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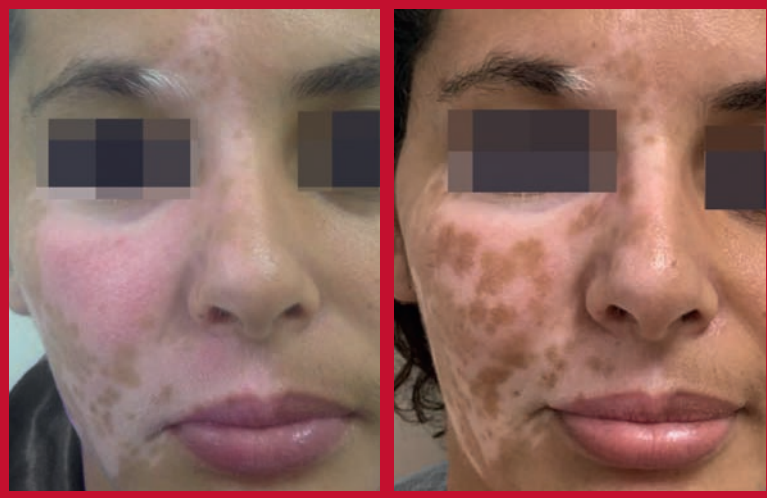

What we know about 5 alpha reductase inhibitors?

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Av. Rio Branco, 39 18º andar
Cep: 20.090-003
Rio de Janeiro-RJ, Brasil.
Fone: 55 (21) 2253-6747
E-mail: surgical@sbd.org.br
website: www.surgicalcosmetic.org.br

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Resumo: deverá conter no máximo 200 palavras e ser estruturado seguindo os itens: Introdução, Objetivo, Métodos, Resultados e Conclusões. Não é permitido afirmar que os resultados ou outros dados serão apresentados ou discutidos.

Introdução: citar as razões que motivaram o estudo, descrevendo o estado atual do conhecimento sobre o tema. Utilizar o último parágrafo para especificar a principal pergunta ou objetivo do estudo, e a principal hipótese testada, se houver.

Métodos: Explicar como o estudo foi feito:

a- Tipo de estudo: descrever o seu desenho especificando a direção temporal (retrospectivo ou prospectivo), o tipo de randomização quando utilizada (pareamento, sorteio, sequenciamento, etc), se o estudo foi cego, comparativo, controlado por placebo, etc.

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c- Procedimentos: descrever as principais características das intervenções realizadas, detalhando a técnica e lembrando que o estudo de investigação deverá ser reprodutível.

d- Descrição dos métodos utilizados para avaliação dos resultados.

e- Inclusão da análise estatística descritiva e/ou comparativa com descrição do planejamento da amostra (representativa do universo a ser estudado), a análise e os testes estatísticos e apresentação dos níveis de significância adotados. A utilização de análises estatísticas não usuais é incentivada, porém neste caso, deve-se fazer uma descrição mais detalhada da mesma.

Resultados: descrever os principais resultados que devem ser acompanhados de estimativas pontuais e medidas de dispersão (p.ex., média e erro padrão) ou de estimativas intervalares (p.ex., intervalos de confiança), bem como os níveis descritivos dos testes estatísticos utilizados (p.ex. "p-value"). Os achados também devem ser interpretados sob o ponto de vista clínico.

Discussão: enfatizar os novos e importantes resultados encontrados pelo estudo e que farão parte da conclusão. Relatar observações de outros estudos relevantes. Mencionar as limitações dos achados e as implicações para pesquisas futuras.

Conclusões: devem ser concisas e responder apenas aos objetivos propostos. A mesma ênfase deve ser dada para estudos com resultados positivos ou negativos.

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Surgical & Cosmetic Dermatology

Table of contents / **Sumário**

Publicação Oficial da Sociedade Brasileira de Dermatologia
APRIL/MAY/JUNE 2018 • Volume 10 • Number 2
ISSN:1984-5510
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Review Articles / *Artigos de Revisão*

Original Articles / *Artigos Originais*

Table of contents / **Sumário**

What do we know about 5-alpha reductase inhibitors?

O que sabemos sobre os inibidores da 5 alfa redutase?

Review Articles

Autors:
Juliana de Lira Machado[1]
Miguel Sánchez Viera[2]
Nerea Felip Santamaria[3]

[1] Skin Dermatologia - Recife (PE), Brazil.
[2] Instituto de Dermatologia Integral (IDEI) - Madrid, Spain.
[3] Hospital del Suest de Arganda del Rey - Madrid, Spain.

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ABSTRACT

Five-alpha reductase inhibitors – finasteride and dutasteride – are drug classes that have antiandrogenic properties. These drugs are commonly used to treat benign prostatic hyperplasia and androgenic alopecia. The U. S. Food and Drug Administration (FDA) has approved finasteride in 1991 for benign prostatic hyperplasia, and in 1997 for male androgenetic alopecia. In 2002, dutasteride was approved by the FDA only for benign prostatic hyperplasia, and is currently approved in Japan and South Korea for treating male androgenetic alopecia. The authors offer a comprehensive and up-to-date review on this drug's efficacy and safety.
Keywords: Alopecia; Androgens; Finasteride; Secondary effect; Dutasteride; Alopecia/therapy

RESUMO

Os inibidores da 5 alfa redutase, finasterida e dutasterida, são classes de drogas com propriedades antiandrogenéticas. Esses fármacos são utilizados habitualmente nos tratamentos da hiperplasia prostática benigna e da alopecia androgenética. Desde 1991, a finasterida é aprovada pelo U. S. Food and Drug Administration (FDA) para hiperplasia prostática benigna e desde 1997 para alopecia androgenética masculina. Em 2002 a dutasterida foi aprovada pelo FDA apenas para hiperplasia prostática benigna, e atualmente no Japão e na Coreia do Sul essa droga tem seu uso aprovado para o tratamento de alopecia androgenética masculina. Apresenta-se uma revisão ampla e atualizada sobre a eficácia e segurança dessas drogas
Palavras-Chave: *Alopecia; Efeito secundário; Finasterida; Dutasterida; Alopecia/terapia;*

In addition to minoxidil, 5 Alpha-reductase (5AR) inhibitors are the most traditionally used treatments for androgenetic alopecia (AA). Finasteride is an inhibitor of 5AR type II and has a variable half-life of 6 to 8 hours, reducing the level of dihydrotestosterone (DHT) by 70% when used at a 5mg / day dose. Dihydrotestosterone levels return to normal 14 days after discontinuation of treatment with oral finasteride, and a reversal of the results is expected to take place 12 months after discontinuation of the treatment.[1] Dutasteride is an inhibitor of 5AR types I and II, with an half-life of 4 weeks, reducing DHT levels by more than 90% when used at a 0.5mg / day dose, being three times more efficient in inhibiting 5AR type I and 100 times more efficient in inhibiting 5AR type II.[2] Type I 5AR is predominantly found in extraprostatic tissues, such as in the skin and liver, whereas type II is found in normal or hyperplastic prostatic tissue.[3,4]

Despite the fact that they have been used for many years, 5AR inhibitors have been the subject of much criticism and

Correspondence:
Juliana de Lira Machado
Av. Rui Barbosa, 370
Graças, Recife, PE
Brasil.
E-mail: drajulianamachado@hotmail.com

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mistrust regarding their safety and effectiveness. In the face of so many doubts, the authors prepared the present review in search of what is new on this subject, using the Pubmed, Cochrane and Google academic databases.

