciente com nodulação solitária no couro cabeludo, apresentando exame anatomopatológico compatível com cilindroma. Foi realizada exérese da lesão, com resultado satisfatório e ausência de recidiva.

Palavras-chave: *Neoplasias das Glândulas Sudoríparas; Neoplasias Cutâneas; Enzima Desubiquitinante CYLD.*

Case Report

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CASE REPORT

A 48-year-old female patient came to the Dermatology Department complaining of the appearance of an erythematous papule on her scalp about a year ago, which had progressed and became a painless nodule. No other associated skin lesions were reported. Her personal history included schistosomiasis and regular follow-up. There was no family history of the same condition or use of continuous medication. Dermatological examination revealed a papulonodular, erythematous lesion with a fibroelastic consistency and a smooth, shiny surface in the parietal region of the scalp (Figures 1 and 2). Dermoscopy showed arboriform vessels on the periphery of the lesion, and bright white striae and ulceration (Figure 3).

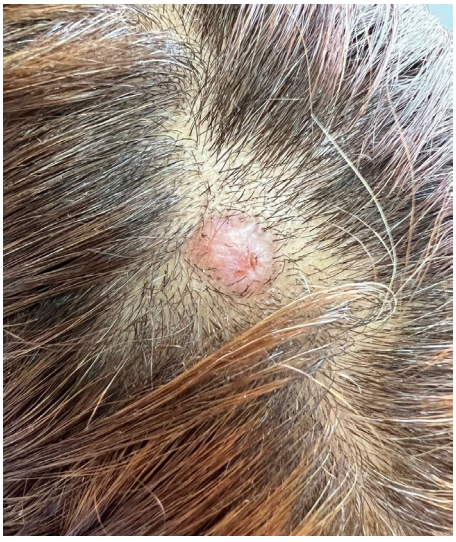

Figure 1: Papulonodular, erythematous, exulcerated lesion on the parietal region of the scalp

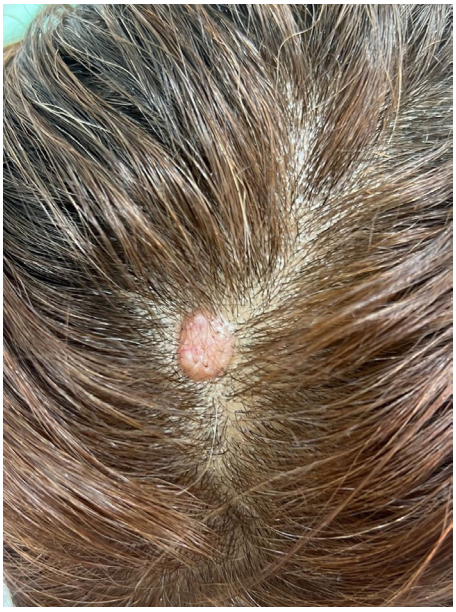

Figure 2: Papulonodular, erythematous lesion with a smooth, shiny surface, located on the scalp

The anatomopathological examination showed basaloid neoplasia, forming cell blocks of different sizes, arranged in the superficial and deep dermis, permeated by collagen matrix and stromal fusocellular proliferation. The cell blocks were well delimited, resembling pieces of a jigsaw puzzle. In addition, the cells were round with monotonous nuclei, no atypia, and a palisade arrangement was identified on the periphery. Sometimes ductal differentiation was seen in the center of the cell blocks (Figures 4 and 5).

The diagnosis of cylindroma was then confirmed, and a decision to completely excise the lesion was made, with closure using a double rhomboidal flap, with an excellent final aesthetic result.

DISCUSSION

Cylindroma is a rare benign neoplasm of the cutaneous adnexa, probably originating in the eccrine sweat glands, although the literature still differs as to its histogenesis.[1,2] Clinically, it presents as papulonodular, firm, fibroelastic, well-circumscribed, painless, slow-progressing, pinkish to reddish or even bluish lesions, measuring from a few millimeters to a few centimeters in size, and may have arboriform telangiectasias on their surface. In general, cylindroma develops as solitary lesions on the head, neck, and scalp.[3-6] The confluent growth of multiple cylindromas covering the entire scalp is historically known as a turban tumor.[3,4] These tumors are frequently seen in middle-aged and older women, and no racial disparity has been reported.[1,6] Although they can rarely be found solitarily and sporadically, cylindromas, especially when multiple or with an early onset, are observed in autosomal dominant hereditary syndromes with

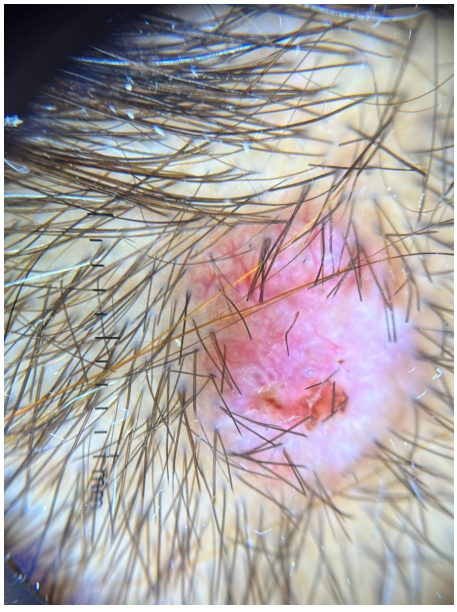

Figure 3: Arboriform vessels on the periphery, bright white striae and ulceration

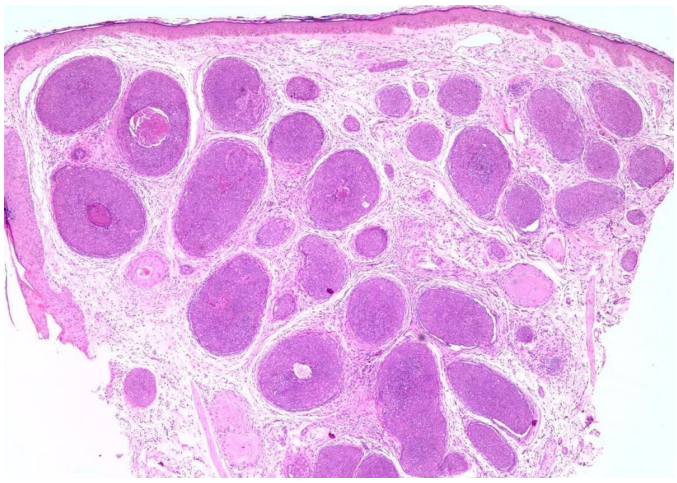

Figure 4: Hematoxylin & eosin, 40x magnification: blocks of basaloid cells arranged in the superficial and deep dermis

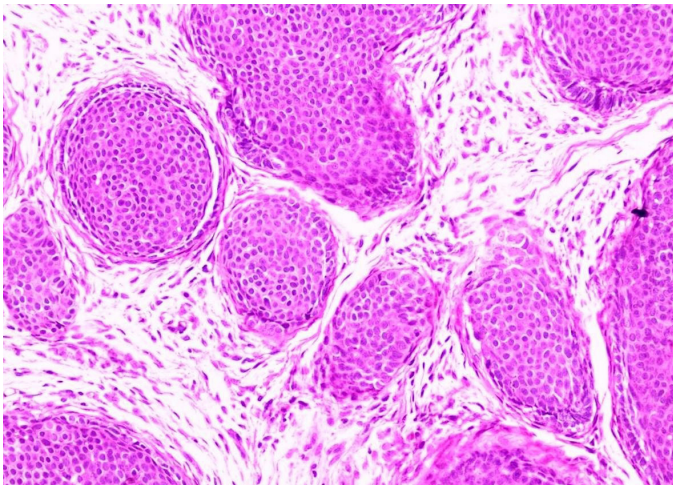

Figure 5: Hematoxylin & eosin, 200x magnification: round basaloid cell nests with monotonous nuclei in a typical jigsaw pattern, separated by a thick eosinophilic basement membrane

mutations in the CYLD gene.[1,2,4,6] Familial cylindromatosis is characterized by multiple cylindromas usually located on the scalp. Cylindromas associated with multiple trichoepitheliomas are found in familial multiple trichoepithelioma syndrome. Brooke-Spiegler syndrome is considered an overlap of these two conditions, characterized by the presence of numerous adnexal tumors, mainly located on the scalp and face, including cylindromas, spiradenomas, and trichoepitheliomas.[3,4,5,7] Genetic counselling may be indicated in patients with multiple cylindromas, spiradenomas, or trichoepitheliomas or in the presence of a single cylindroma in a first-degree relative with a history of cylindroma.[4,5] Dermoscopy shows the presence of arboriform telangiectasias, more prominent in the periphery of the tumor, and a homogeneous pinkish-white background and linear white striae.[8] Histologically, cylindromas consist of dermal nodules, not encapsulated, formed by nests of basaloid cells in a typical puzzle pattern, separated by a thick eosinophilic basement membrane. The peripheral cells are generally small, hyperchromatic, and palisade-shaped. The central cells are larger, pale and have vesicular nuclei.[3,4,6,9] The histological appearance of clusters of basaloid cell nests similar to cylinders when cut transversely has led to the descriptive term cylindroma.[4,5] Cellular pleomorphism and mitoses are generally absent.[3] Although rare, malignant transformation can occur in around 5-10% of patients, being more frequent in those with a mutation in the CYLD gene, given the presence, in general, of multiple lesions.[1,3,4,9,10] Suspicious clinical features for malignancy include rapid growth, bleeding, ulceration and changes in color.[2,3,4,9] In suspicious cases, radiological imaging, preferably MRI, should be considered, given the possibility of local invasion.[5,6] Standard treatment consists of surgical excision and is recommended in cases of suspected malignant transformation, functional impairment, or for aesthetic reasons.[1] For solitary lesions, curettage and cryotherapy are therapeutic options, while for small lesions, CO_2 laser can be a tool.[2,6] Finally, recurrence rates are relatively high, so extensive and complete removal of the tumor is recommended.[2,5]

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Confocal reflectance microscopy in basal cell carcinoma with globular dermoscopic pattern

Microscopia confocal de refletância no carcinoma basocelular com padrão dermatoscópico globular

Case Report

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ABSTRACT
The globular dermoscopic pattern in pigmented lesions of basal cell carcinoma can cause diagnostic confusion, especially in cases in which other more commonly observed structures are absent. Therefore, the use of refletance confocal microscopy becomes important to determine the diagnosis and eliminate the need for biopsies.
Keywords: Carcinoma, Basal Cell; Dermoscopy; Microscopy, Confocal.

RESUMO
O padrão dermatoscópico globular em lesões pigmentadas de carcinoma basocelular pode causar confusão diagnóstica, especialmente em casos nos quais outras estruturas, mais comumente observadas, estão ausentes. Portanto, o uso da microscopia confocal de refletância torna-se importante para determinar o diagnóstico e eliminar a realização de biópsias.
Palavras-chave: *Carcinoma Basocelular; Dermoscopia; Microscopia Confocal.*

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INTRODUCTION

On histopathology, the globular pattern found in pigmented lesions of basal cell carcinoma (BCC) corresponds to pigmented basaloid aggregates located at the dermoepidermal junction (DEJ) or in the dermis.[1,2] When this pattern is predominantly present or in the simultaneous absence of other dermoscopic structures characteristic of basal cell carcinoma, diagnosis using dermoscopy alone can be challenging. In this context, the use of confocal reflectance microscopy (CRM), which shows structures that correlate directly with histopathology, can be of great value. This communication aims to highlight the importance of CRM in the diagnosis of BCC lesions, especially in cases in which dermoscopy does not show the most prevalent characteristics.

CASE REPORT

The authors reported two cases of pigmentary lesions in young women. The lesions were examined using dermoscopy and CRM. Dermoscopy was performed using the Fotofinder ATBM skin imaging system and CRM using the Vivascope 1500 device, which displays images of the epidermis, DEJ, and dermis. Diagnosis was confirmed through anatomopathological examination.

Case 1: A 43-year-old woman, phototype II, with a personal history of melanoma and BCC. During total body mapping, a pigmented lesion, clinically similar to a melanocytic nevus, was identified in the lumbar region. Dermoscopy showed a symmetrical lesion with light and dark brown globules and dots, some of which were aggregated. No other structures were observed. RCM showed the presence of well-demarcated, shiny tumor islands/strands at the DEJ, with a surrounding dark cleft and palisade (Figures 1 and 3).

Case 2: A 34-year-old woman, phototype II, complaining of a six-year pigmentary lesion on her neck, with slow growth, and a previous diagnosis of melanocytic nevus. Dermoscopy showed an asymmetrical lesion with brown globules and dots. RCM showed bright strands at the DEJ, with dendritic structures inside and dark cracks around the strands (Figures 2 and 3).

DISCUSSION

Dermoscopy has a 95% specificity in the diagnosis of BCC.[1] In pigmented BCC lesions, characteristics which have been described as blue-grey ovoid nests or globules, concentric structures, leaf-like areas, and brown dots or globules were observed. The latter correspond, in histopathology, to small pigmented basaloid aggregates at the DEJ or superficial dermis, associated with pigmented BCC.[2] Although it is common to identify more than one dermoscopic feature in the same lesion, there are cases in which this does not occur, making the differential diagnosis challenging and including other lesions.[3,4] RCM shows structures that correlate directly with histopathology from the epidermis to the dermis. In the epidermis, the polarization of the nuclei is oriented along the same axis. The most characteristic structures of basal cell carcinoma stand out at the DEJ, as aggregates of tumor cells, described as shiny strands or nodules, with

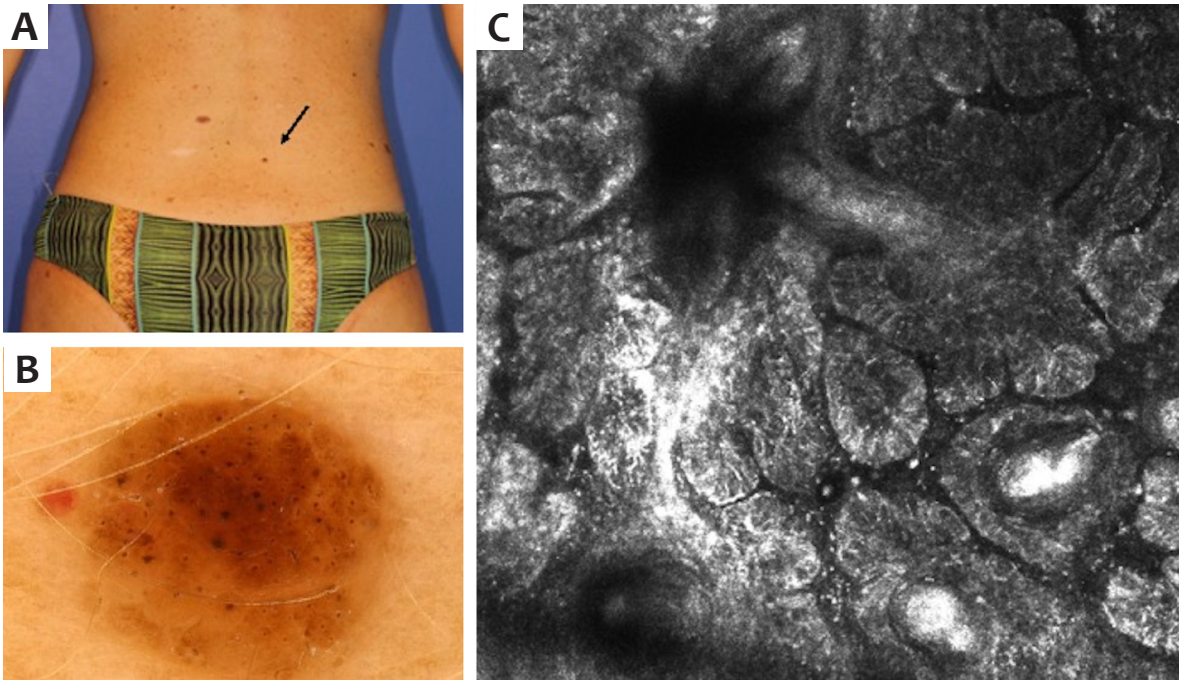

FIGURE 1:
A - Circular hyperchromic papule, measuring 4 mm, in the lumbar region. **B -** Light brown and dark brown globules simulating the cobblestone pattern.
C - JDE confocal microscopy: aggregates of bright tumor cells with peripheral nuclear palisade and dark clefts

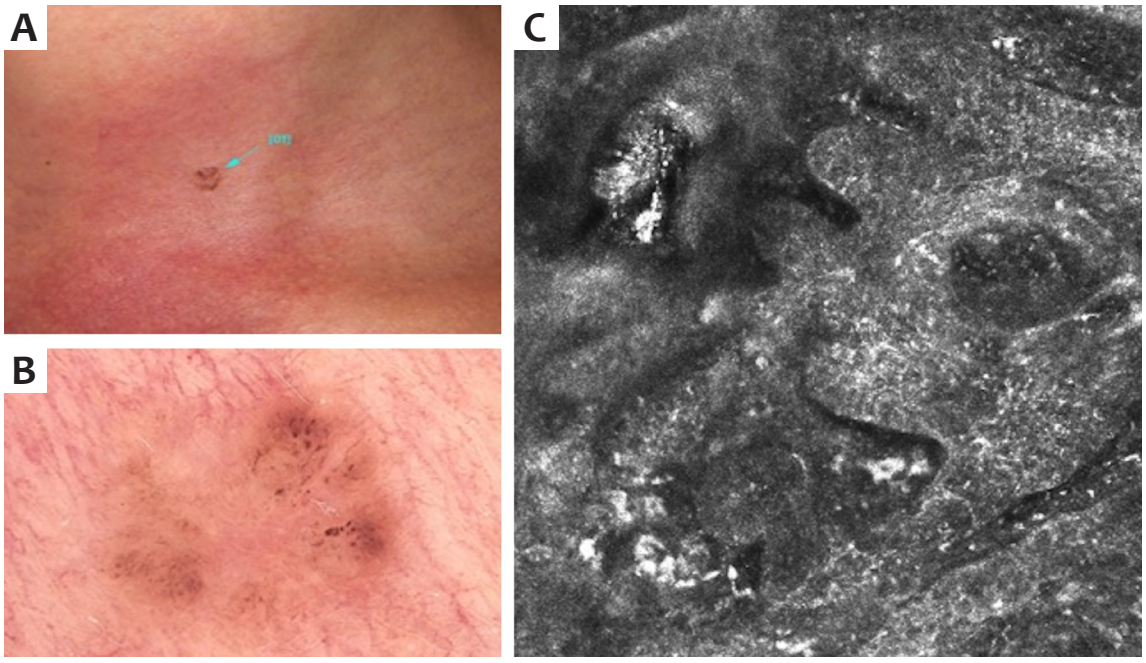

Figure 2:
A - Asymmetric hyperchromic papule, measuring 5 mm, in the left cervical region. **B -** Asymmetric globules and dots. **C -** JDE confocal microscopy: note the presence of strands with areas of high and low reflectance and bright dendritic structures, surrounded by dark clefts

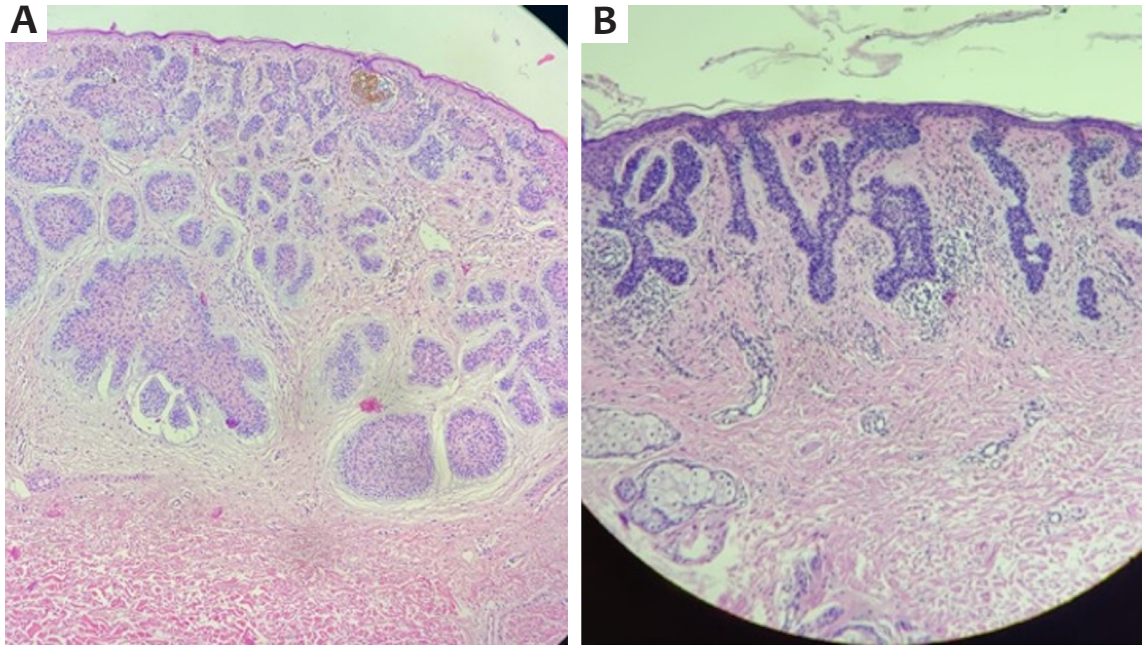

Figure 3:
A - Nests of basaloid cells with peripheral palisade arrangement, reaching as far as the reticular dermis. **B -** Nests of basaloid cells with peripheral palisade arrangement at the dermoepidermal junction

a peripheral nuclear palisade, often showing dendritic structures inside and dark crevices around them.[5-7] These characteristics are more common in pigmented BCC. Therefore, RCM can be a valuable complement to the clinical and dermoscopic evaluation of cutaneous neoplasms, increasing diagnostic accuracy. BCC with a globular pattern, in the absence of dermoscopic features, can be misdiagnosed as a melanocytic nevus. In such circumstances, RCM plays an important role in accurately confirming the diagnosis. ●

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Unpredictable findings after silicone filler: "leonine facies-like" reaction

A imprevisibilidade do preenchimento com silicone: reação "facies leonina-símile"

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ABSTRACT

A 76-year-old woman presented with facial edema and nodules in the front glabellar region and nasal dorsum that clinically resembled leonine facies. A facial ultrasound showed deposits of permanent facial filler with a "snowstorm" aspect characteristic of silicone oil, and an anatomopathological examination suggested a granulomatous reaction to the exogenous substance. Permanent fillers, such as silicone, behave like foreign bodies and cause a chronic granulomatous reaction. Although dermal fillers have been increasingly used, there is still no consensus on the management of their complications. In the present case, a good response to dapsone was observed.