Several studies have already been published on the efficacy of 1mg / day finasteride and 0.5mg / day dutasteride, with both drugs having been classified as Level I evidence in the treatment of male AA.[5]

The pathogenesis of AA is linked to the conversion of testosterone into DHT by the 5AR enzyme. Therefore, 5AR inhibitors are considered classical drugs in the treatment of AA. A clinical trial in 2014 compared 1mg / day finasteride with different doses of dutasteride and a placebo, concluding that dutasteride at a 0.5mg / day dose is more effective than 1mg / day finasteride, within similar safety standards. [6]

In the history of 5AR inhibitors use, there is an association with increased risk of sexual domain related side effects, however clinical practice in general indicates that these symptoms would be low in incidence and reversible.[7] Several studies have shown that side effects of sexual nature are libido reduction, erectile dysfunction and abnormality in the volume of ejaculated sperm.[8] Some articles suggest that these effects are more frequent in patients using dutasteride and that this fact could be justified by interference in the activation of the nitric oxide synthase enzyme.[9]

Some studies dating from the 1990's show the incidence of side effects in the sexual domain in patients using finasteride (5 and 1mg), with a variable percentage of 2% - 15.8%.[10-12] Later on, Tosti et al. found an incidence of sexual domain related side effects of 0.5% with the ingestion of 1mg / day finasteride.[13]

A prospective study in 2014 showed that Korean men with AA who had not responded to treatment with 1mg / day finasteride for 6 months, had a 77.4% improvement after undergoing 0.5mg / day dutasteride, however with transient erectile dysfunction in 17.1% of patients.[14] A multicentric study including 120 patients demonstrated that dutasteride would be a potential drug for the treatment of male AA at doses of 0.5mg / day, with good tolerability and efficacy.[15] In 2016, a meta-analysis reviewed 493 articles, including patients with a mean age of 60 years using finasteride or dutasteride, having demonstrated the presence of a relative risk of sexual dysfunction of 2.56 for patients with benign prostatic hyperplasia (BPH) and 1.21 for patients with AA; for erectile dysfunction the risk was 1.55 in patients with BPH and 0.66 in patients with AA; while the risk of decreased libido was 1.69 in patients with BPH and 1.11 in patients with AA.[16]

For some years, there have been reports and articles questioning persistent side effects in the group of patients who use 5R inhibitors.[17] Some authors describe that sexual domain related side effects may be persistent and might lead to extreme situations of suicidal ideation.[18] In 2017, a review article examining persistent erectile dysfunction (PED) included four variables: prostatic disease, duration of exposure to 5AR inhibitors, age, and concomitant use of non-steroidal anti-inflammatory drugs (NSAIs). That study demonstrated an incidence of 1.4% of PED and 4.45% of transient erectile dysfunction. In the group of younger patients (16-42 years old), the risk of erectile dysfunction was greater when these patients were under prolonged use (> 205 days) of 5AR inhibitors associated with the use of NSAIs, with the risk being 4.9 times greater in these patients. That study also demonstrated some predictors of PED, such as prostate disease, prostate surgery and time of exposure to 5AR inhibitors.[19]

In addition to the side-effects in the sexual domain, the term *post finasteride syndrome* (PFS) has recently been used in studies of low scientific quality aimed at characterizing persistent side effects triggered during or after discontinuation of 5AR inhibitors. Symptoms include: decreased libido, erectile dysfunction, sexual anhedonia, decreased sperm count, gynecomastia, skin changes, cognitive impairment, fatigue, anxiety, depression, and suicidal ideation. In the literature, persistent side effects are only documented in low quality studies with strong bias in the selection of participants, which was carried out via blogs on the Internet. The only good quality study documenting a persistent sexual effect indicates that it is more frequent in the placebo group than in the group of patients using 5AR inhibitors, thus implying the fact that persistent side effects are not necessarily related to treatment with 5AR inhibitors. Secondary psychiatric side effects have only been documented in moderate to low quality studies, including those in patients with sexual domain related secondary side effects, which could have had an influence on the psychological state of the evaluated patients, in addition to the fact that most of the studies recruited patients through websites. It is not yet known whether PFS is real, and this question remains unanswered to date. Secondary side effects related to the sexual and psychiatric domains following the use of 5AR inhibitors are not documented by prospective studies in a way that would otherwise allow establishing the true incidence, frequency, and direct correlation with those drugs.[20]

In the female population there are fewer studies evaluating the efficacy of 5AR inhibitors. Finasteride is classified as Level III of evidence for this group of patients. A retrospective, multicentric study published in 2014 demonstrated similar improvement in the subjective and objective evaluations for the groups of patients who used finasteride and dutasteride. Nevertheless, in the group of patients younger than 50 years old, there seems to be a better response to treatment with 0.15mg / day dutasteride than with 1.25mg / day finasteride.[21] A 2016 review article found few side effects related to the sexual function in studies with finasteride and dutasteride in female AA.[22] Another more recent review article published in 2017 shows that 1mg / day finasteride does not seem to yield better outcomes than the placebo.[23]

Recently published European guidelines (2018) note that studies with 1 mg / day finasteride in male AA has led to a significant outcome in hair counts (evidence Level I) for the use of finasteride in men with AA. In female AA, the use of 1mg / day finasteride is not effective, however, a 5mg / day dose may possibly yield some results (evidence Level III) in pre-menopausal and normoandrogenic women. Nonetheless, no place-

bo-controlled trial was evaluated in female AA. Dutasteride in male AA has a good therapeutic response (evidence Level I) and would be indicated for off-label use in cases in which patients do not respond to treatment with 1mg / day finasteride after 12 months. The article mentions that men taking oral finasteride can not donate blood and that the level of finasteride in their sperm is very low, even in those using 5mg / day, meaning there would not be risk in sexual intercourse with pregnant women. [5]

In light of so many questions about the oral use of 5AR inhibitors, some studies are being published aiming at demonstrating alternative ways to use these drugs. The first study on topical finasteride was published 20 years ago, and included 28 men and 24 women who were randomized to use 0.005% finasteride in topical solution or placebo twice daily. Results in the 0.005% finasteride solution group appeared to be significantly better than in the placebo group, with no significant changes in plasma levels of total testosterone, free testosterone and DHT in the studied groups.[24] Most of the studies related to topical finasteride have been published in the last eight years.[25] One study compared 1% finasteride gel (twice daily) with 1mg / day oral finasteride for six months, with a similar therapeutic response and improvement in the two groups studied.[26] In 2014, Caserini et al. compared topical finasteride (0.25%) with 1mg / day oral finasteride in a group of 24 men with AA, having found that in the first week of treatment both topical finasteride and oral finasteride caused a decrease in serum DHT Levels – which was less evident in the first group.[27] Subsequently, in 2016, this same group compared 0.25% topical finasteride at different dosages, with outcomes suggesting that a single daily application appeared to be more effective than two daily applications, and 100uL (0.2275mg) and 200uL (0.455mg) doses would be the most effective treatment regimens.[28] One study compared the use of 3% minoxidil lotion (Group 1) with 3% minoxidil + 0.1% finasteride lotion (Group [2]): Group [2] yielded better outcomes than Group [1], with no significant difference regarding the side effects in the two groups.[29] Another article, published in 2015 by Indian authors, found that initiating treatment with oral finasteride (1mg / day) associated with 5% minoxidil lotion (twice daily) could be useful at the time of oral finasteride withdrawal. After achieving a good response with oral finasteride, it would be suspended, and the patient would continue with the use of 5% minoxidil + 0.1% finasteride (twice a day), with reasonable maintenance of the results previously obtained with the oral medication.[30] In 2013, Dutch authors presented a study at the 7th World Congress of Hair Research testing the serum and serum level of DHT in patient groups using 0.25% topical finasteride once a day (Group [1]), 0.25% topical finasteride twice a day (Group [2]), and 1mg / day oral finasteride (Group [3]). The level of DHT in the scalp was reduced by 47% in Group [1], 70% in Group [2], and 50% in Group [3]. Given that it was a pilot study with 18 men bearers of AA, further prospective studies with a greater number of patients would be necessary so that a more robust analysis could be performed. For the treatment of AA, the variability in the efficacy of topical finasteride also depends on the vehicle used.[31] To date, several topical presentations, such as gels and solutions with different concentrations, are being tested and all appear to be effective in the treatment of AA. [25] There is, however, no study comparing gels and topical solutions, and it is not known which vehicle would yield better outcomes. Some investigators try to optimize the penetration of topical finasteride through nanoparticles and liposomes, as well as through the inclusion of ethanol and propylene glycol in the formulations. [32-36] Studies on topical finasteride range from 0.005% to 1% concentrations, with diverse vehicles (solutions and gels) and one or two doses per day. Although most studies use two daily doses, a single application per day appears to be more effective in lowering DHT levels in the scalp. Further studies are needed in order to allow that an optimal vehicle, posology and concentration be defined, and a better evaluation of the side effects' profile is obtained.

Finally, capillary mesotherapy with dutasteride has been studied by several groups, and is emerging as a therapeutic option. In 2013, a study in Egypt evaluated mesotherapy in female AA, comparing 86 patients using dutasteride mesotherapy with a placebo group of 40 patients. The patients who underwent mesotherapy with dutasteride obtained improvement of 62.8%, while in the control group the improvement was of 17.5%. There seemed to be a better response when the development time of female AA was shorter, with minimal side effects and no statistical differences between the two groups.[37] Another study in the same year evaluated mesotherapy with 0.05% dutasteride in 90 patients with male AA for three months. The patients did not present complaints linked to the libido or erectile dysfunction during this period, nevertheless the study takes into consideration that systemic absorption with effect on spermatogenesis would be possible, especially when mesotherapy is performed unlimitedly. It is important to note that dutasteride's half-life is 4 weeks and that its effect on the sexual function is questionable; it would therefore not be recommended for patients wishing to become pregnant and with borderline sperm or ejaculatory / erectile dysfunction, with a greater number of studies being needed to ascertain these data.[38] A recently published study shows improvement in hair density and hair diameter in patients bearers of male AA treated with monthly 0.01% dutasteride mesotherapy, with absence of side effects or significant DHT alterations.[39]

FINAL CONSIDERATIONS

Five alpha-reductase inhibitors have been studied for a long time, especially in male AA. In general, most studies show reversible side effects and low incidence in the sexual related domain. Despite the fact that the authors of the present paper have recently found some studies describing the existence of persistent side effects, including PFS, it is not yet known if this is a reality, calling for further well-designed prospective studies aimed at establishing the actual incidence, frequency and direct correlation with 5AR inhibitors. Some articles on alternative routes for the use of 5AR inhibitors, such as the topical route, mesotherapy and even associations, have been published in recent years. However, although experience with and knowledge

of these drugs is increasing, available studies are still precarious and do not offer conditions for the indiscriminate adoption of these approaches. It should be borne in mind that even if the medication is not taken orally, systemic absorption is possible in these new administration routes (topical, mesotherapic), since the scarce current research does not present conclusive results. For the future, the authors of the present study hope that further prospective studies with high evidence level are capable of assessing persistent side effects and new paths for the use of 5AR inhibitors. ●

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DECLARATION OF PARTICIPATION:

Miguel Sanchez Viera | ORCID 0000-0001-7144-546X
Conceptual development and planning of the research project, preparation and write up of the manuscript; data acquisition, analysis and interpretation.

Juliana de Lira Machado | ORCID 0000-0002-8060-5549
Conceptual development and planning of the research project, preparation and write up of the manuscript; data acquisition, analysis and interpretation.

Nerea Felip Santamaría | ORCID 0000-0003-1327-8725
Conceptual development and planning of the research project, preparation and write up of the manuscript; data acquisition, analysis and interpretation.

Review Articles

Literature review: auricular disorders Part 2 – benign neoplasms

Revisão da literatura: afecções auriculares, parte 2: neoplasias benignas

Autors:
Bhertha M. Tamura[1]
Ana Carolina Junqueira Ferolla[1]
Cândida Naira L. e L. Santana[2]

[1] Dermatology Department, Ambulatório de Especialidades Barradas, Bourroul – São Paulo (SP), Brazil.
[2] Clínica Dermacare - São Luís (MA), Brazil.

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ABSTRACT

Knowledge, diagnostic ability and surgical skills for approaching diverse cutaneous conditions in the auricular region are parts of a dermatologist physician's daily routine. In the second part of this review article, will be approached the benign neoplasms of the auricular region, describing their particularities and ideal methods of treatment.

Keywords: Ear; Nevus; Cysts; Keloid

RESUMO

Faz parte do dia a dia dos dermatologistas o conhecimento, a capacidade de diagnóstico e a habilidade cirúrgica para várias afecções da pele na região da orelha. Na segunda parte deste artigo de revisão, serão abordadas as neoplasias benignas da região auricular, descrevendo-se suas particularidades e métodos ideais de tratamento.