Keywords: Silicones; Dermal Fillers; Granulomatous Disease, Chronic; Foreign-Body Reaction.

RESUMO

Paciente do sexo feminino, 76 anos, com edema facial e nódulos localizados na região frontoglabelar e dorso nasal que, clinicamente, assemelhavam-se à face leonina. Ultrassonografia facial mostrou depósitos de preenchimento facial permanente em "tempestade de neve", característicos de preenchimento por óleo de silicone, e o anatomopatológico sugeriu reação granulomatosa à substância exógena. Os preenchedores permanentes, como silicone, comportam-se como corpos estranhos e determinam reação granulomatosa crônica. Apesar do uso cada vez maior de preenchedores dérmicos, ainda não há um consenso no manejo de suas complicações. Neste caso, houve boa resposta ao uso da dapsona.

Palavras-chave: *Silicones; Preenchedores Dérmicos; Doença Granulomatosa Crônica; Reação a Corpo Estranho.*

Case Report

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INTRODUCTION

The ideal soft tissue filler is one that is effective, nonimmunogenic, nontoxic, noncancerous, nonmigratory, easy to apply, nonpalpable, and painless. Unfortunately, no such product yet exists, and we are increasingly seeing unforeseen manifestations for injectable products used as esthetic fillers. In the middle of the 20th century, a purified synthetic polymer in the form of injectable silicone began to be used for this purpose. Although it seemed promising, it was banned in the USA by the Food and Drug Administration (FDA) in 1991 due to complications.[1] In Brazil, it was suspended in 2006, although new complications secondary to its use have been reported to this day.[2]

A 76-year-old woman presented with intense facial edema and indurated erythematous nodules located in the frontoglabellar region and dorsum of the nose, which clinically resembled a leonine face (Figure 1). The lesions began 12 months ago after a dental procedure and only improved during oral corticosteroid therapy, with recurrence when attempts to stop it were made. She reported only mild local discomfort and no systemic symptoms. In her previous medical history, she had undergone facial rhytidoplasty with placement of a silicone menton prosthesis approximately 40 years previously, facial filling with an unknown substance 30 years ago, and had controlled hypothyroidism, hypertension, and rhinitis.

A facial ultrasound was requested and showed permanent facial filling deposits, characterized by areas of increased echogenicity in the dermis and subcutaneous tissue, determining "snowstorm" posterior reverberation artifacts, characteristic of silicone oil filling associated with oval anechoic images, with posterior acoustic reinforcement, superficial and smaller than 0.3cm, consistent with small deposits of pure silicone associated with silicone oil, located in the lower eyelids and infrapalpebral region, and a silicone implant in the chin, in a deep situation, with no signs of extravasation (Figure 2).

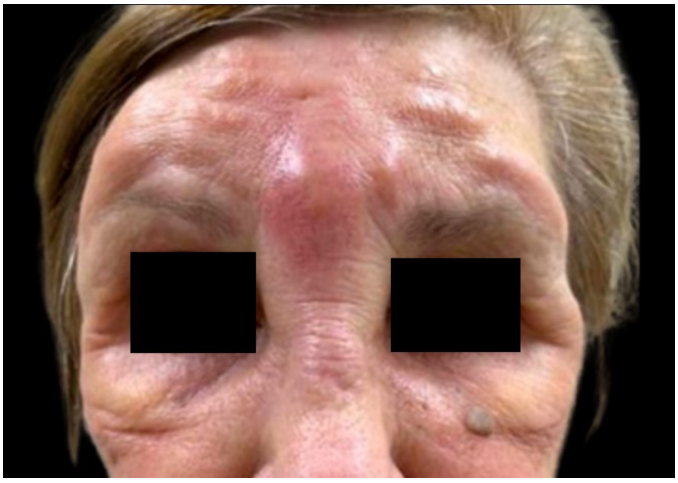

Figure 1: Leonine face after reactivation of facial filling with silicone, performed 30 years previously

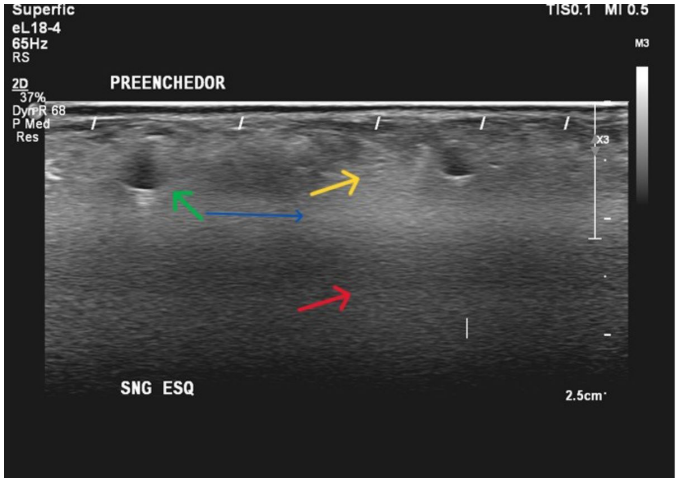

Figure 2: Dermatological ultrasound showing deposits of exogenous material characterized by a superficial hyperechogenic matrix, determining "snowstorm" artifacts of posterior reverberation (red arrow), suggestive of silicone oil (yellow arrow). There are small anechoic images in between, with strong posterior acoustic reinforcement, suggestive of small deposits of pure silicone (green arrow)

No areas of abscesses or liquid collections were evident. Histopathological examination of the skin identified numerous spherical spaces of different sizes, associated with a giganto-histiocytic reaction and negative tests for acid-fast bacilli (AFB) and fungi using the Ziehl-Neelsen, Grocott, and periodic acid-Schiff (PAS) stains. The morphological findings suggested a granulomatous reaction to the exogenous substance (Figures 3A, 3B, 3C).

Bacteriological, mycobacteriological, and mycological cultures were negative. General laboratory tests, including serology for viral infections such as SARS-CoV-2 and autoimmunity markers (antinuclear factor - ANF - and rheumatoid factor - RF), and glucose-6-phosphate dehydrogenase (G6PD) were unremarkable. The initial treatment recommended was prednisone 40mg (0.5mg/kg/day), moxifloxacin 400mg/day, and clarithromycin 500mg every 12 hours for 30 days (until the definitive results of the cultures) with total remission of the lesions. After 30 days, the corticosteroid therapy was gradually reduced and dapsone 50mg/day was introduced, with an increase in the second month to 75mg/day, with laboratory control (blood count, transaminases), reaching 100mg/day; however, with this dose, the patient showed a drop of one point in hemoglobin

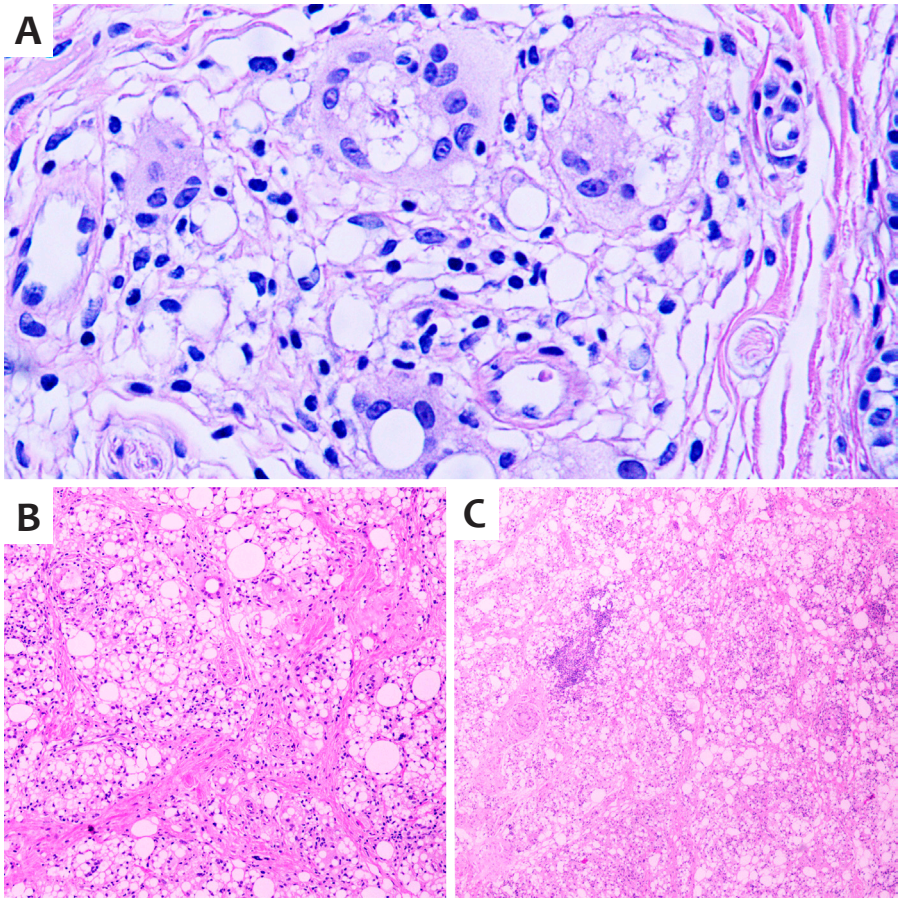

Figure 3: Histopathology of the skin showing numerous spherical spaces of different sizes, associated with the giganto-histiocytic reaction (Hematoxylin & eosin A: 40x, B: 200x, C: 400x)

(g/dL), so the dose of 75mg/day was resumed to avoid recurrence of the lesions. The patient used dapsone for 10 months and, at the time of completing this report, there had been no worsening (Figure 4).

DISCUSSION

Injectable liquid silicone, or fluid polydimethylsiloxane, was a product used for tissue filling, considered unstable, with a high risk of migration and triggering local and systemic immune responses.[2,3] Its most common late complication is the appearance of a single, nodular-granulomatous lesion, also known as "late siliconoma," and when the affected area is small, it can be treated with intralesional corticosteroids or antimitotic agents such as 5-fluorouracil; however, in extensive cases, the use of systemic corticosteroid therapy is necessary.[4]

In the present case, the exuberance of the manifestation is noteworthy, with the presence of around 20 nodules, widening of the nasal base, and an infiltrated appearance in the supraciliary region, which led to the analogy with the "leonine facies" (a condition that can be observed in lepromatous leprosy and cutaneous lymphomas, for example).[5] It is also noteworthy that the first clinical manifestation occurred 30 years after the procedure,

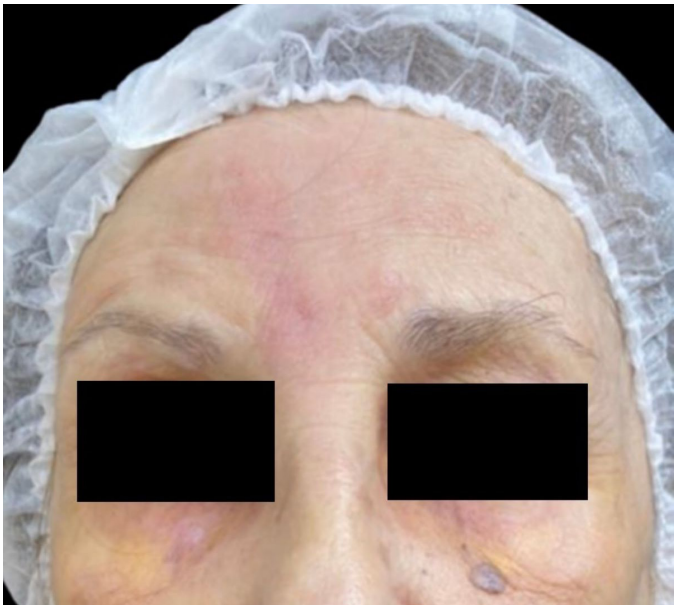

Figure 4: Significant improvement in siliconomas after treatment with systemic corticosteroid therapy and dapsone for 10 months

and the probable trigger was the dental procedure. Beleznay et al. described that 39% of patients with late complications after filling with hyaluronic acid have a respiratory tract infection or previous dental procedure as a trigger.[6] Lloret ***et al***. reported two cases of granulomatous reaction after silicone skin filling, in which the patients had positive antinuclear antibodies.[7]

In view of the constant recurrences of facial granulomas when systemic corticosteroid therapy was reduced, dapsone was added to the therapeutic regimen in this case. The choice of this antineutrophilic drug was based on its lower long-term morbidity and experience in treating other facial granulomatous diseases.[7,8] There is still a need for scientifically relevant publications on the best treatment regimen for granulomas secondary to fillers and, for the time being, the options described range from surgical excision, intralesional corticosteroids, tetracyclines, tacrolimus, imiquimod, methotrexate, mycophenolate mofetil, alupurinol, cyclosporine, and azathioprine to etanercept.[9-12] Some authors have had good experience with the use of isotretinoin, similar to how it is used in granulomatous rosacea.[7] However, there is still no data defining whether any of these drugs are superior among the treatment options.

CONCLUSION

Complications from facial fillers are becoming increasingly common. Permanent fillers, which were widely used decades ago, are particularly challenging due to their unpredictability in terms of the onset time of their complications (from days to decades) and clinical variations. Scientifically relevant publications are needed to guide the best treatment regimen, as it is believed that the number of cases will increase exponentially given the wide range of aesthetic procedures available today. ●

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Eyebrow transplant using the Follicular Unit Extraction Technique (FUE)

Transplante de sobrancelhas com a técnica de extração de unidade folicular (FUE)

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.2024160239

ABSTRACT

Hair transplant is a common procedure worldwide, and the method of extracting follicular units is currently the most used. This technique is used not only for androgenetic alopecia but also for other areas such as eyebrows and beard. It is essential to observe the angle of the incisions and implantation of the hairs to conduct the eyebrow transplant so the result is as natural as possible. However, in addition to being rigorous with the design of the shape and position of the eyebrow, care must be taken with the preparation from the receiving site.

Keywords: Transplants; Alopecia; Hair follicle

RESUMO

O transplante capilar é um procedimento muito realizado em todo o mundo, sendo que o método de extração de unidades foliculares é o mais empregado atualmente. Esse método está sendo utilizado não apenas para a alopecia androgenética, mas também para outras áreas, como sobrancelhas e barba. Para a realização do transplante de sobrancelhas é importante observar a angulação das incisões e a implantação dos fios para que o resultado seja o mais natural possível. Contudo, além do rigor com o design da forma e da posição da sobrancelha, é preciso cuidado com a preparação do local receptor.

Palavras-chave: *Transplante; Alopecia; Folículo piloso*

How do I do it?

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INTRODUCTION

The trend for thicker eyebrows, with greater visual and aesthetic appeal, has increased patient demand for eyebrow transplants in recent years. Hair restoration in this region represents a very refined art, requiring a high skill to be correctly executed, as it is necessary to respect the arrangement and positioning of the hair to obtain a good result.[1]

The eyebrows have biological functions, such as protecting the eyes and helping with facial expressions.[2] They can be divided into three anatomical segments: head, body, and tail. Its hairs are generally shorter, thinner, and less flexible, with a slight curvature along the body. Furthermore, its shape tends to be slightly thinner towards the tail. Regarding the orientation and density of the hair, each segment has its own particularities.[3] (Figures 1 and 2)

The most common indications for eyebrow transplant are burns, trauma, alopecia areata, scarring alopecia (such as frontal fibrosing), trichotillomania, hypothyroidism, leprosy, and hypotrichia.[5,6,7] However, it is essential to highlight that, in some of these conditions, such as alopecia areata, frontal fibrosing alopecia, and trichotillomania, careful medical evaluation is necessary to ensure there are no signs of disease activity for proper scheduling of the surgical procedure.[1,8]

MATERIALS AND METHODS

Eyebrow transplant surgery is performed using the follicular unit extraction (FUE) technique, currently considered the best option for restoring this region.[9]

The procedure begins with a small scrape of the donor region (generally the occipital region of the scalp), followed by asepsis with chlorhexidine degerming agent in sufficient quantity to clean the area. Then, the anesthetic solution is infiltrated, which, considering an average of 70 kg of patient weight, is prepared with 10 ml of 2% lidocaine without vasoconstrictor, 20 ml of 0.75% ropivacaine and 0.3 ml of adrenaline (300 mcg). Thus, this total volume of anesthetic will be used both in the donor region (scalp) and the recipient region (eyebrows) later. The amount of anesthetic will depend on the size of each area, and the doctor must be careful to inject only what is necessary, avoiding large doses of the medication. Also, a small amount of tumescent solution can be applied, consisting of a mixture of 100 ml of Ringer's lactate solution and 0.3 ml of adrenaline to help the vasoconstriction of the area and superficialize the follicles to protect the deeper blood vessels during extraction. In general, 4 ml of this solution is already satisfactory for use in the donor region.

Follicular extraction uses the FUE technique, preferably with a 0.9 mm punch. The number of follicular units to be extracted depends on the size of the recipient region that will be

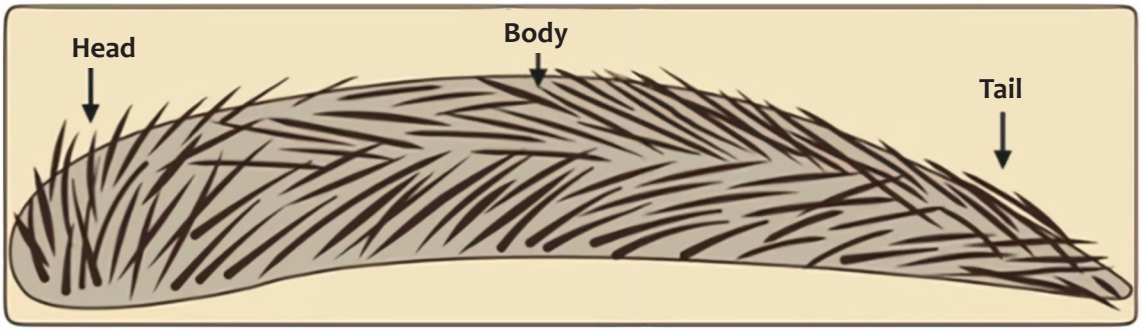

FIGURE 1: Anatomy of the eyebrows

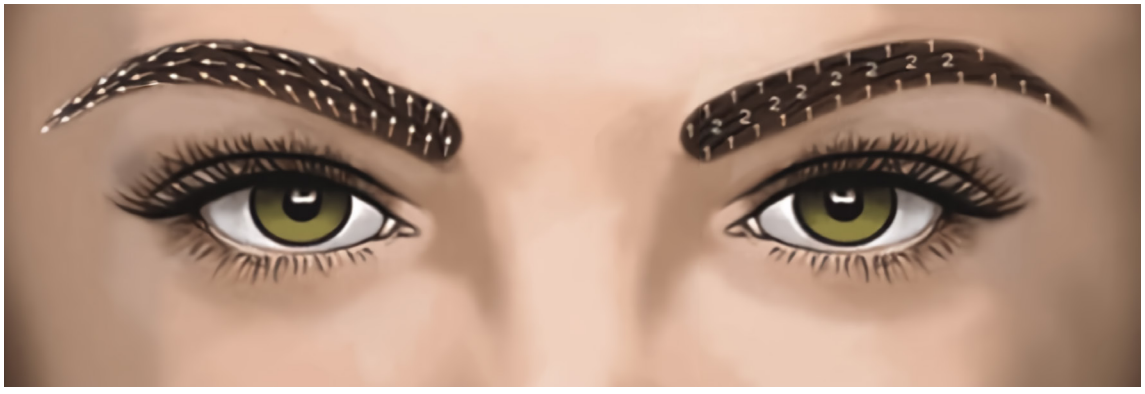

FIGURE 2: Representation of the distribution and angle of the eyebrow hairs. Own authorship

covered in the transplant. Each eyebrow may require, on average, 150 to 300 follicles for a complete and well-done reconstruction. Furthermore, the preference is to use follicular units with one and two hairs, while those with three and four hairs must be cut and transformed into smaller units.

After extraction, the patient remains in the prone position for better access to the eyebrow region. Then, we conduct the asepsis and local anesthetic infiltration in the recipient region using the same previously prepared solution; however, in a smaller quantity and proportional to the area where it will be implanted. It is a highly innervated site (due to the presence of the infratrochlear, supratrochlear, supraorbital, lacrimal, and zygomaticotemporal nerves) and, therefore, this stage is essential for the patient's comfort throughout the surgery. A small volume of corticosteroids, such as triamcinolone acetonide, can be added to the anesthetic solution to reduce the periorbital edema that may occur in some cases. However, this practice is not essential and depends on the surgeon's preference.