Palavras-Chave: *Orelha; Nevo; Cistos; Queloide*

Correspondence:
Bhertha M. Tamura
Av. Ministro Gabriel de Rezende Passos, 500 Conj. 1506
04521 022 - São Paulo - SP, Brasil
E-mail: bhertha.tamura@uol.com.br

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CYSTS

Cystic lesions of the auricula are preferentially located in the space between the cartilage and the perichondrium, in the skin and subcutaneous tissue.

Endochondral pseudocyst of the auricula

Cartilaginous cyst that presents as a fluid collection between the cartilage and the perichondrium, resulting from chronic traumas of low intensity. In this case, the perichondrium not only detaches from the cartilage, but can also produce another cartilaginous tissue within which there is formation of the liquid content that originates the auricle pseudocyst. This cyst of firm consistency requires surgery: it must be incised, drained and curetted or cauterized using electrocoagulation or caustic substances, so that its walls can coapt.[1]

Epidermal cysts

They occur due to the proliferation of epidermal cells that produce keratin within the dermis. In some cysts it is possible to observe a central point corresponding to the obstructed pilosebaceous orifice that eliminates malodorous keratinous

material. They are usually well defined, mobile, non-adherent, superficial and of various sizes. Sometimes they become infected or inflamed. Treatment consists of complete excision, including the pilosebaceous orifice and the capsule.[2]

Pilar cysts

They occur preferentially in the scalp, but also arise in the retroauricular area or earlobe, while preauricular cysts (Figure 1) are generally congenital and might be associated with the preauricular fistula (Figure 2). They contain keratin in their core and are less common than the epidermal variant. Treatment includes the complete removal of the cyst and fistulous tract.

Multiple steatoma (sebocystoma)

A condition of autosomal dominant genetic nature, characterized by the presence of multiple cysts containing sebum. Lesions range from a few millimeters to two or three centimeters, yellowish, with an orifice through which material drains. Treated with exeresis.

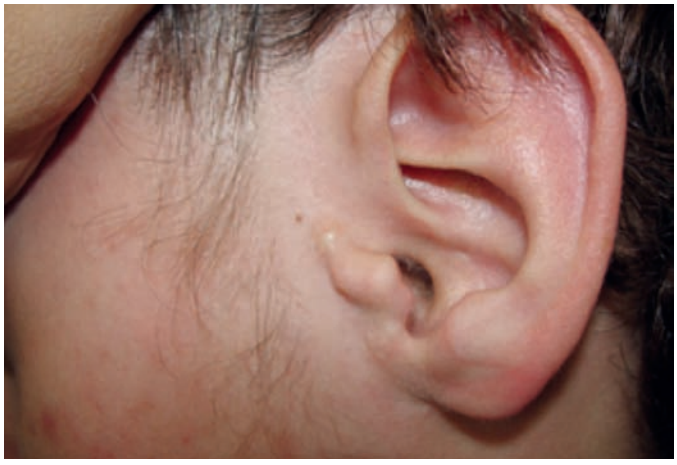

Figure 1: Congenital pre-auricular cyst

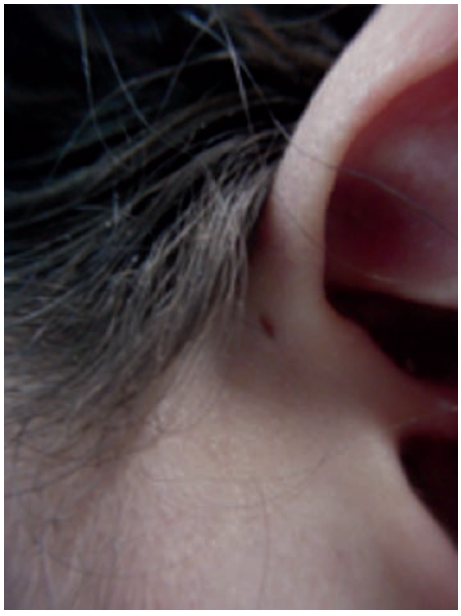

Figure 2: Preauricular fistula

Milia *en plaque* is an entity characterized by an agglomerate of miliums in the form of erythematous and / or edematous plaques, with or without comedones, located in the retroauricular or periorbital region. They predominate in women and might regress spontaneously. Therapeutic options include manual extraction, topical tretinoin, electrocauterization, cryotherapy, excision and photodynamic therapy.[3]

Other cystic lesions: Sweat glands tumors, dermoid cysts, myxoid, eruptive velum cyst, milium and even follicular keratosis and perforating folliculitis can be found.

ORGANOID NEVI

Nevus verrucosus

It is a congenital lesion characterized by hyperplasia of epidermal structures. It arises as well-defined irregular papules or plaques, often multiple or generalized (ichthyosis histrix), [4] linear or unilateral (nevus unius lateralis) and sometimes inflamed (inflamed linear verrucous nevus). Differential diagnosis is performed *vis à vis* linear lichen planus, lichen striate, incontinentia pigmenti in its verrucous phase, linear psoriasis and linear porokeratosis. Nevus verrucosus may be accompanied by skeletal lesions, and organic, urologic and angiomatous malformations, as well as hypoplasia of underlying structures, constituting the epithelial nevus syndrome.

Treatment depends mainly on the location and extent of the lesions. Except for total or partial excision, other procedures – such as dermabrasion, electrocoagulation, electrodissection, cryosurgery and chemosurgery – offer only temporary relief, since there is a trend for the lesion to recurr.

Nevus sebaceous of Jadassohn

It is usually present from birth in the form of papules, sometimes shiny or grooved superficial plaques, eventually developing into single or multiple thick, verrucous or yellowish papillomatous lesions on the scalp and / or auricular region.

It should be treated with surgical excision due to the possibility of progression into papillary syringocystadenoma, basal cell carcinoma and other benign and malignant neoplasms.

Nevus comedonicus

Comedo-like papules (central part with a dark brown corneal plug) that arise grouped, in a unilateral or linear manner. They can progress into inflammatory reactions and scarring. Treatments comprise total or partial excision, topical retinoic acid or systemic isotretinoin.

Other nevi

Eccrine, apocrine, conjunctival and lipomatous nevi are rare, especially in the auricular region.

Eccrine nevi are well-defined areas with a history of localized hyperhidrosis or an orifice that drains liquid or mucoid substance and / or skin color plaques. Apocrine nevi may be associated with sebaceous nevi in the form of papules, nodules, or cysts. Conjunctival and lipomatous nevi are present from birth as nodules, plaques or tumors, usually of skin color, irregular and

tending to grow as the child develops. They can be treated with primary excision and suture or in partial exeresis.

BENIGN TUMORS

Epithelial tumors that may occur in the auricular region are: seborrheic keratosis, dermatosis papulosa nigra, verrucous dyskeratoma and acanthoma fissuratum. The first is frequent in the elderly, while the second often occurs in the dark skinned and Oriental Asian individuals. They usually arise in the periauricular regions.

Seborrheic keratosis is the most common benign tumor of the external ear, arising in the dermatological examination as a verrucous papule with adherent and greasy scale, more rarely in circumscribed plaques, ranging from light to dark brown in color. Can also be multiple, resulting from epithelial cells proliferation. It spreads with age, reaching the entire ear, including the external auditory canal. Treatment options are trichloroacetic acid, cryotherapy, and mild electrocoagulation.[5]

Pigmentary nevi

Pigmentary lesions of importance to the facial area that are rarely located in the auricular regions, are the nevus of Ota (nevus fuscoceruleus ophtalmomaxillaris), blue nevus and pigmented melanocytic nevi[6,7] (Figure 3).

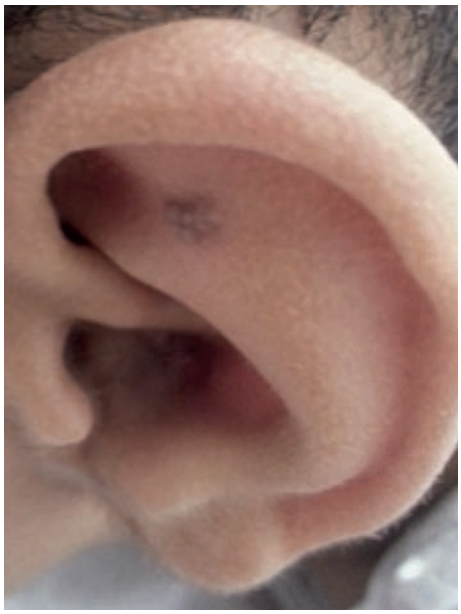

Figure 3: Melanocytic nevus

Keloids

Normal scars usually increase in volume up until the second month, while hypertrophic ones increase for six months and progressively recede. In contrast, keloids present an anomalous healing process, increasing during 12 months or more, showing no signs of involution.

These lesions are very common in the auricles, especially in the lobule (Figure 4), resulting from trauma to the dermis with consequent fibrous proliferation. Its precise etiology is still unknown, however vascular-tissular, immunological, antigenic and interleukin related factors appear to be involved in its formation mechanism.[8] There is predilection for the dark skinned and Oriental Asian origin individuals, being equally distributed between genders and more common in individuals under 30 years of age. The most frequent sites of occurrence are: the deltoid, pre-sternal, preclavicular, scapular, pubic, nape and ears regions. Keloids are histologically characterized by wide bands of eosinophilic collagen. They can emerge after any type of trauma, however in the ear they are most often linked to the use of earrings. It arises as a cicatricial reaction that extends beyond the area of the trauma and does not recede with time. Generally pruritic, they consist of firm nodules with smooth surface. Lesions van be erythematous when occurring in occur in Caucasian individuals; hyperchromic or darkened and bright when occurring in dark skin or Oriental Asian origin individuals. Sometimes they present local heat or pain to pressure.

Therapeutic approaches for keloids are diverse. In the initial inflammatory phase, the most appropriate choice is intralesional injection with corticosteroids, occlusive dressings, silicone gels or sheets, or pressure earrings.

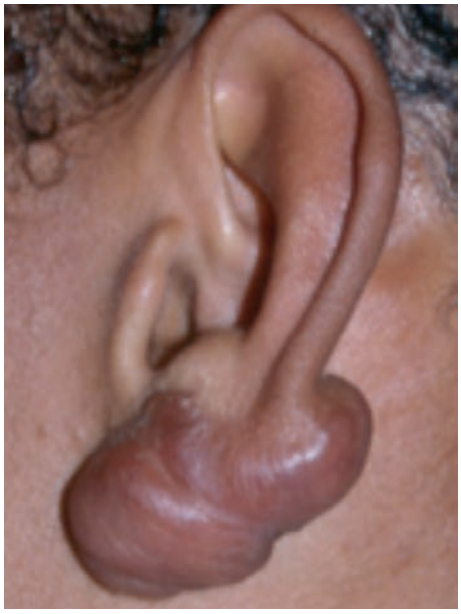

Figure 4: Keloids

In more stable phases, cryosurgery, radiotherapy, [9] intralesional injections with bleomycin sulfate[10] and 5-fluorouracil are indicated, among other possibilities.

There are studies describing the use of retinoids, interferon, methotrexate, D-penicillamine, colchicine and botulinum toxin, although without encouraging results.

Surgical removal, indicated in elevated and stable lesions, should always be followed by some of the therapeutic options mentioned above, due to the fact that as an isolated therapy, it leads to a high rate of recurrence.

For the prophylaxis of keloids in genetically predisposed individuals, procedures should be avoided and patients should be educated about the areas of greatest risk. When necessary ex-

ereses are performed in these patients, in addition to avoiding areas of risk, it is crucial that the incisions always agree with the skin's tension lines in order to cause as little trauma as possible to the area to be treated. Electrocoagulation and any elements that favor infection or inflammation, such as threads that cause an inflammatory reaction, should also be avoided. Suture should be carried out with the least possible traction.

Lipomas

Lipomas are well-defined slow growth nodules or tumors, usually painless, soft to palpation, mobile, skin-colored, or slightly bluish (angiolipomas). They can arise isolatedly or in multiple, measuring from 0.5 to 10cm or more. Despite being common, they are rare in the auricular region (Figure 5), occurring generally in the trunk, limbs and nape. Angiolipomas (with vascular component) can be painful. Lipomas are composed by mature adipose tissue lobes. Surgical excision is the treatment of choice. Although some surgeons approach lipomas with liposuction, there is a need for diagnostic certainty, when sarcomas, liposarcomas, myxosarcomas, and others must be excluded before implementing this technique.

ADNEXAL TUMORS

Tumors involving glands are rare, however they may arise in the ear due to the presence of a great amount of ceruminous glands – modified apocrine glands – which are found in the upper wall of the auditory canal. Their secretion combines with sebaceous secretion in the upper portion of the hair follicle forming a complex substance, the cerumen, which has antimicrobial action and forms a layer that lines the auditory canal, thus protecting it. The rate of migration of cerumen varies in each individual, sometimes leading to the obstruction of the auditory canal.

Cerumen can be removed via irrigation or with the assistance of instruments, the first method being simpler than the latter. Nevertheless, this procedure should only be performed after examination of the tympanic membrane. Irrigation can be carried out with syringes, after rectifying the canal by lifting and pulling the ear. Once direct vision of the canal is possible, the solution is carefully injected towards the wall, gently removing the cerumen with aid of the liquid flow. If irrigation is carried out hastily, the eardrum might be perforated, which would allow the solution to penetrate the middle ear, possibly causing otitis media. The liquid must be collected in a dome or kidney-shape dish. If the masses are large and compacted, in order to prevent trauma it is first necessary to soften them with topical compounds, which should be applied carefully due to the fact they cause irritation and external otitis. There are appropriate surgical instruments such as handles, curettes and forceps. They should be used carefully and, regarding children, general anesthesia is recommended due to the fact any sudden movement can lead to trauma.