The next step consists of pre-incisions (Figure 3) using 0.8 mm sapphire scalpel blades, 0.7 mm customized blades, or 23 G needles at a 90-degree angle (Figure 4). The detail of this step is that the cuts must occur at a very acute angle concerning the skin, following the direction of the existing hair in each region.

The incisions are made in the coronal axis to facilitate the implantation of the follicles, but the direction may vary depending on the anatomy of each part of the eyebrow. At the medial end, a few staggered rows are created so the hair grafts are placed pointing upwards. As they reach the body, the slits slope outward and downward along the upper edge of the eyebrow while becoming parallel to the middle rows. Then, they slope downward toward the tail.

Two lines placed in this pattern along the top edge will define and highlight the curvature of the eyebrow. Then, other two lines are placed horizontally along the longitudinal axis for proper body structure. Finally, two more lines of slits are created along the bottom edge so the grafts can be at right angles to the top edge, creating a crisscross pattern that overlaps along the central axis.

Because women's eyebrows are thinner and more curved, the total number of rows in women is generally smaller. But, in any case, it depends on the patient's desire for the final result. Thinner follicles are preferred for the upper edge and tail, while thicker ones are placed along the body and lower edge.

It is essential to implant the grafts close to the skin so the growth of the hairs does not affect the region's harmony. After applying a small amount of methylene blue to the pre-incisions,

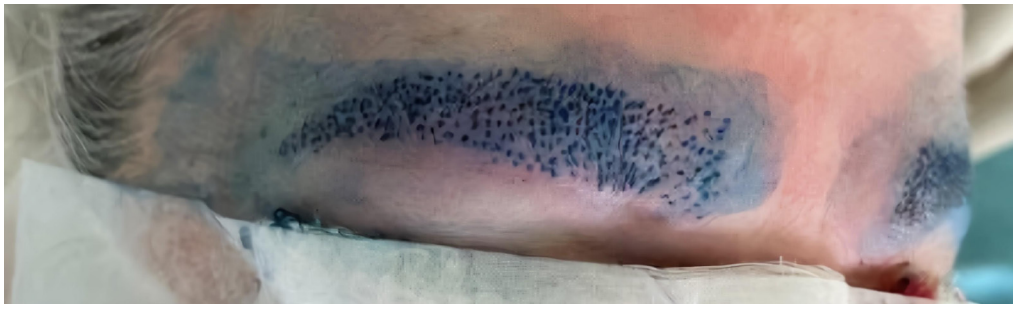

Figure 3: Demonstration of pre-incisions. Own authorship

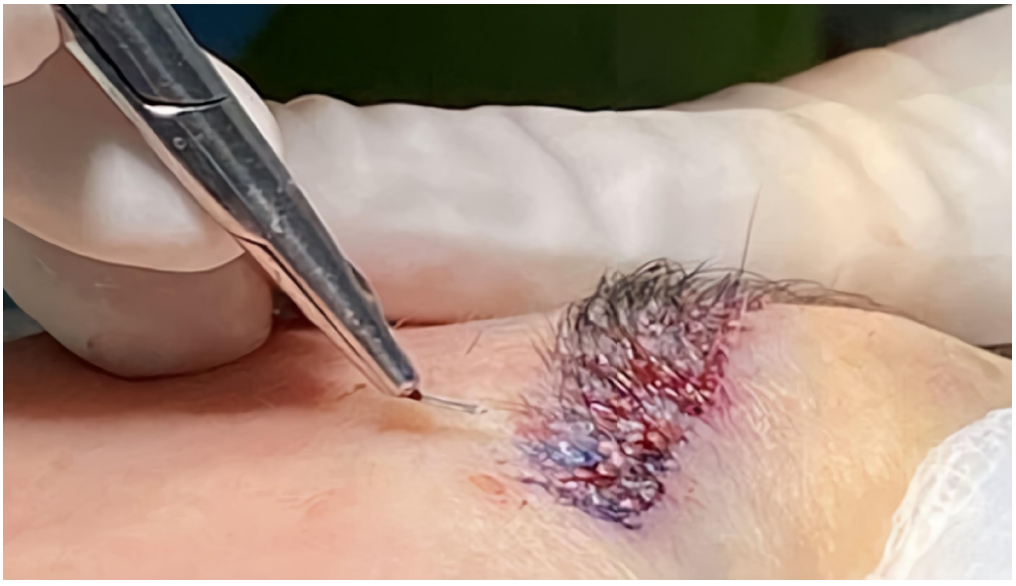

Figure 4: Representation of the angulation, customized blade, and implantation of the follicles. Own authorship

they become more visible, making the implantation process easier. Generally, 0.65 mm implants are used for single-hair units and 0.8 mm for two-hair follicular units.

In the post-operative phase, it is recommended to hydrate the region with the application of thermal water every hour after the procedure for at least one day. Cleaning must take place delicately after 24 hours with a drain rinse, and it is not necessary to apply bandages throughout the recovery process. Regarding oral medications, the recommendation is prophylactic antibiotics for seven days (such as cefadroxil, with a dose of 500mg every 12/12 hours) and dexamethasone 4 mg per day, for five days, to reduce local edema.

RESULTS

Transplanted follicles grow at different speeds as they are in different hair cycle phases. A partial result (on average 50%) is expected three to four months after the procedure. Eight to nine months is necessary to obtain the result, with complete restoration of the eyebrows.

Depending on the needs of each case, a second session can be planned after an average of ten months. However, many patients already meet their expectations in the first surgery when the technique is performed correctly and the postoperative period is uneventful.

Figures 5, 6, and 7 show eyebrow transplant results on different postoperative days.

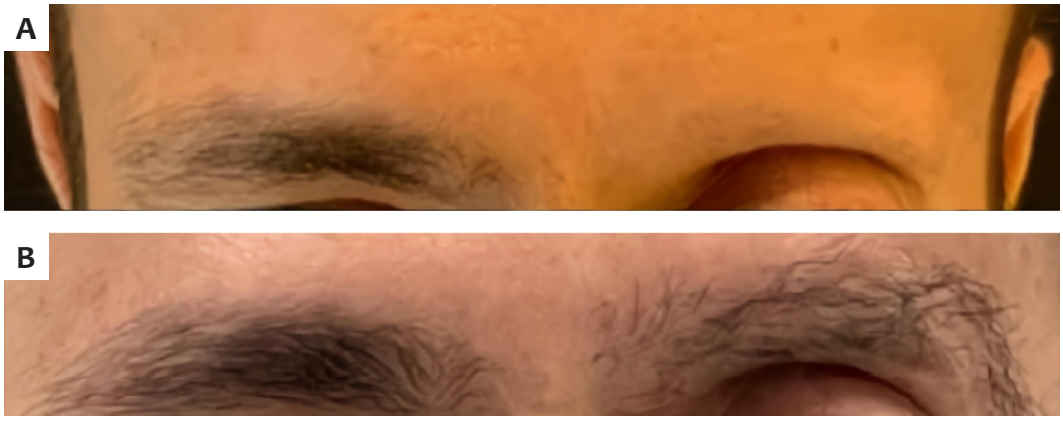

FIGURE 5: Area of alopecia in the left supraorbital region secondary to previous radiotherapy **(A)** and six months after eyebrow CT **(B)**. Own authorship

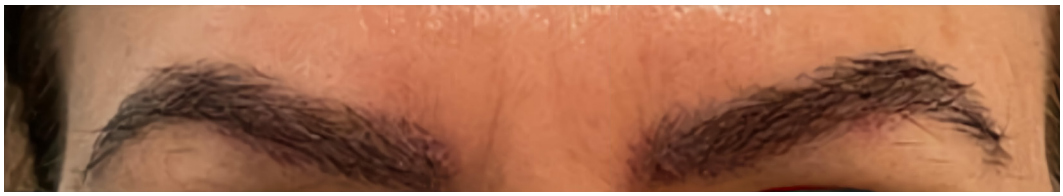

FIGURE 6: Post-operative eyebrow hair transplant after 10 days. Own authorship

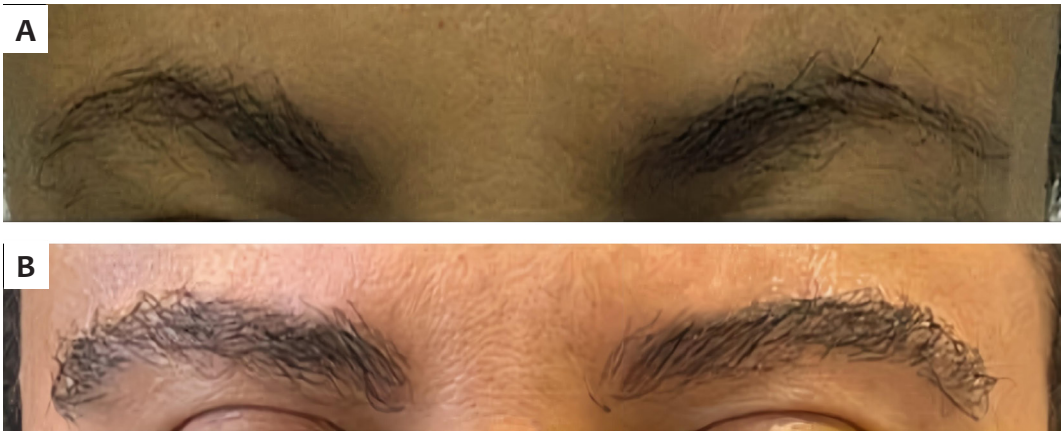

FIGURE 7: Before **(A)** and after **(B)** one year of eyebrow hair transplant to correct asymmetries and flaws. Own authorship

DISCUSSION

Hair transplant is a procedure highly sought in Dermatology and Trichology. Patients are seeking the surgical procedure following the trend towards thicker, more natural-looking eyebrows. Previously used techniques, such as eyebrow micropigmentation, are becoming less and less attractive since their results are more artificial and do not value the individuality of each patient, which further favors the search for other alternatives, such as transplants.

The FUE technique allows a more natural restoration than other surgical techniques, guarantees a more thorough follicular extraction, and is minimally invasive. Furthermore, it favors a smoother recovery for patients, with excellent results.

The strategic distribution of follicular units is directly related to the density of the eyebrows, and it is crucial for patient satisfaction. For the implantation of the hair, it is essential to maintain a more acute angle concerning the skin, following the direction of pre-existing threads when these are present.[1,8]

When the eyebrows already have some previous scar tissue, whether due to old trauma or specific types of alopecia, performing a hair transplant is a challenge for the surgeon due to the compromised vascularization in this region. Therefore, it is more difficult to predict the degree of success regarding follicular integration in these patients.[10]

All types of measures must be considered to improve graft viability during the surgical procedure. Bleeding at the incision site can lead to displacement of the follicles and changes in angle and direction, which can impact the final result. This event is common when there are (recent) pink scars in the eyebrow area. Therefore, even if patients insist on undergoing the transplant early to correct this change, doctors must wait for the scars to mature. Additionally, some fat grafting may be applied before surgery to soften the hard layer of scar tissue or in patients with insufficient skin area.[10]

Successful results are achieved when all factors with potentially adverse events on graft viability are considered. Thoroughly planning the surgery and avoiding additional intraoperative trauma also contribute to the success of the procedure.[10]

Some patient particularities can influence the shape of the eyebrows, such as the variability between ethnicities and gender.[4] For example, in women they are a little thinner than in men, in addition to presenting in a "C" shape, reaching maximum curvature at the most lateral edge.[9] Men's eyebrows tend to be less arched, with the medial and lateral ends practically level or even with the tail slightly higher.[9]

A few months after surgery, there may be a need to trim the new hairs more frequently. After all, the anagen phase of the scalp follicles (donor area) is greater, and the transplanted hairs follow their original pattern, even though they are in a new region.

CONCLUSION

Eyebrows play an important role in harmonizing the face and, currently, they tend to be increasingly fuller and more shaped, which justifies the greater interest of patients in hair transplants in this region.

The FUE technique is currently the most appropriate methodology for reconstructing this region, being the primary choice of doctors, both for reducing surgical trauma to the follicular units and for delivering more natural results.

Eyebrow transplants are becoming more widespread in medical practice and gaining prominence among patients seeking more effective procedures. Furthermore, restoring the eyebrows permanently is an advantage of the technique. Thus, a well-trained doctor will be in the spotlight in hair and eyebrow restoration. ●

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Systematization of labia majora augmentation with hyaluronic acid filler: the vulvar anatomical vector technique

Sistematização do preenchimento vulvar com ácido hialurônico: apresentação da técnica vetores anatômicos vulvares

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ABSTRACT

Despite the therapeutic success described by recent studies, the procedure of labia majora augmentation lacked systematization in order to achieve more assertive and reproducible results. To this end, we developed the vulvar anatomical vector technique, in which we mapped five anatomical structures of the vulva where the injection of hyaluronic acid is capable of promoting coaptation, augmentation, reduction of prolapse, and/or improvement of the skin quality of the labia majora. This technique has allowed us to precisely define the sites to be injected and estimate the adequate volume and type of hyaluronic acid to achieve the intended results.

Keywords: Hyaluronic Acid;Vulva; Dermal Fillers; Rejuvenation; Female Genitalia.

RESUMO

Apesar do sucesso terapêutico descrito na literatura médica recente, o preenchimento de grandes lábios carecia de uma sistematização para resultados mais assertivos e reprodutíveis. Para tanto, desenvolvemos a técnica vetores anatômicos vulvares, por meio da qual mapeamos cinco pontos anatômicos vulvares, nos quais a injeção de ácido hialurônico é capaz de promover a coaptação, a volumização, a diminuição da ptose e/ou a melhoria da qualidade de pele dos grandes lábios. Tal técnica tem nos permitido definir de forma precisa os locais a serem preenchidos e estimar o volume e o tipo de ácido hialurônico a ser injetado para atingir os resultados pretendidos.

Palavras-chave: *Ácido Hialurônico; Vulva; Preenchedores Dérmicos; Genitália Feminina; Rejuvenescimento.*

How do I do it?

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INTRODUCTION

The injection of cross-linked hyaluronic acid (HA) for augmentation of the labia majora (LM) has been employed with excellent results and low complication rates.[1-4] Despite the therapeutic success reported in recent studies, the procedure lacked systematization to determine the best products and methods to achieve reproducible results.[4] Since 2019, we have successfully used a technique for LM augmentation with HA fillers, termed vulvar anatomical vectors, with the aim of ensuring that, after individual assessment, the procedure can be performed safely and effectively.

METHODS

Four key aspects need to be assessed before LM augmentation, namely:

- LM coaptation: Prolapse of the labia minora and the clitoris are common complaints, which may result from hypertrophy of the labia minora and clitoris or hypotrophy of the LM. If the LM are hypotrophic, their coaptation via filling may reduce prolapse of the labia minora and clitoris.
- LM augmentation: Loss of volume in the LM can cause laxity and wrinkling.
- LM tone: Loss of tone in the area between the LM and the suprapubic region, along with loss of volume, can cause sagging of the LM.
- LM wrinkling.

Eighty-six women aged 27 to 66 years with complaints of LM laxity, wrinkling, and prolapse of the labia minora and clitoris received injections of HA filler. All participants were evaluated and photographed before and immediately after the procedure. Follow-up was conducted at 30 and 180 days.

Injection of HA filler in the LM was systematized according to the vectors and amounts injected per side as follows (Figure 1):

VA1: medial border of the LM, deep fat pad injection / 1.0–2.0 mL.

VA2: 0.5 cm lateral to VA1, 0.5 cm shorter than VA1, deep fat pad injection / 0.6–0.8 mL.

VA3: 1 cm lateral to VA1, 1 cm shorter than VA1, deep fat pad injection / 0.4–0.6 mL.

VA4: the area between the LM and mons pubis, superficial subcutaneous injection / 0.5–1.0 mL.

VAS (surface): entire surface where there is LM wrinkling, superficial subcutaneous injection / 0.5–1.0 mL.

First, asepsis and antisepsis of the selected area were performed, followed by injection of 1% lidocaine. Then, punctures were made with a 21-gauge needle to insert a 22-gauge 70 mm disposable cannula for the filler injections.

In vectors VA1, VA2, VA3, and VAS, punctures were made at the upper limit of the LM bilaterally, and multiple small boluses of HA were injected using the retrograde technique. In VA4, a puncture was made approximately 2 cm above the anterior labial commissure, and a retrograde injection of HA in the superficial subcutaneous tissue was performed using the fanning technique.

We used cross-linked products with an HA concentration of 20 mg/mL, while products with a lower G prime were used in the VAS vector. No more than 3.0 mL was injected into each side of the LM in a single session. In most cases, 2 mL was injected into each side, and the need to increase the volume was reevaluated after 30 days. Subsequent fillings were performed every 12 months.

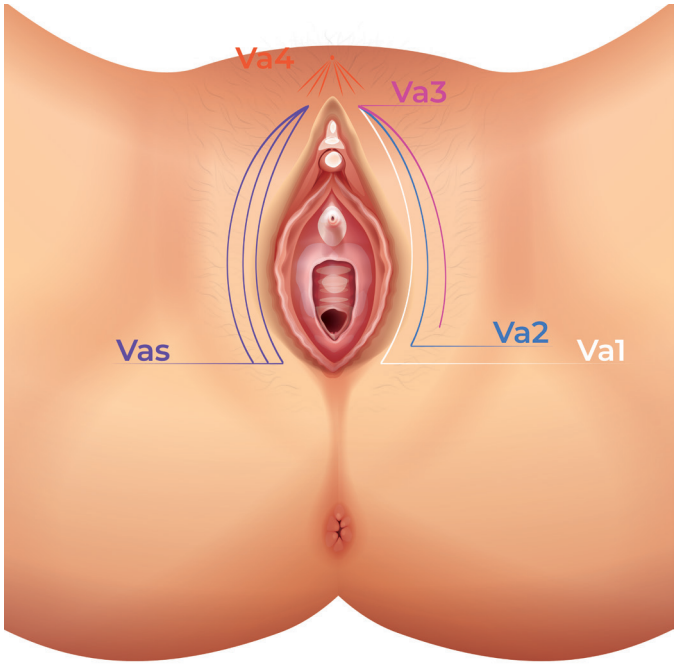

FIGURE 1: Vulvar anatomical vectors: Systematization of hyaluronic acid (HA) filler injection in the labia majora (LM). Vulvar anatomical vectors for injection of HA filler in the LM were systematized as follows:
- VA1: medial border of the LM, deep fat pad injection / 1.0–2.0 mL of HA per side.
- VA2: 0.5 cm lateral to VA1, 0.5 cm shorter than VA1, deep fat pad injection / 0.6–0.8 mL of HA per side.
- VA3: 1 cm lateral to VA1, 1 cm shorter than VA1, deep fat pad injection / 0.4–0.6 of HA per side.
- VA4: the region between the LM and the mons pubis, superficial subcutaneous injection / 0.5–1.0 mL of HA per side.
- VAS (surface): entire surface where there is LM wrinkling, superficial subcutaneous injection / 0.5–1.0 mL per side.

RESULTS

The filling procedures yielded the following results according to each vector:

VA1: increased coaptation of the LM, with better accommodation of the clitoris and the labia minora (Figure 2).

VA2 and VA3: adequate augmentation with increased anterior projection of the LM; well-suited for treating LM laxity (Figure 3).

VA4: increased LM tone and reduced visibility of the superior limit of the clitoris when hypertrophic (Figures 4 and 5).

VAS: reduced wrinkling (Figure 6).

Some complications were observed among participants, including biofilm formation 14 days after the procedure due to a wound caused by waxing, promptly treated with oral antibiotics without further complications. In addition, four cold nodules due to accumulation of product were observed and easily resolved with vigorous massage of the affected area. Finally, small bruises at the entry points and local edema also occurred but resolved within 7 days. There were no cases of intravascular injection.

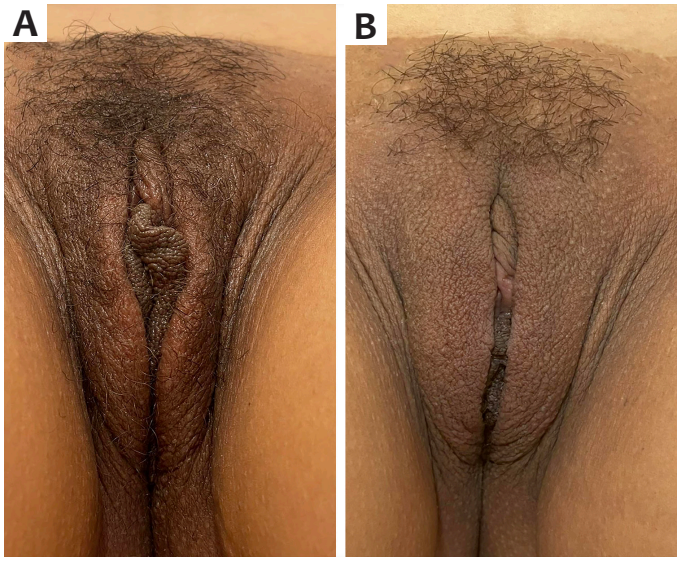

Figure 2: VA1 injection alone – 2 mL of hyaluronic acid (HA) per side. (**B:** before / **A:** after / standing position). Note that HA filler injection according to VA1 not only improved coaptation, reducing the exposure of the labia minora, but also improved laxity as the filling expanded laterally, providing partial lateral augmentation.
Note: In the second image, the vulva appears lighter due to the patient undergoing lightening procedures (patient in supine position)

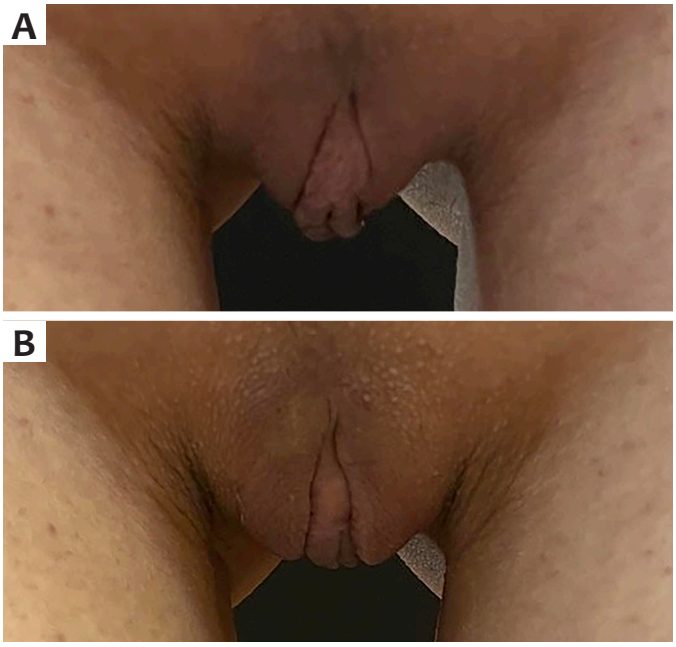

Figure 3: VA1, VA2, and VA3 injections – 1.0 mL of hyaluronic acid (HA) per side in VA1, 0.6 mL of HA per side in VA2, and 0.4 mL of HA per side in VA3, totaling 4.0 mL of HA injected (**B:** before / **A:** after / standing position).
The patient was photographed in a standing position to demonstrate the significant hypotrophy of the deep fat pad (DFP). Compare this image with Figure 2 to see how, unlike the previous patient, this patient had very reduced volume in the labia majora (LM), which caused exposure of the clitoris and labia minora, which were within normal measurements. The reduced DFP caused functional impairment, as the patient reported discomfort during impact activities such as intercourse, cycling, and horseback riding. Due to the need for significant augmentation, VA1, VA2, and VA3 injections were performed. VA1 increased coaptation, while VA2 and VA3 significantly increased LM projection, effectively "padding" the injected area.

DISCUSSION

LM and labia minora dimensions are extremely variable. To avoid over or undertreatment, we considered the dimensions below[5] as reference:

Length: LM 7–8 cm / labia minora 3–3.5cm
Width: LM 2–3 cm / labia minora 1–1.5 cm

VA1 injections in patients with LM length > 8 cm were avoided to prevent the distal portion of the LM from becoming saggy. If the area remained wrinkled, the patient was reevaluated after 30 days, and VAS injection was performed with a low-G prime product or collagen biostimulators if necessary.

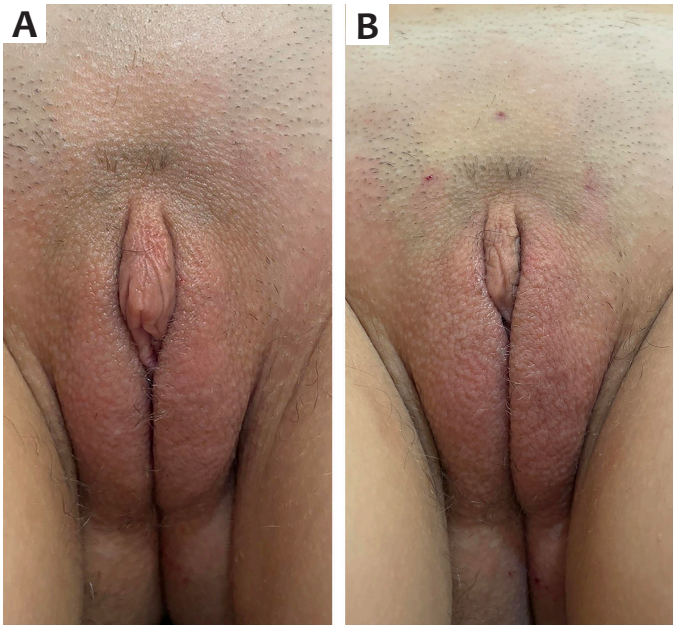

Figure 4: VA1 and VA4 injections, with 1 mL of hyaluronic acid (HA) per side in VA1 and 1.0 mL of HA per side in VA4, totaling 3.0 mL of HA injected (**B:** before / **A:** after / prone position). The patient had clitoral hypertrophy and voluminous LMs. To avoid excessive augmentation, only the upper third of VA1 was filled to increase LM coaptation specifically in the area of clitoral exposure. An additional VA4 injection was performed to reduce the exposure of the upper portion of the clitoris and to improve LM tone in the upright position.

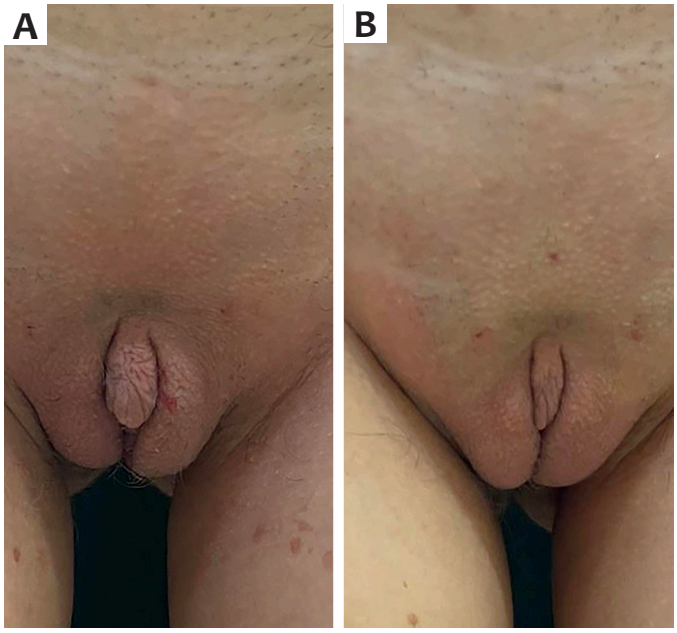

Figure 5: Same patient from Figure 4, now in a standing position (**B:** before / **A:** after / standing position). The patient was photographed in a standing position to highlight the improvement in LM tone. Note the reduction in clitoral exposure resulting from VA1 and VA4 injections and the improvement in LM tone after the VA4 injection

Patients with significant hypertrophy of the clitoris or labia minora (> 3 cm), grades 2 and 3 by the Colaneri classification,[6] were not treated. In these cases, injection of HA filler would not coapt the vulva and could result in excessive augmentation.

The LM are two large cutaneous folds of adipose, connective, and muscle tissue that extend from the mons pubis to the perineum. The adipose tissue is divided into superficial subcutaneous tissue (SST) and deep fat pad (DFP). The SST extends anteriorly toward the pubis as a thick layer of fat, continuous with the SST of the mons pubis, and posteriorly toward the perineum as Dartos fascia, composed of smooth muscle fibers.

SST and DFP are separated by a fibrous tunic, which projects itself from the inguinal canal in a finger-like shape, containing DFP and forming the suspensory ligament of the clitoris. The anatomy of the DFP is closely linked to the inguinal canal, an area that must be protected from contamination. The inguinal canal connects the genital area to the abdominal cavity and conveys the round ligament of the uterus, ilioinguinal nerve, genital branch of the genitofemoral nerve, and blood and lymph vessels.

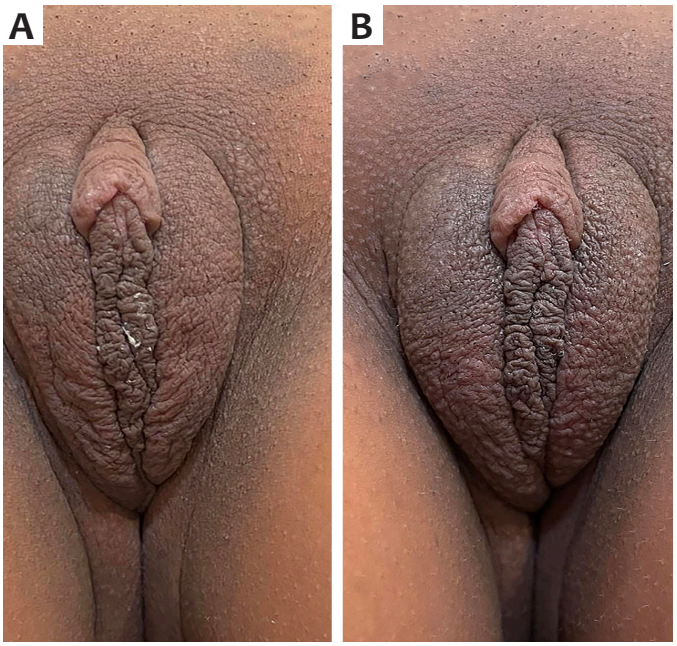

Figure 6: Injection in VAS alone, 0.5 mL of hyaluronic acid (HA) per side, totaling 1.0 ml of HA injected (**B:** before / **A:** after / supine position). Note that VAS injection alone does not provide significant increase in volume but improves wrinkles and lines on the LM, resulting in more uniform skin.

Because the tissue is very thin, injections in the SST are performed to reduce skin wrinkling but not to increase volume. Therefore, the coaptation and volumizing vectors (VA1, VA2, and VA3) should be done in the DFP, while the VAS vector, which aims to improve skin quality, should be done in the SST.

It is also important to note that VA2 and VA3 injections should not be performed without prior VA1 injection to avoid lateral augmentation from causing LM separation and increased exposure of the clitoris and labia minora. In fact, the natural accommodation of HA in the DFP often means that VA1 injection alone will achieve the desired results without additional injections in VA2 and VA3.

The vulva is supplied by the anterior labial arteries, branches of the external pudendal arteries, posterior labial arteries, and branches of the internal pudendal arteries. To avoid intravascular injection, a thorough understanding of this vascular anatomy is essential, and care should be taken to proceed with prior aspiration and slow, gentle injection. We also use large caliber, blunt-tip cannulas.

CONCLUSIONS

HA filler injection in the LM is an excellent technique for beautifying the female genitalia, delivering outstanding results with few complications. We propose a reproducible systematization of the procedure, which takes into account patient complaints and the adequate anatomical sites to be treated, achieving a high therapeutic success rate. ●

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Assessment of depressions and projections in facial aging and their correlation with anatomical structures to assist in facial volumization

Avaliação das depressões e projeções do envelhecimento facial, correlacionando-as com estruturas anatômicas, para auxiliar na volumização

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ABSTRACT

Facial volumization techniques have been widely discussed by several authors. However, there is a dearth of publications on techniques for patient assessment. In this article, we describe how we assess, in our clinical practice, the anatomical changes associated with facial aging in a practical and didactic way, as it is a fundamental step when choosing products and filling techniques.

Keywords: Dermal fillers; Skin; Collagen; Inflammation; Blindness; Necrosis.

RESUMO

As técnicas de volumização facial são amplamente discutidas por diversos autores, porém existem poucas publicações sobre técnicas de como avaliar o paciente. Neste artigo, relatamos como avaliamos, em nossa prática clínica, as alterações anatômicas do envelhecimento facial de forma prática e didática, sendo essa avaliação uma etapa fundamental na definição da escolha dos produtos e das técnicas de preenchimento.

Palavras-chave: *Ácido hialurônico; Pele; Colágeno; Inflamação; Cegueira; Necrose.*

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INTRODUCTION

Diagnosing and identifying which areas should be treated, projected, and volumized is a major difficulty for the novice injector. We have noticed that literature is missing a step-by-step didactic approach to assessing the face, allowing for the development of clinical reasoning and an accurate diagnosis. We suggest that this diagnosis should be based on three pillars: loss of volume, loss of thickness and sagging, and loss of skin texture, or a combination of these. Therefore, treatment can only be indicated after evaluation and diagnosis of each case.

In 2012, Carruthers et al. defined an evaluation scale and the limits of the lower 2/3 of the face, dividing it into the upper cheek (UC) and lower cheek (LC) using a line that extends from the labial commissure to the upper edge of the tragus.[1] The UC is limited superiorly by the infraorbital concave and extends from the lateral epicanthus of the eye to join the upper part of the helix of the ear; medially, it is limited by the nasal border and nasolabial fold to the labial commissure. Below the dividing line, the LC is limited medially by the mentolabial sulcus and inferiorly by the body of the mandible up to the earlobe. And the lateral limit of the LC extends from the upper part of the tragus to the earlobe (Figure 1).

More recent studies have attempted to establish anthropometric measurements in the quest for the aesthetically ideal and standardized face. However, the concept of beauty is highly variable and often Caucasian standards are used to determine therapeutic approaches, which we believe is not appropriate due to the great cultural and racial variety of the population.

These standards are therefore useful to help assess pre- and post-treatment results, but not to guide the start of treatment.[2]

In our approach, we propose, in addition to the division into superior and inferior, to also define and limit this region into medial and lateral. This division may not have been proposed because of the absence of current anatomical knowledge about the vertical ligament line (VLL), which was recently described by Casabona et al. who, when comparatively evaluating fillers in the middle 1/3 in 12 patients, noted that the lifting effect obtained when filling the face laterally is due to the difference in the arrangement of the medial versus lateral subcutaneous layers.[3] They showed that these layers are delimited by an imaginary VLL, which connects the temporal ligamentous adhesion (TLA) to the lateral orbital thickening (LOT) ligament, zygomatic ligament (ZL) and mandibular ligament (ML) of the face, following a craniocaudal direction, laterally to the orbital rim, up to the mandible. They concluded that when injected medially to this line, the aesthetic result is volumization, while laterally, the effect is to lift the middle and lower third of the face, thus requiring less material for volumization and facial lifting (Figure 2). Recently, Braz *et al.* reviewed this VLL based on the mobile and fixed areas of the face, suggesting that it should end in the mandible, post-jowl, considering the masseteric ligament and not the mandibular ligament.[4] Therefore, dividing the cheek region into medial and lateral is necessary when assessing the patient.

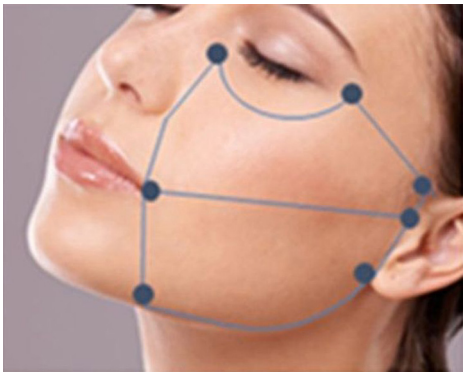

Figure 1: Division of the cheek into upper and lower by the line extending from the labial commissure to the upper edge of the tragus

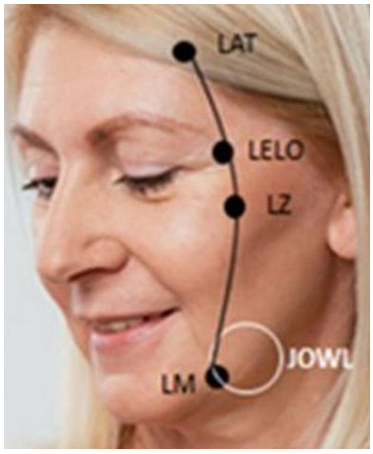

Figure 2: Vertical ligamentous line following a craniocaudal direction that connects the temporal ligamentous adhesion (TLA), latero-orbital thickening (LOT) ligament, zygomatic ligament (ZL), and mandibular ligament (ML)

METHOD

Didactically, the authors suggest adding a vertical imaginary line to the horizontal imaginary line already described,[1] dividing the cheeks into medial and lateral. Associating this study by Braz et al. with an analysis by Nechala et al., who compared various techniques for locating the malar eminence,[5] we propose a division that would start from the orbital bone ridge, where the LOT is located, passing through the ZL and descending perpendicularly to the medial pre-masseteric region of the mandible, thus dividing the face into quadrants: superior medial (SM) and lateral (SL), inferior medial (IM) and lateral (IL) (Figure 3).

The authors follow their observation based on Maio *et al.*[6] Cheeks in young people are convex and progressively become flat or concave with age. This is due to the loss of bone support (orbital and zygomatic) and the redistribution of mid-facial fat, resulting in an accumulation of fat located in the SM quadrant of the cheeks, which is limited medially by the nasal region and nasolabial fold, which remains unnamed in the bibliography studied, and we therefore suggest the name nasolabial prominence (NLP). This NLP can progressively evolve towards

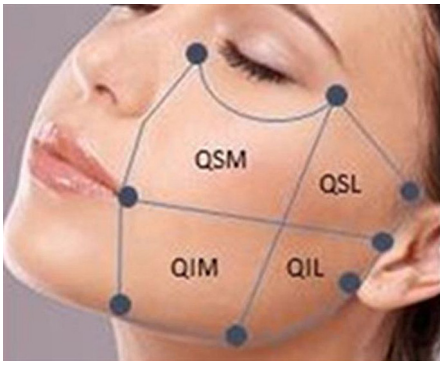

Figure 3: Vertical line dividing the cheek into medial and lateral forming quadrants: superior medial (SM) and lateral (SL), inferior medial (IM) and lateral (IL)

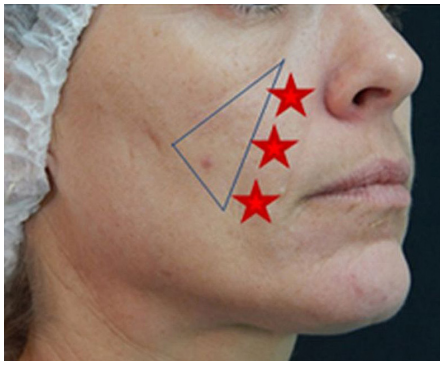

Figure 4: Red stars - nasolabial prominence (NLP): accumulation of fat located in the medial superior quadrant, limited medially by the nasal region and nasolabial fold; blue triangle - malar fold: delimited superiorly by the zygomatic region, laterally by the masseter muscle, the medial superior limit of the NLP

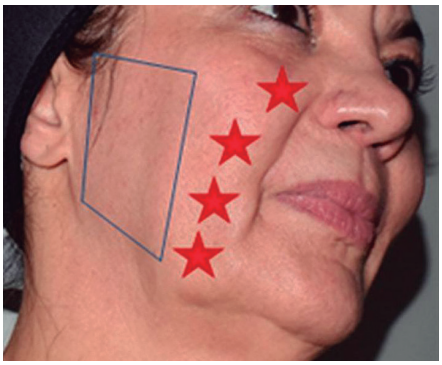

Figure 5: Red stars - nasolabial prominence (NLP); blue rectangle - bounded medially by the NLP and jowl, and superiorly by the zygomatic region; laterally by the preauricular region, and inferiorly by the mandible

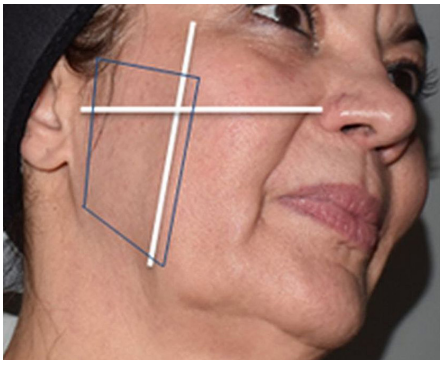

Figure 6: Triangular "valley" area predominates in the SM quadrant; rectangular "valley" area in the SL and IL quadrants; the "peak" area referring to the jowl would be in the IM quadrant

the IM quadrant, forming a projection in the medial region of the mandible, the jowl, which is limited anteriorly by the ML, determining a so-called buccomental crease (Figure 4).

Maio ***et al.*** also described the appearance of a triangular area of depression that extends inferolaterally to the lower eyelid for 2 to 3 cm, called the malar furrow, delimited superiorly by the zygomatic region of the malar and laterally by the masseter muscle. The authors suggest using the NLP described in this article as the superomedial limit, which, with the progression of aging, joins the jowl inferomedially, forming a single structure (Figure 4).

According to the authors, this triangular area can progressively evolve or merge into a rectangular depression due to the depletion of deep fat in the lateral-superior region of the submalar, pre-auricular and masseteric regions, limited medially by the NLP and jowl, superiorly by the zygomatic region, laterally by the pre-auricular region and inferiorly by the mandible (Figure 5).

The authors then refer to these depressed areas as "valleys," and the elevated areas of the face, such as the bony projections, the jowl itself and now the NLP, as "peaks," which should be used as a parameter for leveling the skin surface and repositioning the face, which can be done using various facial volumization techniques and products.