Tumors involving the glands are extremely rare, nonetheless the fact that the ear presents a large number of ceruminous glands, makes it susceptible to the onset of benign and malignant tumors.[11] Among the benign ones are the ceruminous adenomas, apocrine cystadenoma, the Pringle-type sebaceous adenoma, trichoepitheliomas, and eccrine spiradenoma (Figure 6). Benign adenomas usually present obstructive symptoms of slow development and, being treated with local excision.

The other tumors may emerge in the face, neck and scalp regions, thus possibly located in the auricular and periauricular regions. These tumors are less frequent, however according to our experience they are not extremely rare. All of them may arise as papules (most often the chondroid syringoma, papillary syringocystadenoma and trichilemmoma), single cysts (chon-

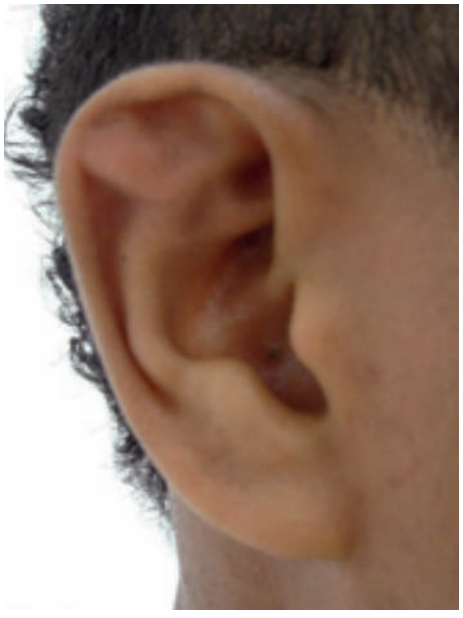

Figure 5: Lipoma

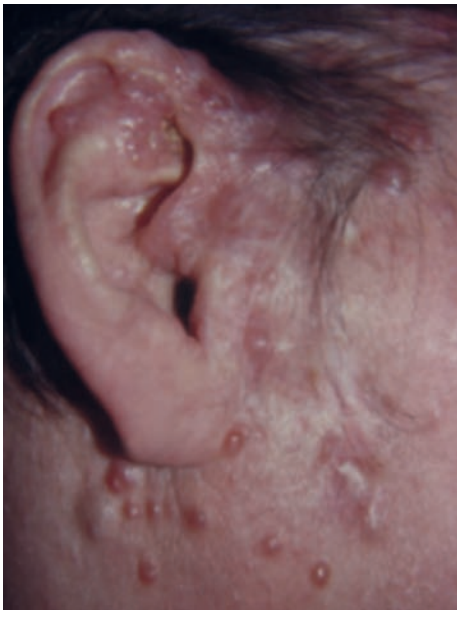

Figure 6: Eccrine spiradenoma

droid syringoma, hidradenoma papilliferum, apocrine hidrocystoma, calcifying epithelioma of Malherbe, trichofolliculoma), multiple cysts or in turban in the scalp (cylindroma), light and bluish coloration (hidradenoma and hidrocystoma), hardened or calcified (pilomatricoma). All of which have their diagnosis confirmed after anatomopathological evaluation, with surgical excision as the basic treatment.

Cylindroma

Also called Spiegler's tumor or turban tumor, it consists of a benign protruding, bright, normochromic, or erythematous lesions located in the head and neck, and might reach the ears (turban tumor). It has controversial, probably eccrine histogenesis, and is treated with exeresis.

OTHER SITUATIONS

Auricular appendices

These structures are not malignant, however they call for the investigation of some syndromes, such as those of Golden-har and Wildervanck, vertebral or cardiac defects, anal atresia, tracheoesophageal fistula, and renal or limb anomalies. The excision should be performed according to the patient's wishes.

Petrified ear

The term *petrified ear* means calcification or ossification of the auricular pavilion, caused by traumatic processes, including thermal or physical damage, inflammation, and endocrine and metabolic disorders, such as hypercalcemia secondary to Addison's disease.[12] The ear becomes stiff and non-malleable. Diagnosis is carried out by imaging or histological examination, and underlying endocrine and metabolic disorders must be investigated for treatment.

CONCLUSIONS

Benign lesions located in the ear can be diagnosed clinically or through anatomopathological examination. Analyzing the probable diagnoses in advance, allows adequate surgical planning with a better prognosis for the patients. ●

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DECLARATION OF PARTICIPATION:

Bhertha M. Tamura | ORCID 0000-0001-7259-2998
Conceptual development, write up and review of the manuscript

Ana Carolina Junqueira Ferolla
Conceptual development, write up and review of the manuscript

Cândida Naira Lima e Lima Santana | ORCID 0000-0002-2693-0025
Conceptual development, write up and review of the manuscript

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Original Articles

Autors:
Farida Tabri[1]
Anis Irawan Anwar[1]
Nasrum Massi[2]
Ilham Jaya Patellongi[3]
Rahmawati Anwar[1]

1 Dermatology and Venereology Department, Faculty of Medicine, Hasanuddin University - Macáçar, Indonesia.
2 Microbiology Department, Faculty of Medicine, Hasanuddin University - Macáçar, Indonesia.
3 Physiology Department, Faculty of Public Health, University Hasanuddin - Macáçar, Indonesia.

Correspondence:
Farida Tabri
Department of Dermatology and Venereology
Faculty of Medicine, Hasanuddin University
Jl. Perintis Kemerdekaan Km. 11, Tamalanrea Indah, Tamalanrea, Kota Makassar, Sulawesi Selatan 90245, Indonesia
Email: farida.tabri.dv@gmail.com

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This study was performed at the Department of Dermatology and Venereology, and at the Department of Microbiology of the Faculty of Medicine, Hasanuddin University, and at the Department of Physiology of the Faculty of Public Health, Hasanuddin University - Macáçar, Indonesia.