DISCUSSION

Initially assessing the patient by marking "valleys" and "peaks" and then applying the facial quadrant division, the triangular "valley" area predominates in the SM quadrant and the rectangular "valley" area in the SL and IL quadrants. The "peak" area referring to the jowl would be in the IM quadrant (Figure 6). Therefore, we will start the volumization in the SL and IL quadrants (post-ligament line) for the effect of lifting and correcting the loss of volume, followed by the SM quadrant. On the other hand, the IM quadrant should not be approached during volumization techniques. In this region, it is preferable to use other techniques to reduce volume and to use tissue contraction to reduce sagging.[7-9]

There is no unique, optimal method for assessing and treating facial aging. Therefore, when we use the areas of volume

loss and the areas of projection, we are often able to treat the patient while maintaining their identity and natural appearance, without trying to transform them into someone else using only anthropometric measurements of what would theoretically be an ideal face, which is very subjective and culturally diverse.[2]

CONCLUSION

Therefore, facial perception in quadrants, together with the identification of "valleys and peaks," would facilitate diagnosis and a customized treatment plan, with a smaller amount of material, since "peaks" would be avoided when performing facial volumization. ●

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Recurrent extramammary Paget's disease successfully treated with peripheric Mohs micrographic surgery associated with rapid immunohistochemistry

Doença de Paget extramamária recidivada tratada com sucesso com cirurgia micrográfica de Mohs periférica associada à imuno-histoquímica rápida

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ABSTRACT

Extramammary Paget's disease is a slow-progressing, cutaneous adenocarcinoma of the apocrine glands with an uncertain etiology. The standard treatment is surgical removal of the tumor. However, the usual surgical methods - wide local excision and Mohs micrographic surgery - pose challenges and high recurrence rates. Often, these are extensive lesions with poorly defined boundaries located in critical anatomical regions. Additionally, they exhibit unpredictable subclinical intraepithelial spread. We present a case of a recurrent extramammary Paget's disease successfully treated with peripheric Mohs micrographic surgery associated with rapid immunohistochemistry for CK8/18.

Keywords: Paget Disease, Extramammary; Mohs Surgery; Immunohistochemistry

RESUMO

A doença de Paget extramamária é um adenocarcinoma cutâneo das glândulas apócrinas, de progressão lenta e etiologia incerta. O tratamento padrão é a remoção cirúrgica do tumor. No entanto, os métodos cirúrgicos usuais - excisão local ampla e cirurgia micrográfica de Mohs - apresentam dificuldades e elevadas taxas de recorrência.

Frequentemente, trata-se de lesões extensas, de limites mal-definidos, e localizadas em regiões anatômicas críticas. Além disso, apresentam disseminação subclínica intraepitelial imprevisível. Apresentamos o caso de um paciente com doença de Paget extramamária recorrente, tratado com sucesso com cirurgia micrográfica de Mohs periférica associada à imuno-histoquímica rápida para CK8/18.

Palavras-chave: *Doença de Paget Extramamária; Cirurgia de Mohs; Imuno-Histoquímica*

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INTRODUCTION

Extramammary Paget's disease (EMPD) is a rare, slow-progressing cutaneous adenocarcinoma of the apocrine glands with an unclear etiology.[1] Raising awareness of this disease is crucial, since diagnosis is often late, and recurrence rates tend to be high.[2]

Desquamative and erythematous plaques affect older people and are common on the vulva, perianal region, pubis, penis, scrotum, and inguinal region.[3] Dermatologists should suspect EMPD in unilateral, chronic lesions located in typical areas, in older patients, and refractory to treatment. Diagnosis is based on pathological examination, with the presence of Paget's cells, associated with positive immunohistochemistry (IHC) for cytokeratin 7 (CK7) or cytokeratin 8/18 (CK8/18).[1,3]

The standard treatment for EMPD is to remove the tumor surgically. This can basically be a wide local excision (WLE) with a predetermined margin or through techniques that evaluate 100% of the operative margins, such as staged surgeries or Mohs micrographic surgery (MMS).

Alternatively, some patients can also be treated with topical application of imiquimod, with good results.[4]

Advanced age, tumor extension, poorly defined boundaries, and an affected anatomical region often hinder the use of wide margins. Although the margin to be applied in these patients is unclear in the literature, some authors agree on 2 to 3cm.[2] In addition, WLE has high recurrence rates, which vary from 22% to 60%, depending on the study and characteristics of the tumor.[5,6]

The typical subclinical spread and high recurrence rates favor the use of MMS or staged surgeries.[5] In the case of MMS, however, it is difficult to identify subtle intraepithelial neoplastic proliferations using hematoxylin & eosin (HE) stain for fresh frozen sections.[5]

On the other hand, this can be overcome in staged surgeries, in which the margins are analyzed in paraffin, possibly using IHC, at the cost of several surgical times until the lesion has been cleared up.

Therefore, rapid IHC techniques have been described to aid the intraoperative assessment of the margins of intraepithelial tumors with extensive subclinical spread.[7] This report describes the case of a patient with recurrent EMPD, successfully treated with MMS associated with rapid IHC for CK8/18.

CASE REPORT

A 73-year-old male patient presented with recurrent EMPD located in the inguinal region and pubis (Figure 1) for years. The patient had coronary insufficiency and was taking warfarin. He was initially treated with imiquimod, administered five times a week for 15 weeks. He was treated once again with imiquimod with no success. He then underwent two surgical resections with a 10mm margin at an interval of 1 year, with a persistent local recurrence. There was no evidence of invasion or involvement of internal organs at any time.

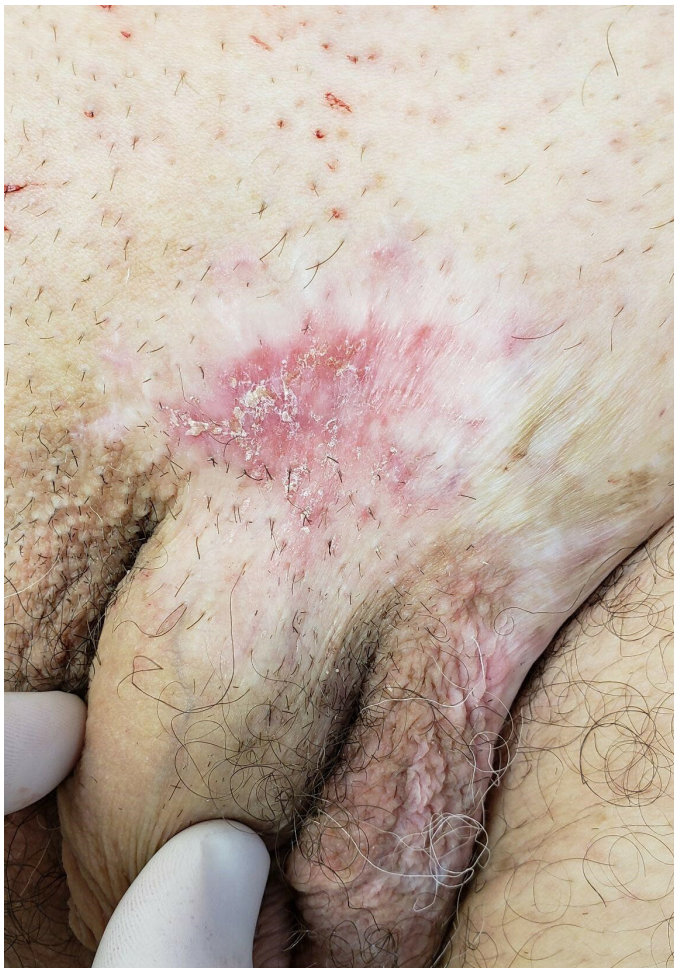

Figure 1: EMPD in the pubic region of a male patient. Desquamative, erythematous lesion with irregular borders and poorly defined boundaries, surrounded by a hypochromic area

The patient was then submitted to peripheral MMS associated with rapid IHC for CK8/18 (Novodiax ihdDirect®). For debulking, the tumor was marked and excised in the superficial subcutaneous plane. We decided to include the perilesional hypochromic area in this stage of the surgery (Figure 2). Debulking was assessed using vertical HE sections, in which Paget's cells were observed between the keratinocytes in all layers of the epidermis (Figure 3). The first phase of MMS was then marked with a 5 to 8mm margin (Figure 4).

The peripheral margin was incised at 90º, processed using en face sections, initially stained with HE, and the slides were examined by an experienced dermatopathologist. Margins that were negative or doubtful on HE were submitted to rapid IHC for CK8/18. In this case, no HE-negative margins were positive on IHC. However, in the margins suspected of being positive,

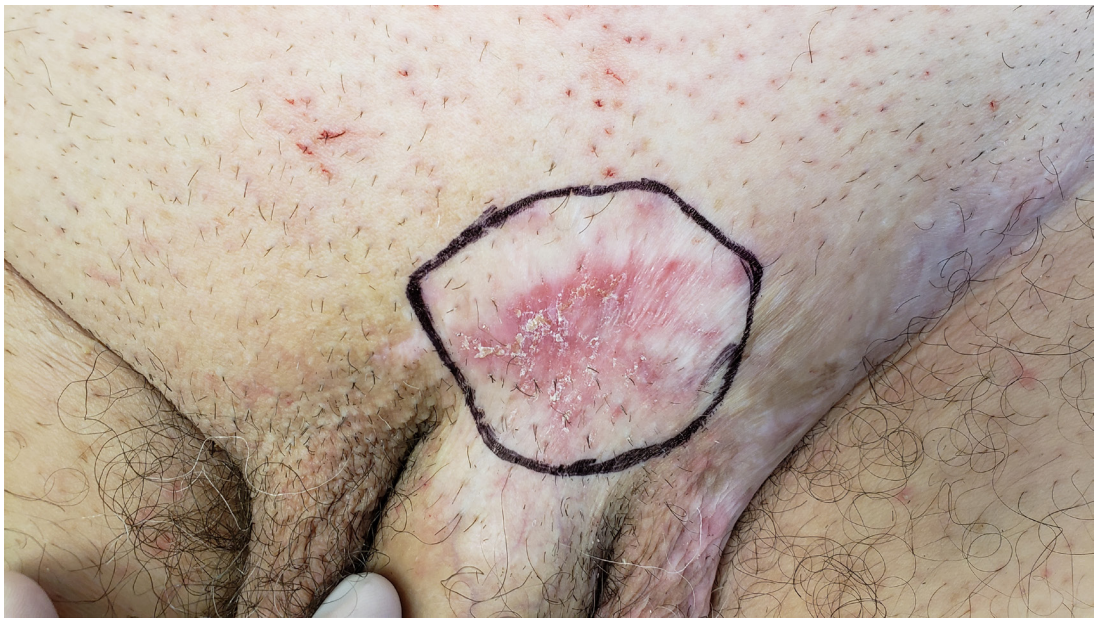

Figure 2: Marking the tumor for debulking. We decided to include the surrounding hypochromic area at this stage

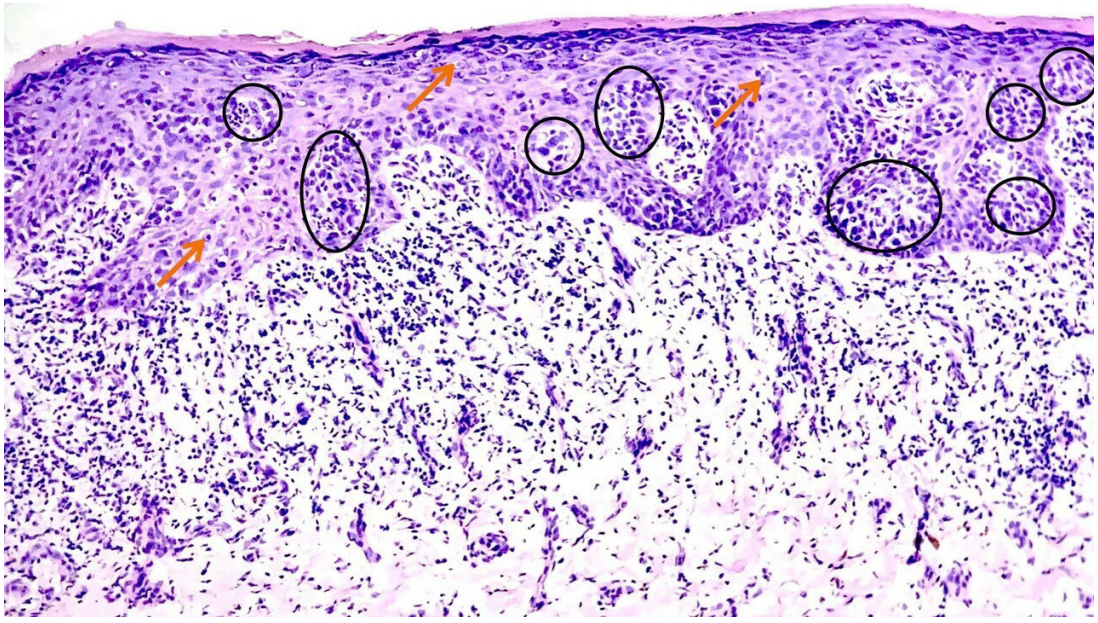

Figure 3: HE-stained histological section obtained during intraoperative examination (frozen). Presence of atypical Paget's cells isolated (arrows) or in clusters (circles) in the epidermis

Paget's cells were stained brown on the IHC, confirming their presence in the keratinocytes (Figure 5).

The lesion required two phases and 14 fragments to clear, creating a surgical defect measuring 90 x 75mm. Reconstruction by approximation of the edges, associated with second intention, was then performed after the margins had been cleared. The patient was followed up in the outpatient clinic for 9 months with no recurrence (Figures 6 and 7). Due to the Covid-19 pandemic, medical interviews were conducted by telephone, the last of which took place 35 months after surgery, when no recurrence was reported. The patient died of other causes 36 months after surgery.

DISCUSSION

The case studied illustrates a frequent situation in EMPD. An older patient with an extensive lesion in the perigenital region and a history of multiple recurrences to treatment. Due to associated comorbidities, treatment was initially attempted with topical treatment with imiquimod. Non-invasive therapies, such as imiquimod, may be indicated for patients in whom surgical morbidity may be considered high. A recent review identified

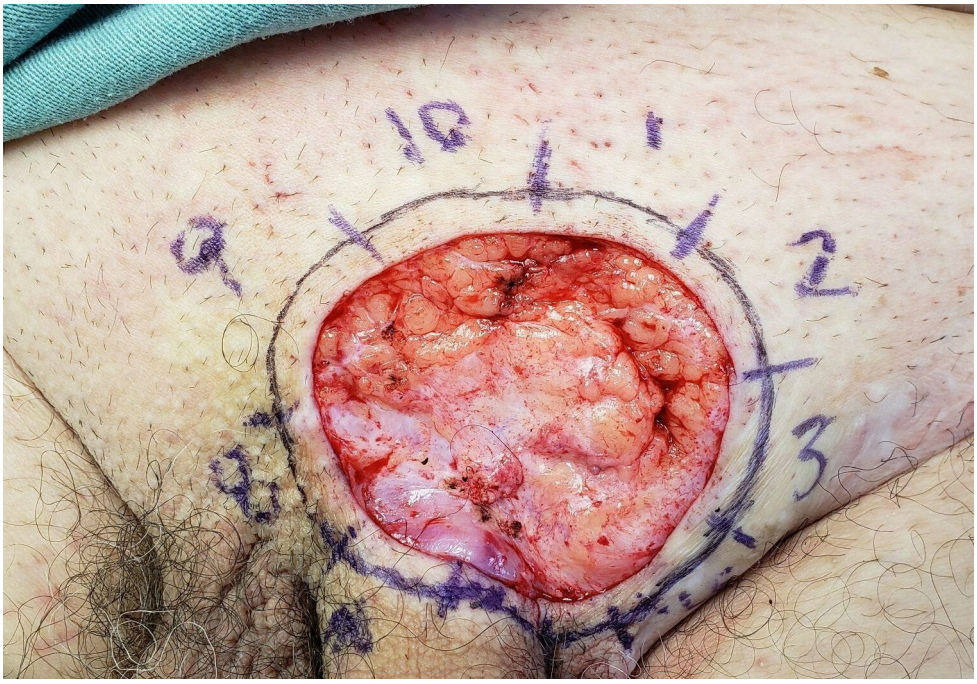

Figure 4: Surgical defect after debulking the tumor and marking the first phase of MMS

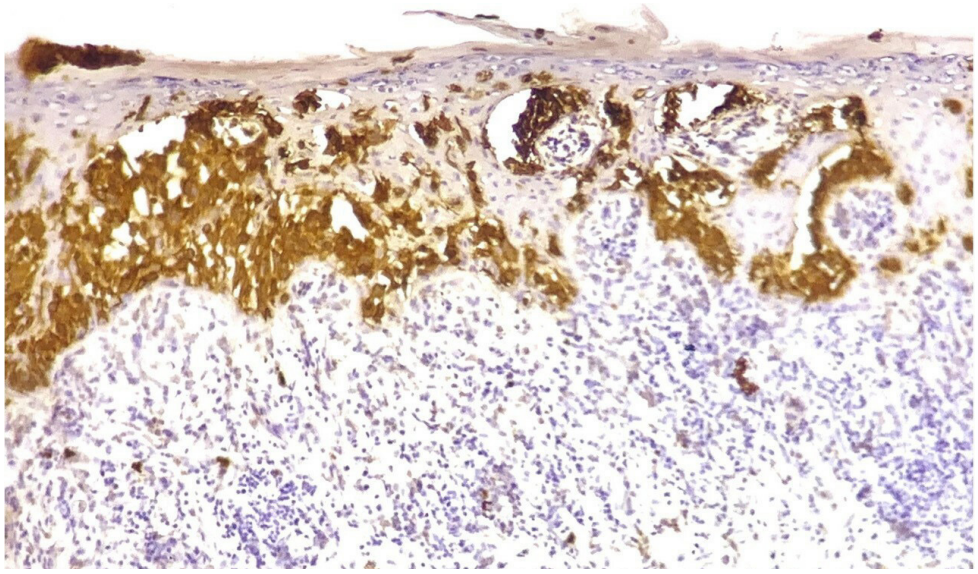

Figure 5: Histological section (100x magnification) subjected to rapid IHC reaction during intraoperative examination (frozen) with CK8/18

276 patients treated with imiquimod, in which a complete response was observed in 30% of cases and a recurrence rate of 35.4%.[8] In our experience, in addition to recurrence rates, prolonged exposure time to the drug and intense local inflammatory reaction also add morbidity and should be considered when choosing a therapy.

Local surgical excision was unsuccessfully attempted after imiquimod proved unsuccessful. In this technique, the vertical processing of the surgical specimen limits the assessment of the margins to less than 0.1%,[5] which is reckless in lesions with poorly defined boundaries, an irregular growth pattern and extensive subclinical dissemination.[7]

In a meta-analysis evaluating the efficacy of MMS in the treatment of EMPD, the recurrence rate observed was 12.2% over a mean follow-up of 27.5 months.[9] This rate is considered high when compared to other skin tumors routinely treated with MMS. Part of these recurrences are believed to be due to the difficulty in visualizing intraepithelial malignant cells in HE

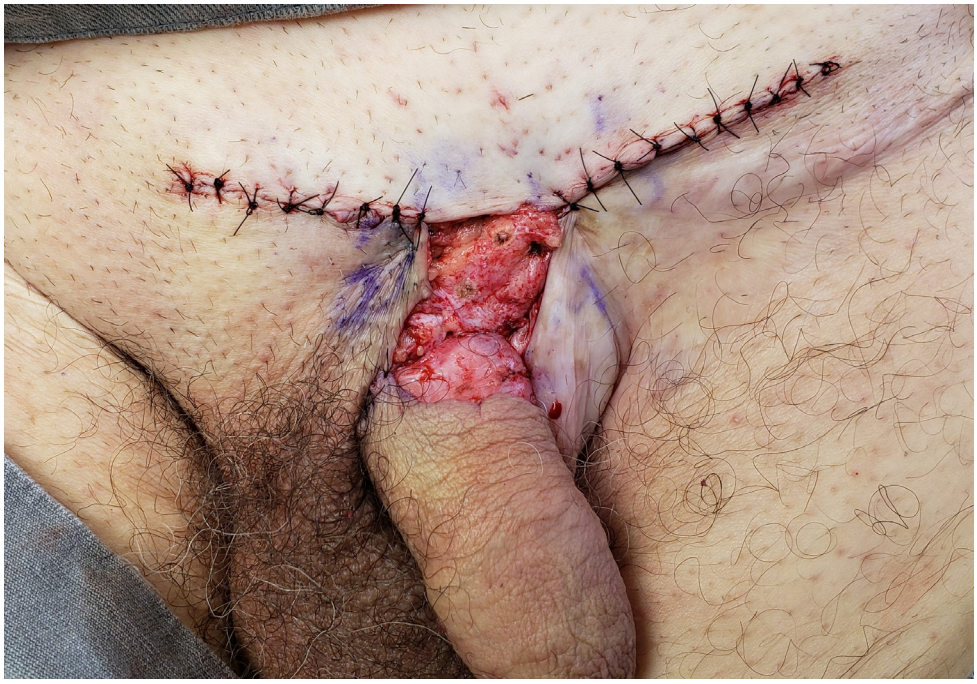

Figure 6: Immediate post-operative procedure with edge approximation associated with second intention

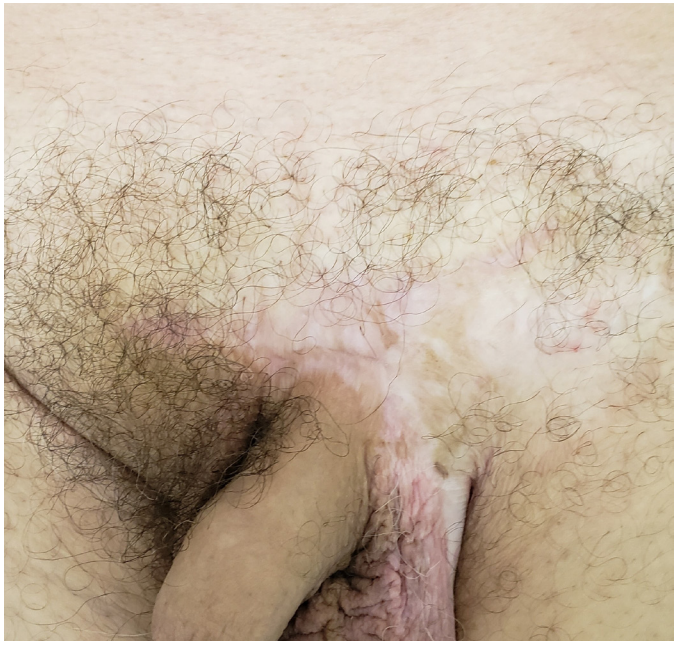

Figure 7: Postoperative appearance 6 months from surgery

frozen sections.[5] In these cases, rapid IHC is useful, as it highlights the malignant cells and can facilitate adequate control of the margins.[7]

In this case, IHC did not change the interpretation of the margins. However, it was performed by an experienced dermatopathologist, which does not reflect the Mohs surgeon's routine. Damavandy et al. in their 2018 study evaluated the use of IHC to interpret margins in EMPD treated with MMS. In this study, the authors reported a recurrence rate of 5.6% in recurrent tumors treated with staged surgery associated with IHC for CK7, compared to a 50% recurrence rate in patients in whom IHC was not used. However, surgical treatment required up to 5 days to complete.[8]

In our experience, peripheral MMS associated with rapid IHC provided prolonged remission of a recurrent tumor; it was performed in an outpatient setting and in a single surgical procedure. It also avoided the use of extensive margins, which reduced the morbidity of the surgery. However, the high cost and low availability of reagents in our setting are still an obstacle to the diffusion of this technique. Future studies will be useful in proving the real value of rapid IHC in the surgical treatment of EMPD.

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A novel neck rejuvenation protocol using a combination of injectables and technologies in a single session

Novo protocolo de rejuvenescimento do pescoço utilizando combinação de injetáveis e tecnologias em uma única sessão

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.2024160283

ABSTRACT

Neck aging encompasses intrinsic and extrinsic factors that need to be understood in order to achieve good treatment outcomes in the area. Minimally or noninvasive methods for neck rejuvenation have gained popularity because they provide individualized, natural, and safe results with no downtime. However, few studies have debated the need for global neck treatment or have offered suggestions and ways to combine different methods in single or multiple sessions.

We report here a novel protocol with the combined use of injectables and technologies in a single session, which act on laxity, fine lines, wrinkles, and skin quality.

Keywords: Neck; Rejuvenation; Combined Modality Therapy.

RESUMO

O envelhecimento do pescoço engloba fatores intrínsecos e extrínsecos, que devem ser compreendidos a fim de se alcançarem bons resultados na terapêutica da área. Os métodos minimamente ou não invasivos para rejuvenescimento do pescoço têm ganhado cada vez mais espaço por apresentarem resultados individualizados, naturais, rápidos e seguros. No entanto, poucos estudos debatem a necessidade do tratamento global do pescoço ou oferecem sugestões e formas de combinar diferentes métodos em uma mesma ou em múltiplas sessões.

Descreve-se aqui um novo protocolo com uso combinado de injetáveis e tecnologias em uma única sessão, os quais atuam na flacidez, linhas finas, rugas e qualidade de pele.

Palavras-chave: *Pescoço; Rejuvenescimento; Terapia combinada.*

How do I do it?

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INTRODUCTION

The combination of minimally invasive procedures in cosmiatry, for patients unwilling to undergo a surgical procedure, aims to provide significant results without scarring and with rapid recovery, safety, and satisfaction. For treatments related to neck rejuvenation, this is no different: more and more patients are looking for alternatives to more invasive treatments. Based on this demand, different methods have been used alone or combined to meet individual treatment expectations, such as injectable agents (botulinum toxin [BTX], hyaluronic acid [HA], poly-L-lactic acid [PLLA], calcium hydroxylapatite [CaHA]), radiofrequency (RF), RF microneedling (RFMN), microfocused ultrasound (MFU), intense pulsed light, and lasers.[1]

Signs of aging, such as laxity and wrinkles, are typically more intense on the neck than other parts of the body and are particularly more visible in patients who have already undergone facial procedures. Complaints related to the neck, such as increased submental fat, loss of contour, laxity, fine wrinkles, and changes in skin texture, are very common and encourage patients to seek procedures capable of addressing them.[2]

The present study aims to report the results of a series of cases in which a novel protocol with a combination of injectables and technologies in a single session was used for neck rejuvenation, the so-called "TD Protocol," aiming to improve outcomes and optimize the patient's time.

METHODS

Four female patients, aged 62 to 81 years, were subjected to the single-session protocol. High-resolution digital photographs of the neck were taken before and 30 to 60 days after the protocol. Topical anesthesia (Dermomax®, Aché, Brazil) was applied in all patients for 20 minutes prior to the procedures.

The protocol includes the following treatments in a single session and in the following order:

- Application of MFU (UltracelQ+®, Jeisys, South Korea) at a focal depth of 2 mm with up to 120 lines on the anterior aspect of the neck and focal depths of 3.0 and 4.5 mm in the submandibular area, cranial to the thyroid gland, between 120 and 200 lines from each tip;
- Application to the anterior rectangle of the neck, in retroinjection with a 22G 70 mm cannula, of the following mixture in the same 10 mL syringe: one 1.5 mL ampoule of CaHA (Radiesse Duo®, Merz, Germany), 20 units of BTX (Xeomin®, Merz, Germany), 1 mL of HA 20 mg/mL (Belotero Balance®, Merz, Germany), 1 mL of 1% lidocaine without vasoconstrictor, and 2.5 mL of 0.9% saline solution, for a total volume of 6 mL to be injected – modification of technique previously described.[3]
- Application of RFMN (Eletroderme®, LMG, Brazil) at 3 different depths (2.5, 2.0, and 1.5 mm), with energy of 25, 20, and 15 J and pulse duration of 130, 120, and 110 ms, respectively, complemented by 2 additional passes with the RF turned off and with a needle depth of 1.8 mm.

Figure 1 provides a schematic representation of the application of the TD Protocol.

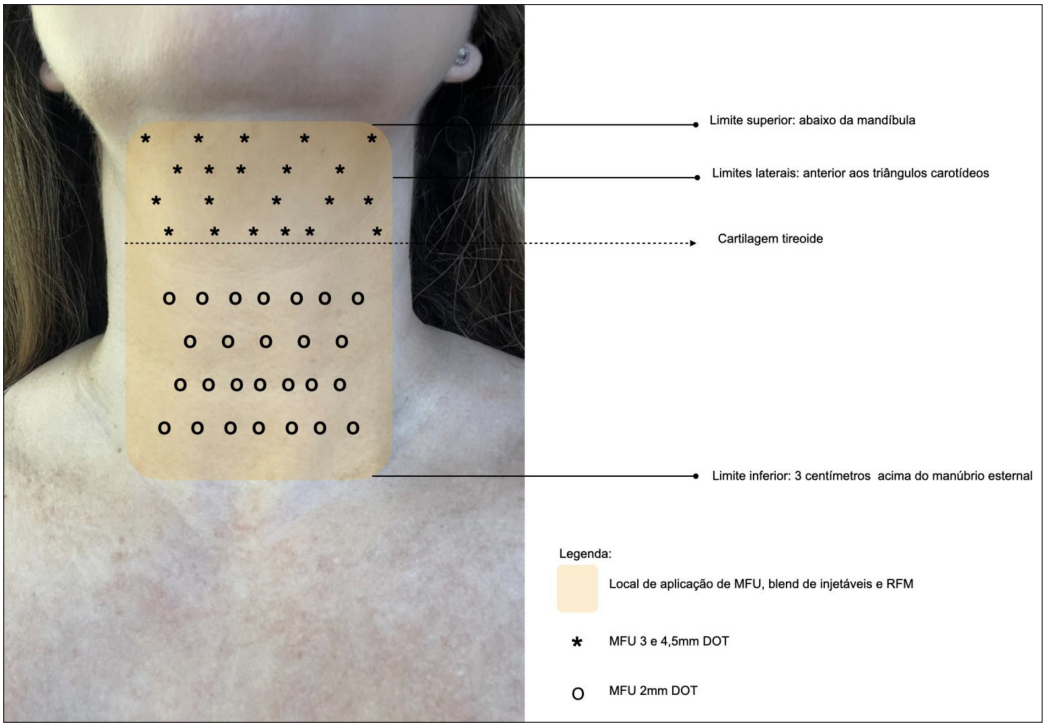
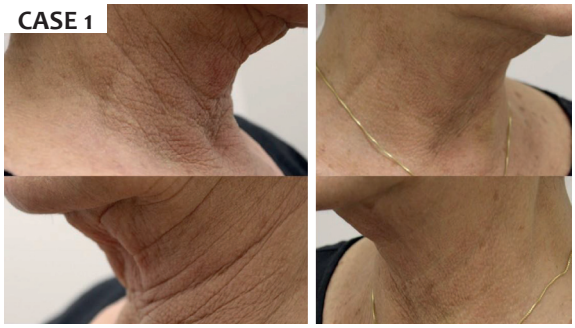
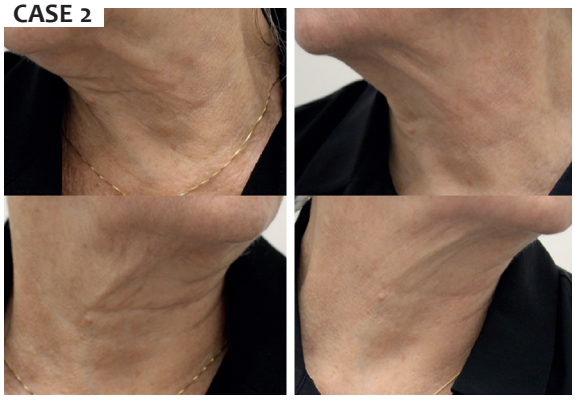


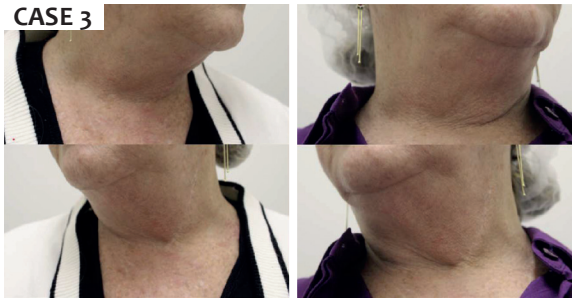
FIGURE 1: Schematic representation of the TD protocol.



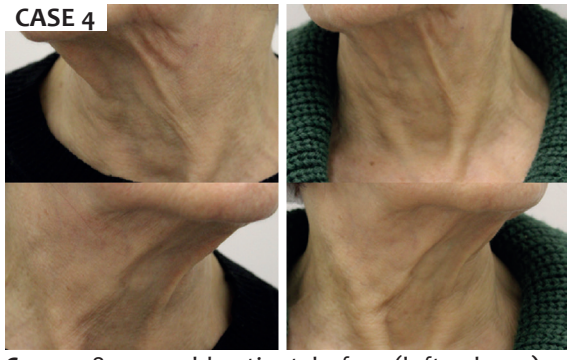
Case 1: 70-year-old patient, before (left column) and 30 days after (right column) the first session



Case 2: 67-year-old patient, before (left column) and 60 days after (right column) the first session



Case 3: 62-year-old patient, before (left column) and 60 days after (right column) the first session



Case 4: 81-year-old patient, before (left column) and 60 days after (right column) the first session

RESULTS

All patients had improvement in skin laxity and quality based on the analysis of photographs taken before and 30 to 60 days after the procedures and reported high satisfaction with the results. Patients had moderate erythema after application, lasting about 6 hours, and mild erythema and bruising for up to 7 days. Notably, patients reported no pain during RFMN.

DISCUSSION

Understanding the intrinsic and extrinsic factors of the aging process is essential for a comprehensive approach in treatments for neck rejuvenation. To obtain optimal outcomes, studies have demonstrated that a combination of the multiple minimally invasive procedures available is superior to their use alone.[4]

Regarding the noninvasive methods used in this study, it is known that MFU is widely used to treat skin laxity,[5] minimizing the appearance of submental fat accumulation,[6] as it induces thermal damage – coagulative necrosis – precisely targeting the superficial dermis and subcutaneous tissue, thus protecting the epidermis and promoting collagen remodeling in the desired area[5]. Edema and erythema may occur after MFU application.[6] Several studies have reported better results with the combined use of this technology and collagen biostimulators, such as CaHA in the short and long term, with current consensus that CaHA should be applied after MFU, based on the assumption that the microspheres left by MFU-induced thermal damage act as a scaffold for new tissue formation, enhanced after injection of the biostimulator.[7]

Attenuation of platysmal bands can be achieved with the use of BTX, with more visible effects in younger patients, as it does not improve laxity or submental fat.[8] When using BTX in conjunction with other therapies, the timing of injection should be considered. For example, it is recommended that BTX be used 3 weeks after using ablative lasers, but it can be performed immediately after vascular/pigment laser treatment with MFU if there is minimal edema after ultrasound. To enhance the correction of neck lines, the use of dermal fillers, such as HA, can be added to the treatment. When combining this with BTX, it is recommended to inject HA before BTX. HA use is safe immediately after vascular lasers and MFU, but its simultaneous use, on the same day, with ablative or nonablative fractional lasers should be avoided, especially on the face.[9] Finally, RFMN produces cell heating through the movement of molecules in a specific tissue using a matrix of needles, leading to collagen denaturation and tissue contraction, thereby promoting dermal remodeling through neocollagenesis. The most common adverse effects include erythema, edema, and pain, alleviated by using topical or injectable anesthetics. Therefore, the use of topical anesthesia and the injectable blend, administered in conjunction with lidocaine before RFMN, reduces patient discomfort in this method. Unlike lasers, RFMN can be used in any skin type as it does not act on specific chromophores, thus being safe in patients with darker skin types.[10]

Regarding the present protocol, it is under debate whether RFMN used after an injectable agent, such as BTX, could reduce its effect due to the heat generated at the site. Further studies should be conducted to evaluate the efficacy and safety of the protocol described here for neck rejuvenation, as well as its histologic effects.

CONCLUSION

Although surgical facelift remains the gold standard treatment to correct neck laxity, the intensive search for novel, less invasive interventions has demonstrated that cosmetic procedures are safe and effective for rejuvenation of the neck. Combining different methods can individualize and enhance outcomes, but there are still few studies evaluating multiple combinations in a single session. This protocol provides, for the first time, visible and safe results after sequentially performing, on the same day, well-established cosmetic procedures associated with 5 different methods, including injectables and technologies, in the single-session treatment of neck aging. ●

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Self-evaluation of disease visibility in patients with neurofibromatosis type 1: development of an online scale

Autoavaliação da visibilidade da doença em pacientes com neurofibromatose tipo 1: desenvolvimento de uma escala on-line

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.2024160268

Keywords: Neurofibromatosis 1; Diagnostic Self Evaluation; Phenotype; Self Report

Palavras-chave: *Neurofibromatose 1; Autoavaliação Diagnóstica; Fenótipo; Autorrelato*

Letters

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Self-evaluation of disease visibility in patients with neurofibromatosis type 1: development of an online scale

Dear Editor,

Neurofibromatosis type 1 (NF1) is a rare genetic disorder that affects approximately one in every 3,000 individuals, regardless of sex or ethnic background.[1,2] The disorder is caused by a mutation in the NF1 gene, which functions as a tumor suppressor.[2] The phenotypic expression of NF1 is highly variable. Nearly all patients develop small benign skin tumors that increase in number and visibility with age. In addition, 30% of adults with NF1 have visible plexiform neurofibromas.[3]

The NF1's visibility of NF1 manifestations is strongly associated with patients' quality of life and well-being of individuals.[1-4] Research suggests that patients' self-perception of their appearance is more important to them than visibility rated by external ratings.[1,4] Therefore, the assessment of disease visibility in NF1 should ideally be based on self-reported questionnaires rather than ratings by specialists.[4]

The aim of this study was to develop a self-rating scale, based on the Ablon Visibility Scale5 to measure NF1 visibility scale5 (Table 1). The scale is designed for remote access and self-administration by patients. It consists of eight yes/no ques-

tions, with NF1 visibility is classified into three levels: 1 (mild), 2 (moderate), and 3 (severe), based on the combination of responses (Table 2). To ensure clarity, we used simple language to make technical terms easily understandable to patients. For remote use, the scale was implemented via Google Forms, incorporating images from the Dermatology Information System to assist individuals in completing the assessment (https://doi.org/10.6084/m9.figshare.14442107.v4).

To assess the feasibility of the scale, we conducted an observational clinical study involving seven adult patients with NF1. Six of these patients had previously participated in research conducted by our group in 2014, during which they were classified in person using Ablon Scale.2 Between April and May 2021, these individuals used the newly developed NF1 visibility self-evaluation scale to rate themselves and were subsequently rated remotely by a dermatologist using the same tool. Table 3 compares the 2014 face-to-face classifications with both the self-assessments and the dermatologist's remote evaluations from 2021. Four patients rated their disease as more visible than in the 2014 face-to-face assessment, but their self-ratings matched the dermatologist's remote classification in 2021. This discrepancy may be attributed to the natural progression of the

Table 1: Ablon Visibility Scale of neurofibromatosis type 1

Degree 1 – Mild case	Tumors are generally not visible outside of normal clothing areas. Gait and posture appear normal to casual observation, although there may be a significant number of neurofibromas under clothing and minor skeletal symptoms.
Degree 2 – Moderate case	Some tumors are visible on the neck, face, and hands. Mild scoliosis or other skeletal features may be present, but there is no noticeable limp.
Degree 3 – Severe case	There are many tumors on the face. An optic glioma (tumor) may affect vision and the eye socket. Severe scoliosis or skeletal features are present, resulting in a noticeable limp.

Table 2: Items for self-evaluation scale of neurofibromatosis type 1 visibility

Feature	Degree of visibility
I have café-au-lait spots (brown patches) on my body	Can be degree I, II, or III*
I have small neurofibromas (pellets on the skin) around my body that are not visible (they are covered by clothes)	Degree I
I have some neurofibromas (pellets on the skin) around my body that are apparent on my neck, face, and hands	Degree II
I have many neurofibromas (pellets on the skin) around my body that are apparent on my neck, face, and hands	Degree III
I have mild scoliosis (deviation in the spine), which is not perceived (noticed) by other people	Degree II
I have more severe scoliosis (deviation in the spine), which is perceived (noticed) by other people	Degree III
I had to have surgery because of scoliosis (deviation in the spine)	Degree III
I have asymmetry of the face, that is, there is a difference between the two sides of my face	Degree III
I have other health problems because of neurofibromatosis type 1. If so, please describe them	—

** Consider degree I if marked separately.*

Table 3: Comparison of classifications by Ablon Visibility Scale (2014) and the online NF1 visibility self-evaluation scale (2021)

Patient	Ablon Visibility Scale (face-to-face evaluation – 2014)	Online NF1 visibility self-evaluation scale	
		Self-evaluation – 2021	Evaluation made by the researcher – 2021
1	Degree I	Degree I	Degree I
2	Degree II	Degree III	Degree III
3	Degree I	Degree I	Degree I
4	Degree I	Degree II	Degree II
5	Degree II	Degree III	Degree III
6	Degree I	Degree II	Degree II
7	—	Degree III	Degree III

disease. Overall, there was complete agreement between the patient self-assessments and the dermatologist's remote evaluations using the NF1 visibility self-evaluation scale.

Visibility and severity of NF1 are important to distinguish. Visibility refers to the outward appearance of a fully clothed individual and how easily symptoms are noticed during casual, impersonal interactions. Many individuals with NF1 may not have visible phenotypic features in commonly exposed areas, but they may have numerous tumors and/or café-au-lait spots in areas that could become visible in certain situations, such as on the beach or during intimate contact.[3,5] In contrast, severity encompasses both clinical and cosmetic factors, including impact on lifestyle, mobility, and even life-threatening complications.1-4 While visibility can be self-assessed by the patient, as it involves only external features that can be observed and reported, severity assessment requires professional analysis. This assessment considers the extent of dermatologic involvement and the presence of disabling complications. Both visibility and severity of NF1 are related to psychosocial well-being and the need for appropriate support.[1-4]

The visibility scale we developed has proven to be a valuable tool that can be used in clinical research as well as in the care of individual patients. By allowing patients to apply the scale themselves, it emphasizes the importance of their personal perception of their condition and can help improve their understanding of the disease and its progression.

Acknowledgments

We are sincerely grateful to the Dermatology Information System (DermIS) for allowing us to use their images during the development of the scale.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Financial support

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Conflict of interest

The authors declare no conflicts of interest.

Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee at Universidade Federal de São Paulo (CAAE 29747620.0.0000.5504), and all participants provided informed consent. ●

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Piebaldism – portraits of hereditary character: a series of cases

Piebaldismo – retratos do caráter hereditário: uma série de casos

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ABSTRACT

Piebaldism is a rare, autosomal dominant dyschromia characterized by circumscribed poliosis and triangular achromia in the frontal region in 90% of affected individuals, with no other systemic involvement. The incidence of dyschromia in this Dermatology Department, in a short space of time, and with plenty of images, motivated the presentation of this series of cases. We show two families with piebaldism, treated at the same Dermatology Department in 2021: the first family, with a mother and son presenting achromic macules on the trunk and poliosis in the frontal region since birth; the second family, with a grandmother, aunt, mother, and son showing the same characteristics described.