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Profile of free fatty acid in patients with acne vulgaris

Perfil de ácidos graxos livres em pacientes com acne vulgar

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ABSTRACT

Introduction: Acne vulgaris is an inflammatory disorder that affects the pilocebaceous gland with high prevalence among young adults. Studies have suggested that FFA may influence acne vulgaris. However, the pathogenesis of acne is not yet fully known.
Objective: To analyze the correlation between free fatty acid and acne vulgaris severity level.
Methods: Forty-three female high school students with mild, moderate, and severe acne were included in this study. Free fatty acid level, represented by palmitic acid level, was measured using gas chromatography and PCR examination was conducted to detect Propionibacterium acnes. Mann-Whitney test was used to analyze the median palmitic level difference between groups with different acne vulgaris severity. A p-value <0.05 was considered as significant.
Results: Fourteen patients (32.6%) had mild acne vulgaris, while 14 and 15 patients had moderate and severe acne vulgaris, respectively. The severe and moderate acne group showed significantly higher palmitic acid level compared to the mild acne group ($p<0.05$). The level of palmitic acid was not associated with the presence of P. acnes.
Conclusions: Increased palmitic acid level was found to be associated with acne severity. Thus, FFA levels may be used as a marker to determine acne vulgaris severity
Keywords: Acne vulgaris; Fatty acids, nonesterified; Polymerase chain reaction; Propionibacterium acnes

RESUMO

Introdução: *A acne vulgar é um distúrbio inflamatório que afeta a unidade pilossebácea, apresentando alta prevalência entre adultos jovens. Estudos sugerem que os ácidos graxos livres (AGL) podem influencia-la, contudo, sua patogênese ainda não é totalmente conhecida.*
Objetivo: *Analisar a correlação entre o nível de ácidos graxos livres e a gravidade da acne vulgar.*
Métodos: *Quarenta e três alunas de ensino médio portadoras de acne leve, moderada e grave foram incluídas neste estudo. O nível de ácidos graxos livres, representado pelo nível de ácido palmítico, foi medido por cromatografia gasosa enquanto a detecção do Propionibacterium acnes foi realizada através do PCR. O teste de Mann-Whitney foi utilizado para analisar a mediana da diferença do nível de ácido palmítico entre os grupos com diferentes graus de severidade da acne vulgar. Os resultados foram considerados significativos para valores de p <0,05.*
Resultados: *Catorze pacientes (32,6%) apresentaram acne vulgar leve, enquanto 14 e 15 pacientes apresentaram acne vulgar moderada e grave, respectivamente. Os grupos com acne grave e moderada apresentaram um nível de ácido palmítico significativamente maior quando comparado ao grupo com acne leve (p <0,05). O nível de ácido palmítico não foi associado à presença de P. acnes.*
Conclusões: *O aumento do nível de ácido palmítico mostrou-se associado à gravidade da acne. Assim, os níveis de AGL podem ser usados como marcadores para determinar a gravidade da acne vulgar.*
Palavras-Chave: *Ácidos graxos não esterificados, Acne vulgar, Propionibacterium acnes, Reação em cadeia da polimerase*

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous units[1]; lesions may be non-inflammatory (open and closed comedones) or inflammatory (papules and pustules).[2] Acne vulgaris occurs mainly in adolescence and may cause hyperpigmentation and the formation of postinflammatory scars.[3] A study by Bhate et al. showed that acne can be found in roughly 20% of young adults. In addition, acne has high persistence, and 43% of people over 30 years of age still have acne. Acne also has a strong genetic predisposition, and 80% of cases may have been inherited from close relatives.[3]

The pathogenesis of acne is still not fully understood. However, four mechanisms (follicular hyperkeratinization, colonization by *Propionibacterium acnes* (*P. acnes*), sebum production and complex inflammatory mechanisms involving the innate and adaptive immune system) have been widely accepted as the underlying processes. *P. acnes* is thought to play an important role in the pathogenesis of acne, as it causes tissue damage through the release of various enzymes, including lipase, which breaks down triglycerides into glycerol and free fatty acids (FFA), leading to an influx of neutrophils through chemotaxis.[5] A study showed that FFA induce the growth of *P. acnes* and abnormal follicular keratinization.[6] It is believed that FFA interfere in the dynamics of intracellular calcium in follicular keratinocytes and in the epidermal intercellular lipid bilayer.[7] Among all types of FFA, palmitic acid is the most abundant.[8] It has been demonstrated that palmitic acid can stimulate the release of several proinflammatory cytokines, contributing to the hyperkeratinization of the pilosebaceous duct and inflammation in acne.[9]

Interestingly, another study by Desboies et al., Showed that FFA have the ability to prevent bacterial fixation in the skin. The mechanism of action of these fatty acids usually occurs in cell membranes, through the active transport system of electrons and oxidative phosphorylation. Free fatty acids also inhibit enzymatic activity, nutrient uptake, peroxidase formation, and auto-oxidation. Free fatty acids also have the potential to assist in the reduction of the severity of acne vulgaris.[10]

These conflicting data stimulate further research on the role of FFA in the pathogenesis of acne. Thus, the present study was aimed at evaluating the association between FFA, the severity of acne and the presence of *P. acnes*, with palmitic acid as the measured component in the facial skin.

METHODS

This cross-sectional study was carried out at a high school in an urban area (Makassar City, Indonesia) between July and August 2017. After receiving an explanation about the study, the volunteers who agreed were asked to sign a Free and Informed Consent Form (Ref. Number; 145 / H4.8.4.5.31 / PP36-KOMETIK / 2017, Hasanuddin University Ethics Committee). Those who had not used retinoids, antibiotics or anti-inflammatories in the previous month were assessed for acne severity according to the Lehman criteria, having been classified into bearers of mild, moderate or severe acne vulgaris.[11] These participants also received questionnaires aimed at collecting family history of acne and dietary consumption.

Sebum was harvested using an absorbent paper moistened with 1:1 acetone and diethyl ether, being subsequently methylated with 0.2M phenyl trimethylamine hydroxide solution in methanol. Gas chromatography was used to examine the product. The standard reference used was the FAME Mix component of Supelco® 37. The standard concentration used for palmitic acid was 601ppm, injected into the gas chromatograph. The analysis was performed using a GC-MS QP 2010 Ultra Shimadzu Autosampler, with a splitless injector. Separations were performed using SH-Rxi-5Sil MS capillary column (30m x 0.25mm). Helium gas was used as the carrier gas at flow rates of 1.99 mL/min and a splitless ratio of 1:10. The temperature of the injector was set at 2,500 °C. The oven temperature was programmed to stay constant at 1,400 °C for 10 minutes, being subsequently increased to 2,500 °C, with a flow rate of 7 °C / min. This temperature was maintained for additional 10 minutes, resulting in a total analysis time of 35.71 minutes. Mass spectrometry was obtained in a range corresponding to 40-500 m/z, with the temperatures of the ion source and the interface at 2,100 °C and 2,550 °C, respectively, and solvent cut-off time of 3 minutes. A sample of comedo lesions was analyzed for the presence of *P. acnes* using PCR (Biorad®, California, USA) according to the following primer sequence: forward (PR 264): 5-GCA GGC AGA GTT TGA CAT CC -3, reverse (PPA.R): 5-ATG TTG AGG GCG GTG ACG TT-3, and target ban 344 bp.

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) 18.0 for Windows (SPSS Inc., Chicago, IL, USA). The Mann-Whitney test was used to analyze the difference in median palmitic acid levels between groups with different degrees of severity of acne vulgaris. Differences were considered significant for $p < 0.05$.