Keywords: Piebaldism; Pigmentation Disorders; Skin Diseases; Genetic

RESUMO

O piebaldismo é uma discromia rara, autossômica dominante, caracterizada por poliose circunscrita e acromia triangular na região frontal em 90% dos indivíduos acometidos, sem outros acometimentos sistêmicos. A incidência da discromia neste Serviço de Dermatologia, em curto espaço de tempo e com riqueza de imagens, motivou a exposição desta série de casos. Exibimos duas famílias com piebaldismo, atendidas no mesmo Serviço durante o ano de 2021: a primeira família, com mãe e filho apresentando máculas acrômicas pelo tronco e poliose na região frontal desde o nascimento; e a segunda família, com avó, tia, mãe e filho apresentando as mesmas características descritas.

Palavras-chave: *Piebaldismo; Transtornos da Pigmentação; Dermatopatias*

Letters to the Editor

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INTRODUCTION

Piebaldism is a rare dyschromia characterized by circumscribed poliosis and triangular achromia in the frontal region in 90% of affected individuals. The incidence of dyschromia in the same Dermatology Department, within a short period of time and with plenty of images, motivated the presentation of this series of cases. We show two families with piebaldism, from different cities near the region, treated in the same department during 2021 (Figures 1 and 2).

Case series:

Case 1: One-year-old, male child. Referred from the BHU due to achromic macules on the body and poliosis in the frontal region since birth.

Mother with the same characteristics.

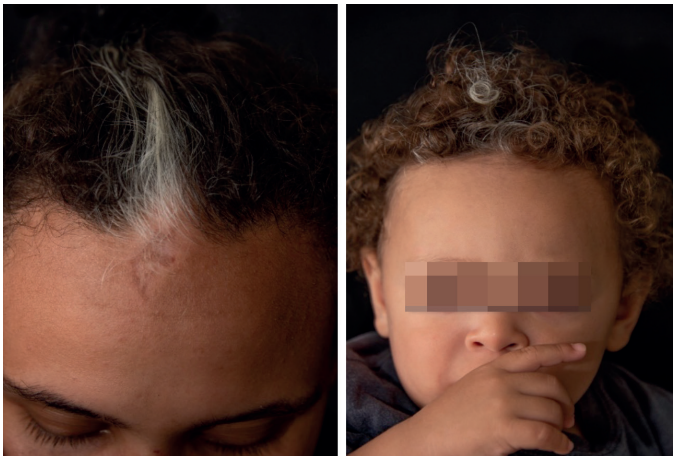

FIGURE 1: Poliosis in the frontal region of mother and child since birth

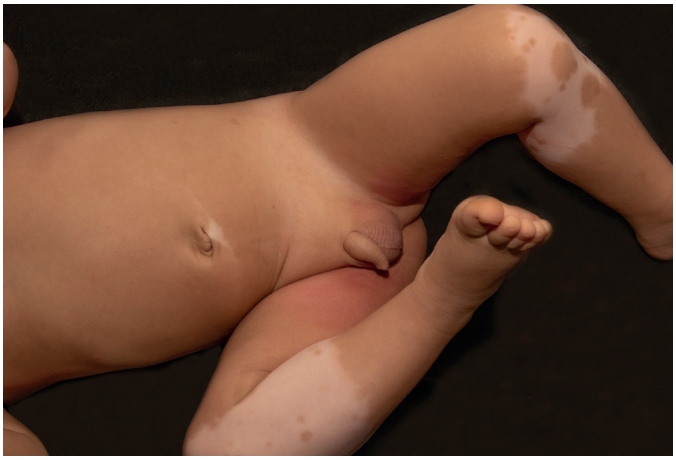

FIGURE 2: Achromic macules located bilaterally on the lower limbs

Case 2: Eight-month-old, male child. Referred from the Pediatrics Department due to achromic macules on the body and poliosis in the frontal region since birth (Figures 3 and 4).

Mother with the same characteristics. Maternal grandmother and aunt had the same phenotypic characteristics.

FIGURE 3: Poliosis in the frontal region of the maternal grandmother, mother, and son since birth

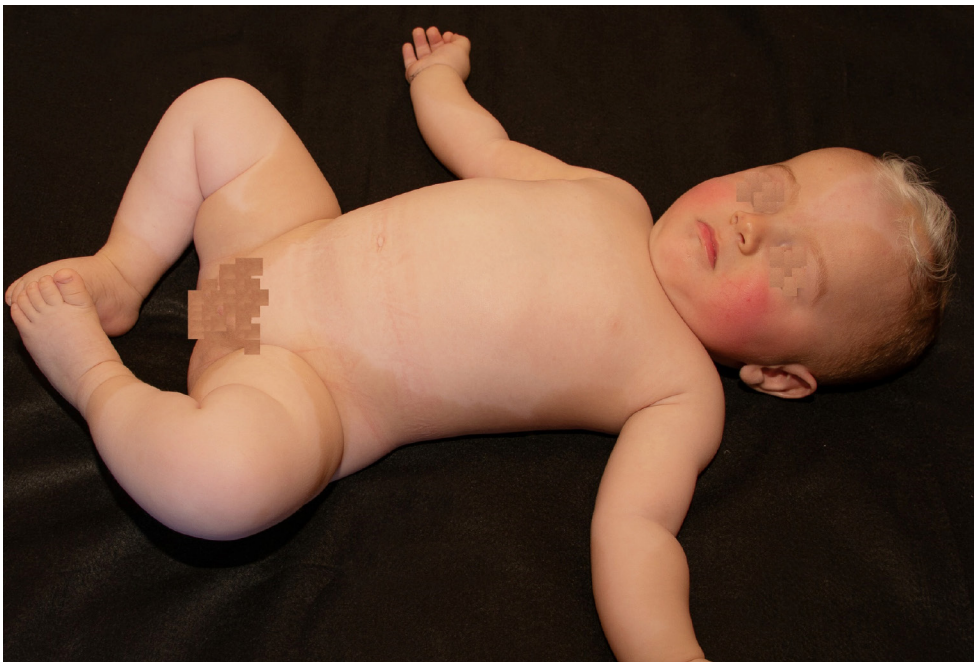

Figure 4: Achromic macules located bilaterally on the abdomen and lower limbs

DISCUSSION

Piebaldism is a rare dermatosis that affects around 1:20.000 individuals, regardless of sex or ethnicity. In 90% of cases, poliosis and areas of achromic skin are present, unrelated to systemic alterations.[1] This dyschromia has been described since Egyptian reports[2] and occurs due to mutations in the C-KIT 4q12 proto-oncogene, an autosomal dominant disorder, with abnormal migration of melanoblasts in the neural crest, resulting in body areas without melanocytic activity.[3]

Poliosis is typical of the disease, characterized by an area with no pigment in the frontal region of the scalp, which extends in a triangular shape to the forehead, converging towards the midline of the face. Achromic and hypochromic macules that affect the body are characteristically of a central pattern, located predominantly on the abdomen, the middle third of the upper and lower limbs, sparing the involvement of the hands, feet, and back.[1] The central pattern of dyschromia is explained because the mutation affects the neural crest. Affected individuals may present with hyperchromic macules and axillary ephelides.[3]

The diagnosis of piebaldism is clinical and, if it is suspected, a thorough clinical, ophthalmological, neurological, and gastrointestinal investigation is necessary, even in the neonatal period, to rule out differential diagnoses with possible systemic and deleterious symptoms, such as Waardenburg syndrome, which not only has achromic macules, but also iris heterochromia and sensorineural deafness.[1,3] Other differential diagnoses are vitiligo, Ito hypomelanosis, Wolf syndrome, and achromic nevus.[4]

As this is a benign condition, no treatment is required, but photoprotection guidelines are essential. Melanocyte transplants have been reported to reduce areas of achromia in patients with aesthetic complaints.[5]

CONCLUSION

Isolated piebaldism has no known systemic complications. As an autosomal dominant genodermatosis, it is necessary to question the family pattern when the diagnosis is suspected. ●

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Ultrahigh-frequency ultrasound imaging of the dorsum of the hand for aesthetic procedures

Anatomia do dorso da mão por ultrassom de frequência ultra-alta aplicada a procedimentos estéticos injetáveis

Diagnostic Imaging

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ABSTRACT
Hand rejuvenation has become increasingly popular in recent years. Knowledge of the layered anatomy of the hand is crucial for better aesthetic results. In this context, ultra-high-frequency ultrasound (UHFUS) has been used in minimally invasive procedures all over the body, including the hands. To the best of our knowledge, this is the first study to correlate UHFUS evaluation of the dorsal aspect of the hand before, during, and after injectable procedures. We discuss the layered local anatomy of the hand, whose knowledge is crucial for performing safe and effective aesthetic treatments for rejuvenation, and the correlation of the imaging aspects of different procedures and products, as well as its possible complications.
Keywords: Ultrasonography; Rejuvenation; Hand; Anatomy.

RESUMO
Os procedimentos de rejuvenescimento das mãos tornaram-se cada vez mais populares nos últimos anos. O conhecimento da anatomia em camadas do dorso da mão é essencial para alcançar melhores resultados estéticos com segurança e confiança. Nesse contexto, o ultrassom de ultra-alta frequência (UHFUS) tem sido cada vez mais utilizado em procedimentos estéticos minimamente invasivos em todo o corpo, podendo também ser utilizado nas mãos. Até onde sabemos, este é o primeiro artigo que correlaciona imagens do dorso da mão por UHFUS antes, durante e após procedimentos injetáveis. O artigo discute a anatomia local estratificada que é crítica para a realização de tratamentos estéticos seguros e eficazes para o rejuvenescimento das mãos. O artigo também correlaciona os aspectos de imagem de diferentes procedimentos e produtos, bem como suas possíveis complicações.
Palavras-chave: *Ultrassonografia; Rejuvenescimento; Mão; Anatomia.*

INTRODUCTION

After the face, the hands are one of the most visible parts of the body, and undergo characteristic changes with aging, such as dyschromias, lentigines, actinic keratosis, roughness, and seborrhea. In addition, loss of subcutaneous fat volume and muscle atrophy accentuate the prominent tortuous veins, tendons, joints, and bony prominences beneath the skeletal skin of the dorsum of hand.[1,2] All of these changes contribute to an older appearance. The literature shows that patient age may be estimated based solely on the appearance of the hands.[1] Indeed, the appearance of the hands is also considered the second most telling indicator of chronological age, surpassed only by the appearance of the face.[3] Hand rejuvenation procedures have therefore received special attention.

Hand rejuvenation for aesthetic purposes has become increasingly popular among both professional injectors and patients [4,5] seeking to restore the appearance of smooth, youthful hands with satisfactory volume and improved skin quality. To achieve the best results with these emerging aesthetic and cosmetic procedures, a thorough understanding of the local anatomy, accurate determination of the precise anatomical plane of application, and familiarity with the composition and properties of the products used, as well as the proper procedural techniques, are essential.

High-resolution ultrasound (HRUS) may be used to improve safety and accuracy prior to, during, and after these procedures. Ultrahigh-frequency ultrasound (UHFUS) has become increasingly popular for minimally invasive procedures. This is not only because of its unprecedented level of detail, which allows identification of structures previously unimaginable with radiological imaging techniques, but also because it correlates in vivo anatomical, clinical, surgical, and radiological findings with incredible precision.

Although the hands are highly visible, aesthetic procedures are popular, and UHFUS has potential, there are relatively few studies regarding hand rejuvenation. Very few of these studies have used radiological imaging, and none have included detailed anatomical and procedural information along with the use of UHFUS (22–33 MHz).[6,7,8]

Therefore, the aim of this article is to describe the techniques and procedures performed on the hands as well as the associated imaging findings and detailed anatomy of the hands, thereby adding an innovation to the literature.

ANATOMY OF THE DORSUM OF THE HAND

Knowledge of the layered anatomy of the hand is crucial for a successful preprocedural and ultrasound analysis. This knowledge is also essential for safe and effective aesthetic treatments, as performing procedures in the wrong anatomical layer can lead to poor aesthetic outcomes and increase the risk of adverse events, such as hematoma formation, intravascular injection, and nerve damage.

The first anatomical discussion of the dorsum of the hand was in 1939 by Kanavel,[9] who described two fasciae: a superficial fascia covering the extensor tendons and a deep fascia covering the interosseous muscles and metacarpal bones. In 2010, Bidic et al.[9] correlated histological, anatomical, and ultrasound sections of the dorsum of hand and described three compartments of areolar fatty tissue and three fascial layers. They identified the dorsal superficial, intermediate, and deep laminae, separated by three fascial layers: i) dorsal superficial fascia, which separates the dorsal superficial lamina from the dorsal intermediate lamina; ii) dorsal intermediate fascia (a continuation of the antebrachial fascia of the forearm), which separates the dorsal intermediate lamina from the dorsal deep lamina; and iii) dorsal deep fascia, the muscular fascia that extends from the periosteum on the dorsal side of the metacarpals. The sensory nerve and the dorsal vein are in the dorsal intermediate lamina, and the extensor tendon is in the dorsal deep lamina (Figure 1).

Studies in the last decade have also adopted this layered anatomy approach. For example, Lefebvre-Vilardebo et al.[10] describe the fascia and laminae between the skin and tendons as inseparable, forming a 3D sponge-like fascial scaffold in which veins, their perforators, and nerves are found. The studies by Bidic et al.[9] and Lefebvre-Vilardebo ***et al***.[10] agree that the safest layer for application of volumizing material is the subdermal layer because it is at a safe distance from the neurovascular bundle. Dorsum of hand is compartmentalized by strong septa, so bolus injection of product is less likely to be easily redistributed throughout the dorsum of hand.[2]

ULTRASONOGRAPHIC ANATOMY OF THE DORSUM OF THE HAND

To the extent of our knowledge, after an extensive search of the medical literature, this is the first study of the ultrasonographic anatomy of the dorsum of the hand using UHFUS (22 MHz—GE LOGIC E, General Electric, Milwaukee, WI; and 24 and 33 MHz—Canon Aplio i700 and i800, Canon Medical System Corporation, Japan). By using UHFUS, we

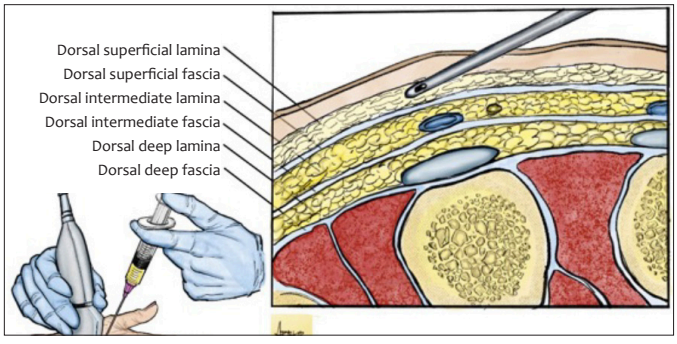

FIGURE 1: Anatomy of the dorsum of the hand, adapted from Bidic. [9]

found consistency in the ultrasound imaging patterns of the dorsal layers of hand. From surface to deeper layers, the following layers can be identified (Figure 2):

Epidermis: Thin hyperechoic line due to higher keratin content.

Dermis: Hyperechoic band (less hyperechoic than the epidermis), rich in collagen.

Dorsal superficial lamina: Thin hypoechoic band, a very thin layer of fat/areolar tissue, generally not noticeable.

Dorsal superficial fascia: Hyperechoic line.

Dorsal intermediate lamina: Hypoechoic band, a layer of areolar fatty tissue where the dorsal veins are located (oval anechoic structures in the transverse plane and tubular in the longitudinal plane).

Dorsal intermediate fascia: Hyperechoic line, a continuation of the antebrachial fascia of the forearm.

Dorsal deep lamina: Hypoechoic band, a layer of fat/areolar tissue in which the extensor tendons run.

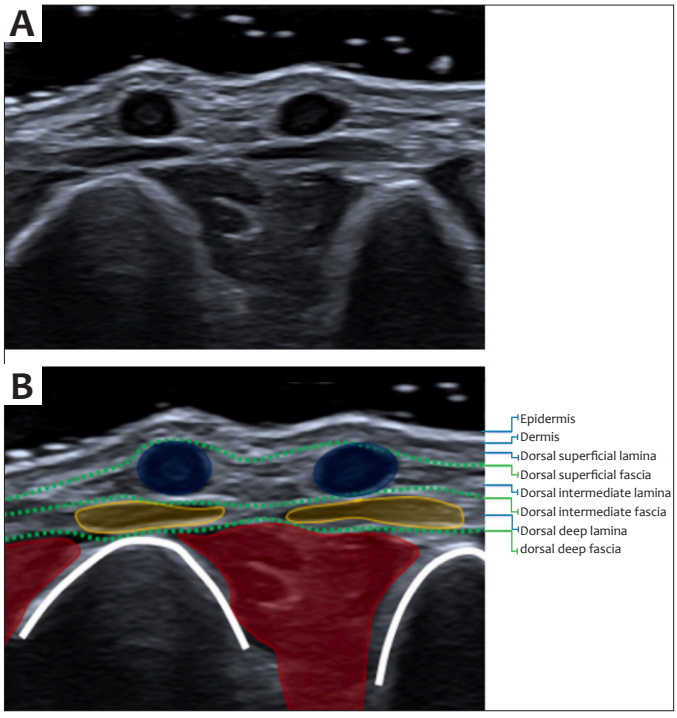

Figure 2: Transverse-plane UHFUS image **A** - and schematic **B** - with a 24 MHz multifrequency probe (Canon Aplio i700) documenting the layered anatomy of the dorsum of hand: green dotted lines indicate the dorsal superficial, intermediate, and deep fasciae. These fasciae delineate the fatty spaces/loose areolar tissue as superficial, intermediate, and deep layers.
Dorsal veins are circled in blue, extensor tendons are circled in yellow, interosseous muscles are circled in red, and the blank lines indicate the cortex of metacarpals

Dorsal deep fascia: Hyperechoic line, the superficial muscular fascia that continues to the periosteum of the dorsal surface of the metacarpals.

By reviewing the literature, we can see that the studies by Bidic et al.[9] and by Lefebvre-Vilardebo et al.[10] present different descriptions of the anatomy of the fascia and laminae of hand. However, this discrepancy can be attributed to their use of transducers with different frequencies and lower resolutions than those used in the present study.

Understanding the layered anatomy of the dorsal hand and its normal appearance on ultrasound is critical to performing injectable aesthetic procedures, not only in preprocedural evaluation but also in guided injections. The recommended target plane for hand rejuvenation injections is the undersurface of dermis, which can be clearly identified via UHFUS. During evaluation, it is also possible to visualize and confirm the proper positioning of the cannula, which appears as a round hyperechoic structure in the transverse plane and tubular in the longitudinal plane (Figure 3).

INJECTABLES FOR REJUVENATION OF THE DORSUM OF HAND AND THEIR ULTRASONOGRAPHIC ASPECTS

Hand rejuvenation is a safe, effective procedure. The first study identified in the literature on dorsal hand rejuvenation was published in 1992 and reported results with fat grafting.[11] Since that time, a variety of techniques have been described with similar aesthetic results.[3] Major techniques for hand rejuvenation include autologous fat transfer (transfer of the patient's own fat), dermal fillers (synthetic materials), and collagen stimulants. Currently, only two fillers are U.S. Food and Drug Administration-approved for hand rejuvenation: Radiesse® (CaHA; Merz North America, Inc., Raleigh, NC) and Restylane-Lyft® (hyaluronic acid; Galderma Laboratories, Fort Worth, TX).[7]

All of these procedures can be performed with local anesthesia, provide good aesthetic results, and patients report high satisfaction with fewer complications.[7] A systematic review showed that Radiesse® and fat grafting were the most commonly used products for hand rejuvenation with the lowest complication rates.[3]

Ultrasound can be used before procedures to analyze local anatomy and identify previously applied products, an important step in reducing risk. Ultrasound is the only radiological imaging modality capable of being used for product identification or during and after injections. In postprocedural assessment, this method can diagnose and assist in the management of aesthetic and surgical complications.[12,13]

1. FAT

Once fat is obtained, it is possible to fill the dorsal region of the hand, allowing it to cover visible veins and tendons, resulting in subtle and uniform contours. In addition to the volumizing effect, the fat cells have a beneficial stemming effect,

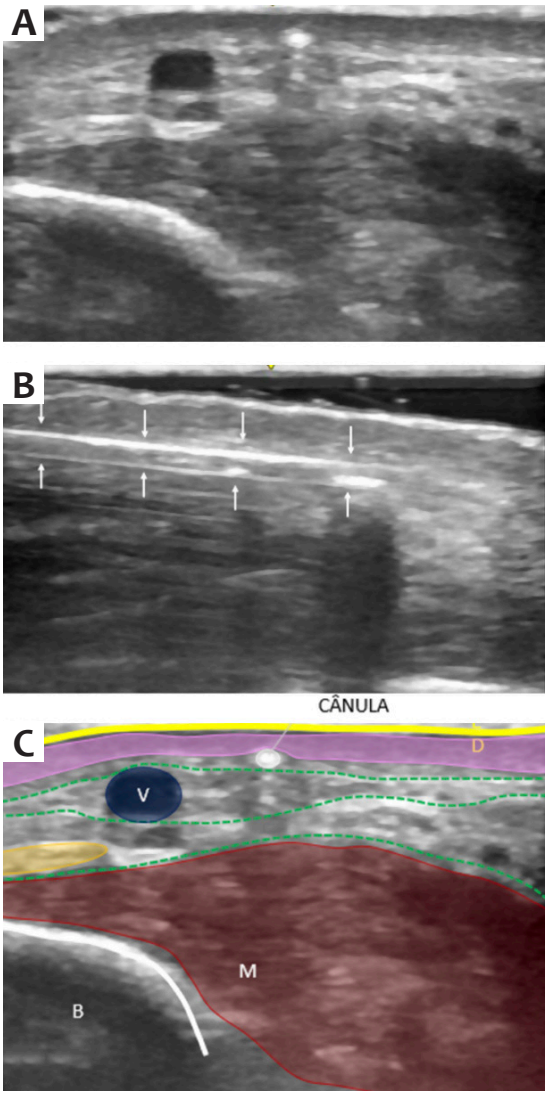

Figure 3: Transverse **A** - and longitudinal **B** - UHFUS images with a 22 MHz multifrequency probe (GE LOGIC E) show the proper positioning of the cannula to inject the product in the correct and safe location. Anatomical schemes in the trans-verse **C** - and longitudinal (**3D??**) planes show the following: yellow line for the epidermis; pink band for the dermis; green dotted lines for the dorsal superficial, intermediate, and deep fasciae; blue circle for the dorsal vein; yellow circle for the extensor tendon; red circle for the interosseous mus-cles; and white lines for the cortex of the metacarpal bones. Cannula is shown as a white circle under the dermis

with growth factors that rejuvenate the superficial and deep tissues. The results are stable and, in the long term, the effects and aesthetic satisfaction can last more than 4 to 5 years.

Liposuction sites, material preparation protocols, and injected volumes vary in the literature. The body regions most involved in the harvesting of autologous fat for grafting include the abdomen, flanks, and medial thigh. There was no consensus on centrifugation prior to injection. The fat grafting technique is most commonly performed with cannula, with low pressure, low speed, low volume, multi-tunnels, multi-planes, and multi-points (3L3M). Volumes ranges from 10 to 30 mL, with a total average of 15 mL per hand, using a proximal to distal fan technique.[8,11] The exact anatomical layer in which the fat cells are deposited is controversial; there is a greater consensus on the safety and efficacy of injections into the dorsal superficial lamina.[11]

In UHFUS, the main characteristics of autologous fat grafts depend on the preparation or composition: whether when liquefied it appears as anechoic or a "pseudocystic" deposit,[14] or if not liquefied, as a local tissue disorganization or lobulated hypoechoic deposits with permeating hyperechoic septa (Figure 4).

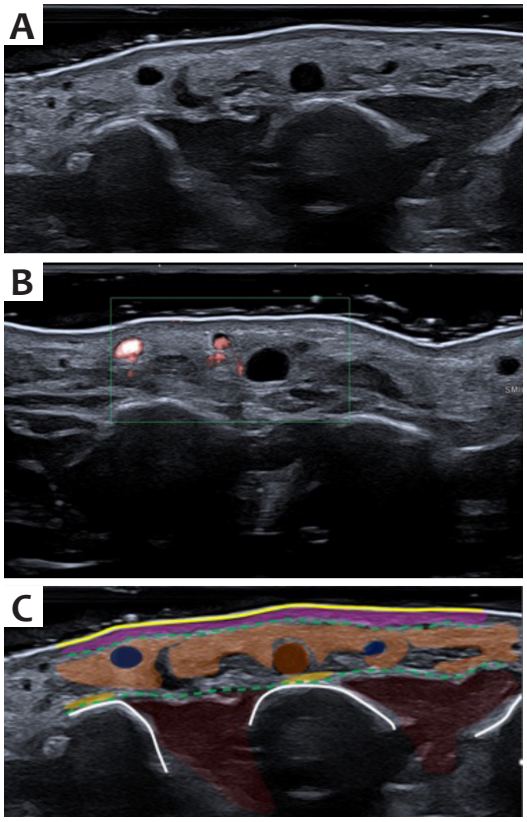

Figure 4: A -Transverse plane images with a 24 MHz multifrequency probe (Canon Aplio i700) in B-mode ultrasound and superb microvascular imaging (SMI) Doppler **B**, along with an anatomical scheme **C**, show the ultrasound anatomical layers of the dorsum of hand and the presence of fat grafting. Annotations are as follows: yellow line for epidermis; pink band for dermis; green dashed lines for dorsal superficial and deep fasciae; blue circles for dorsal veins; orange shading for fat graft; dark orange circle for liquefied fat (pseudocyst); yellow circle for extensor tendons; red for interosseous muscles; and white for the cortex of metacarpals

2. HYALURONIC ACID

Hyaluronic acid can improve the appearance of wrinkles, provide optimal coverage of prominent veins and visible tendons, and improve subcutaneous atrophy. Typically, 1 ml of hyaluronic acid is used on each side. Results last approximately 12 months.[15,16,17,18]

In the ultrasound image (Figure 5), the appearance of hyaluronic acid depends on its composition, combination, and density. Pure hyaluronic acid (HA) appears as millimeter-sized anechoic, "pseudocystic" areas.[19]

3. POLY-L-LACTIC ACID

Injectable poly-L-lactic acid (PLLA) (SCULPTRA® Aesthetic, Galderma Laboratories) is a semipermanent, biocompatible, biodegradable, immunologically inert product. The induction of neocollagenesis by fibroblasts results from the placement of PLLA in the reticular dermis and subcutaneous tissue planes. Results last up to 2 years, sometimes longer.[20]

Redaelli described the first series of PLLA cases for hand rejuvenation in 2006. He observed a measurable decrease in the visibility of extensor tendons and an improvement in the appearance of tortuous veins. In the 16 patients available for evaluation at 15 months, results were maintained or improved.[21] In UHFUS, PLLA is generally difficult to detect unless it forms nodules, which may or may not be palpable and may present as isoechoic or slightly hyperechoic nodules. With direct application of the product diluted in distilled water, only the anechoic aspect of the diluent infiltrating the tissue can be identified (Figure 6). With ultrasound-guided application of PLLA on the dorsal superficial lamina, we observed its delivery also to the dorsal intermediate and deep laminae, similar to the 3D model reported by Lefebvre-Vilardebo et al.[2,10] (Figures 6a and 6b).

4. CALCIUM HYDROXYAPATITE

In 2007, Busso and Applebaum[22] first described the use of calcium hydroxyapatite (CaHA) (Radiesse, Merz Aesthetics) to restore a fuller, more youthful appearance to the hands, reduce skin laxity and wrinkles, and minimize the appearance of prominent underlying structures such as bone, tendons, and veins. Because CaHA is an identical compound to that found in bone, it has high biocompatibility and a low risk of adverse events.

Since that initial report by Busso and Applebaum, additional publications have demonstrated successful restoration of the volume of hand with CaHA in over 100 patients using a variety of techniques and dilutions. Results have ranged from 12 to 24 months.[23,24,25]

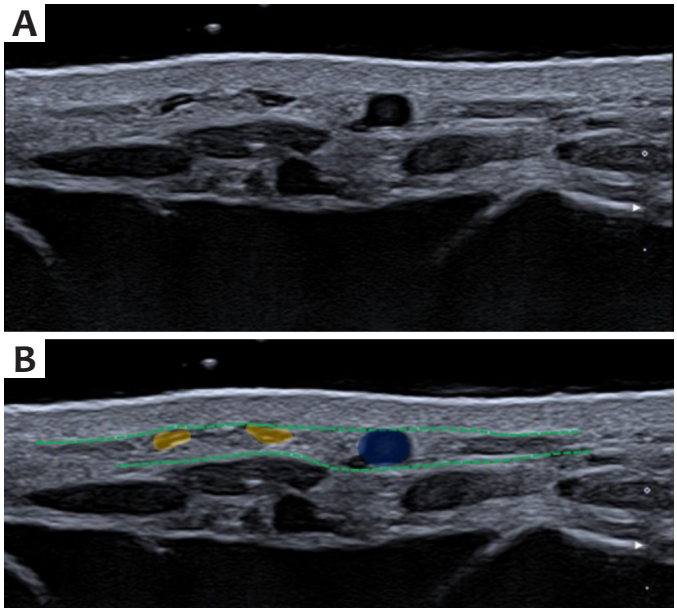

Figure 5: Transverse UHFUS image **A,** and anatomical scheme **B,** with a 33 MHz multifrequency probe (Canon Aplio i700) showing the anatomical layers of the back of the hand and the presence of hyaluronic acid: green dotted lines for the dorsal superficial and dorsal intermediate fasciae; blue for the dorsal vein; and yellow for the hyaluronic acid deposits

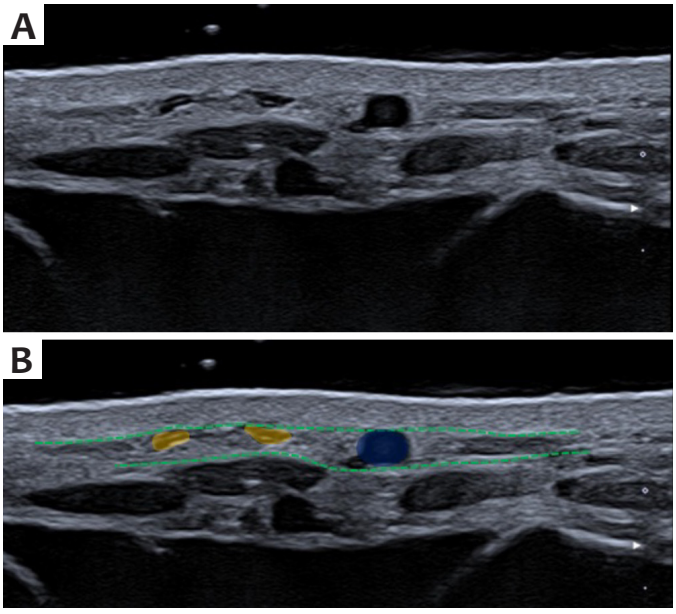

Figure 6: Longitudinal UHFUS image **A,** with a 24 MHz multifrequency probe (Canon Aplio i700) showing the correct plane of the cannula in the dorsal superficial lamina where the product was delivered. Transverse UHFUS image **B,** with a 24 MHz multifrequency probe (Canon Aplio i700) immediately after product injection, showing that although the product was delivered to the dorsal superficial lamina, it was also distributed to the dorsal intermediate and deep laminae

On HRUS, CaHA appears as continuous or focal hyperechoic deposits with or without posterior acoustic shadowing, depending on the concentration (Figure 7 and Figures 8a and 8b).[26] On UHFUS, it appears as continuous or focal hyperechoic deposits with or with no posterior acoustic shadowing, depending on the concentration (Figure 7 and Figure 8).[27]

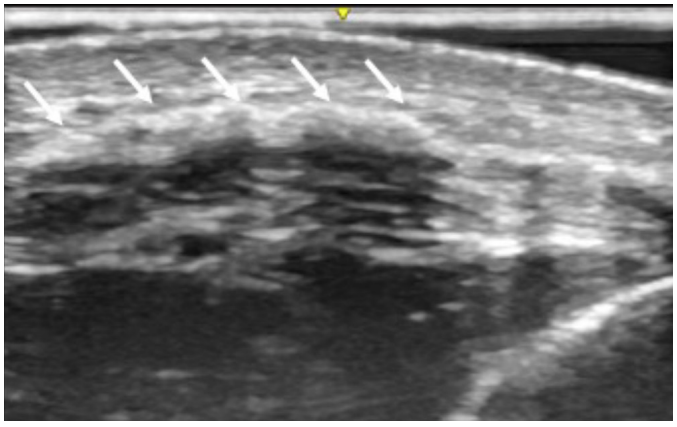

Figure 7: Transverse UHFUS image with a 22 MHz multifrequency probe of the same patient from Figure 3, immediately after injection of calcium hydroxyapatite on the correct surface. After vigorous massage, calcium hydroxyapatite (white arrows) reached the dorsal superficial and intermediate laminae, thereby confirming the hypothesis by Lefebvre-Vilardebo et al.[10]

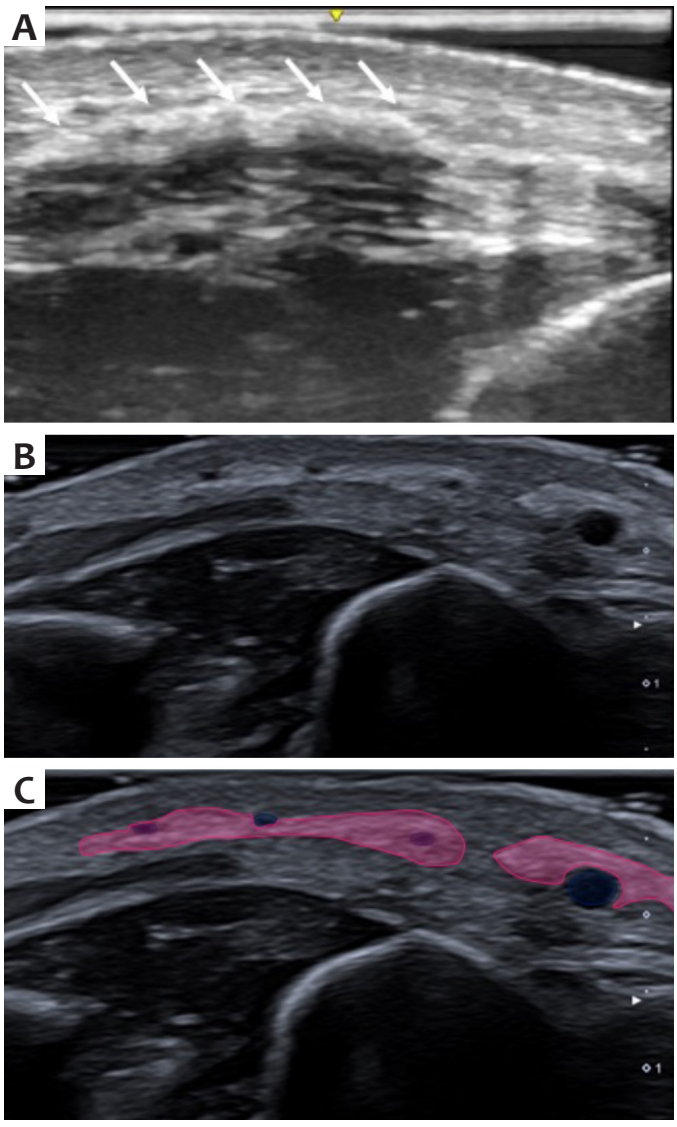

Figure 8: Transverse UHFUS image **A,** and anatomical scheme **B,** with a 24 MHz multifrequency probe (Canon Aplio i800) of the same patient from Figure 3 and Figure 7, taken 10 days after the procedure, showing the product mainly in the dorsal intermediate lamina. Notably, there is almost circumferential involvement of most of the dorsal veins in this layer (hyperechoic areas in **A** and pink areas in **C**).

5. HARMONYCA

HArmonyCa™ (Allergan Aesthetics, an AbbVie Company) is a hybrid filler that combines the collagen biostimulant calcium hydroxylapatite (55.7%) plus the hyaluronic acid volumizer.[28] On UHFUS, it appears as hyperechoic areas with a cloudy pattern without posterior acoustic shadowing[22] (Figure 9).

COMPLICATIONS

The two most common side effects reported after injectable procedures are hematoma and edema, which are typically mild, transient, and resolve spontaneously within a few days or weeks.[7] Ecchymosis and paresthesia have also been reported and can be minimized with the use of cannulas and ultrasound-guided procedures.[11] Potential long-term complications include persistent edema, sensory dysfunction, and the formation of nodules or foreign body granulomas[7] (Figure 10). More serious complications include local infections that may progress to abscesses[11] (Figure 11).

CONCLUSION

Hand rejuvenation has become an increasingly popular procedure because it is a safe and effective method. Different techniques and products are described with similar results.[3] Knowledge of the anatomy is critical for injectors to ensure accurate and safe placement of fillers and collagen stimulators on

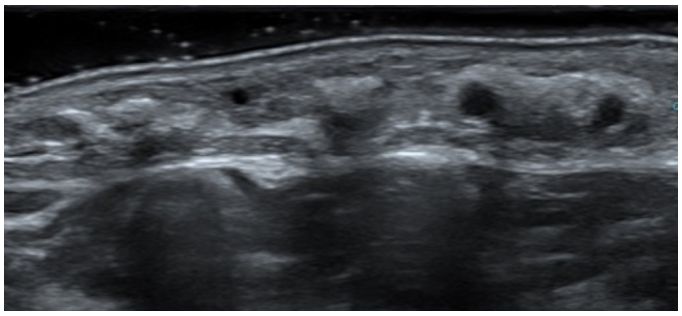

Figure 9: Transverse UHFUS image with an 18 MHz multifrequency probe (Canon Aplio A) taken several weeks after the procedure (HarmonyCA™), showing hyperechoic areas in the dorsal superficial and intermediate laminae

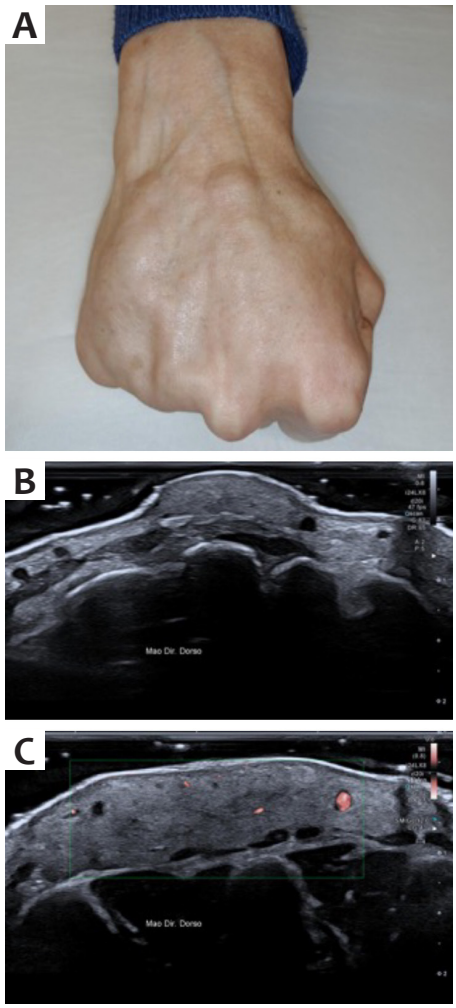

Figure 10: Clinical aspect **A,** shows palpable and visible nodules. Transverse UHFUS images with a 24 MHz multifrequency probe (Canon Aplio i700) in B-mode **B,** and longitudinal SMI Doppler **C,** obtained 2 years after calcium hydroxyapatite injection, show hyperechoic nodules in the superficial and intermediate layers with mild vascularization

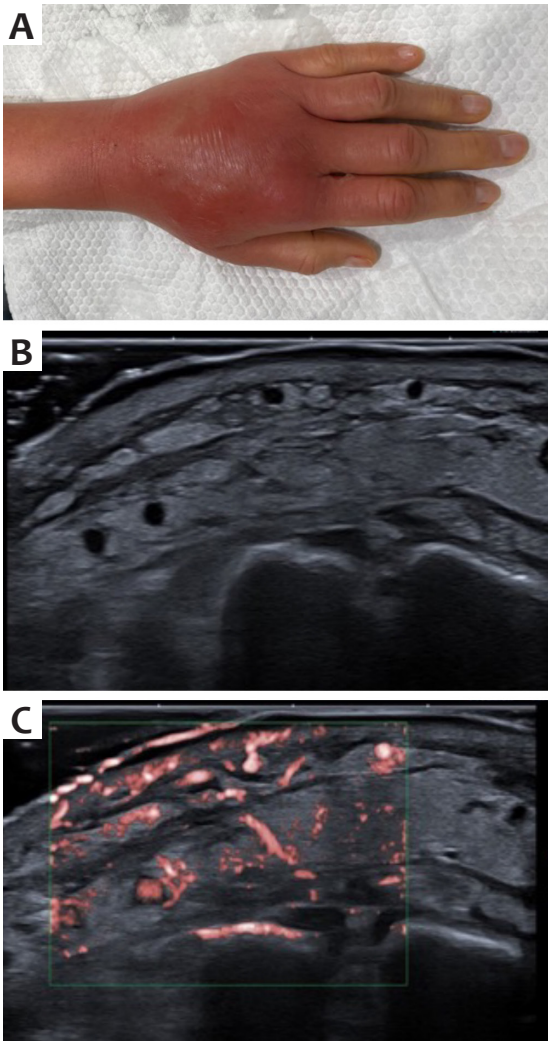

Figure 11: Clinical aspect **A,** shows edema and erythema. Transverse UHFUS images with a 24 MHz multifrequency probe (Canon Aplio i700) in B-mode **B,** and SMI Doppler **C,** taken a few days after calcium hydroxyapatite injection, show the product as hyperechoic areas in the dorsal superficial and intermediate laminae along with significant edema/anechoic lamina and increased vascularization of the laminae on the dorsum of hand

the dorsum of hand.[7] UHFUS can assist before the procedure by identifying previously applied products and providing detailed anatomy. During the procedure, UHFUS can guide application of product in the correct layer, avoiding veins and nerves. After the procedure, it can help manage complications.

Comprehensive knowledge of anatomy, product characteristics, and procedural techniques, as well as the ability to evaluate ultrasound at multiple levels (prior to, during, and after procedure), is important for the safe, effective application of all aesthetic hand rejuvenation procedures. ●

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