RESULTS

Table 1 shows the demographic data and basic characteristics of the study population. A total of 43 individuals were included, with most being males (76.7%) and adolescents (15.77 ± 0.84 years). It was possible to observe that 25 patients (58.1%) had a positive family history, while 18 patients (41.9%) had no history of the disease. Regarding eating habits, 7 patients (16.3%) consumed milk and 3 patients (7.0%) consumed chocolate, while 31 patients (72.1%) consumed fatty foods. Two individuals (4.7%) consumed foods high in sugar. Fourteen (32.6%) individuals fell into the mild and moderate acne categories, respectively, while 15 patients (34.9%) were included in the severe acne category. The median value for the level of acid free fatty acids was 24,358 ppm, with the PCR being positive for *P. acnes* in 5 patients (11.6%), and negative for 38 patients (88.4%).

The concentration of FFA in severe acne (median = 30,400 ppm) was significantly higher than in the mild degree of the condition (median = 12,746 ppm) ($p < 0.05$). The verified level of fatty acids in moderate acne was also significantly higher than in the mild degree. However, there was no significant difference in FFA levels among patients with moderate and severe

Table 1: Basic Characteristics of the population

Category	Frequency (n)	Percentage (%)
Gender		
Male	33	76.7
Female	10	23.3
Age (mean, SD)	15.77 ± 0.84 years	
Family history		
Present	25	58.1
Absent	18	41.9
Eating habits		
Milk	7	16.3
Chocolate	3	7.0
Fatty foods	31	72.1
Food rich in sugar	2	4.7
Acne severity degree		
Mild	14	32.6
Moderate	14	32.6
Severe	15	34.9
FFA levels (ppm) (median, IQR)	24.358 (12.946-39.838)	
***P. acnes'* PCR**		
Positive (+)	5	11.6
Negative (-)	38	88.4

acne (Figure 1). There was no significant difference between the level of FFA in patients with positive PCR who were negative for *P. acnes* (Figure 2).

DISCUSSION

The present study shows that the level of FFA influences the severity of acne vulgaris. This result is in line with another study that found evidence of an important role of *P. acnes* in the pathogenesis of acne through the release of lipase enzymes, that break down triglycerides into glycerol and free fatty acids, which cause inflammation and tissue damage.[5] Moreover, a review article also showed that fatty acid peroxidation products are capable of inducing inflammation through the activation of peroxisome proliferator-activated receptors (PPARs), with PPARα and PPARγ acting as the main isoforms.[12]

Data obtained in the present study showed that the higher the levels of palmitic acid in the face, the higher the degree of severity of acne. The levels of palmitic acid in the facial skin of patients with severe and moderate acne were found to be significantly higher than in those with mild degree. Katsuta et al. (2005) have shown that the application of FFA in the ears of rabbits and mice induces hyperkeratinization and epidermal hyperplasia similar to that of comedos formation.[5] In addition, it is suspected that FFA also affect follicular keratinocytes and epidermal lipid bilayer structures that may affect the occurrence of acne. This was demonstrated by Youn in a 2015 study in which a greater amount of sebum was found in the facial skin of patients with acne, nevertheless there was no analysis of the content of sebum.[13]

In contrast, an interesting result was shown in a recent clinical trial in which the administration of lymecycline led to an increase in FFA levels.[14] However, the pre- and post-treatment clinical condition was not studied, meaning that it was not possible to conclude that the presence of correlation with an improvement or worsening of the disease. One possible explanation for this difference is a deficiency in linoleic acid and α-linoleic acid in the patients evaluated in the present study, causing a compensation in the form of increased levels of palmitic and oleic acids.[15] Studies have suggested that linoleic acid deficiency may increase PGE- 2, a potent inflammatory mediator commonly found in patients with acne vulgaris.[16] This might explain the higher level of palmitic acid in the individuals with more severe acne who took part in the present study.

A different result was also described by Pappas (2009), when levels of FFA in patients with acne were low. In this study, the number of patients was limited and the authors did not explain how many individuals and controls participated in the analysis.[7] This difference might be caused by eating habits, for a low glycemic index diet has been found to be associated with increased levels of FFA and incidence of acne.[17]

Data from the present study showed that levels of FFA in patients with PCR-positive results for *P. acnes* did not differ significantly from those in patients with PCR-negative results. Similar conclusions were obtained by Akaza et al., where al-

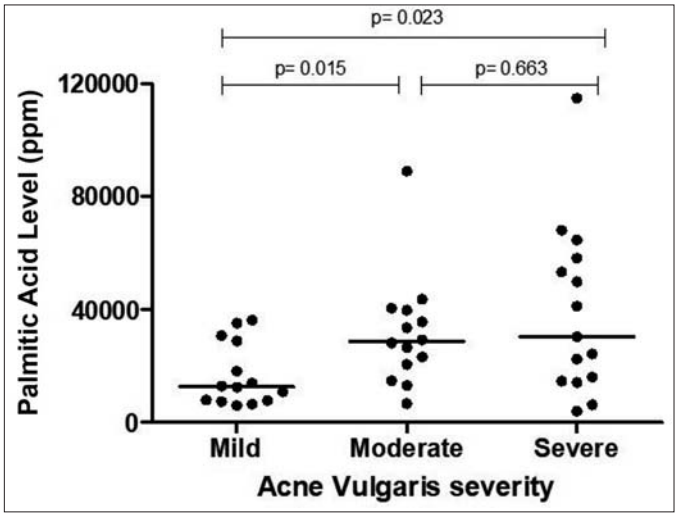

FIGURE 1: Comparison of FFA levels between different groups of acne vulgaris

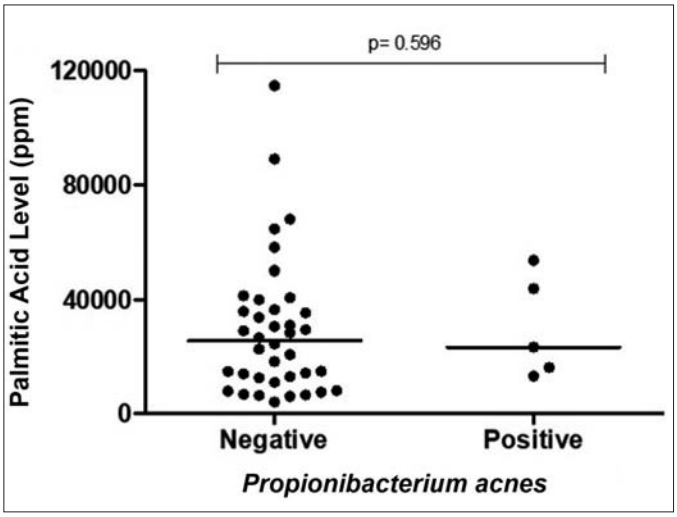

FIGURE 2: Association of FFA levels and P. acnes, evidenced by PCR

though FFA levels played a role in abnormal keratinization and induced comedo formation, the number of *P. acnes* in patients with and without acne were not found to be significantly different.[18] This may be due to other commensal bacteria, such as *S. epidermidis*, which can produce lipase, that in turn causes the hydrolysis of sebum triglyceride and produces FFA.[6] These findings suggested that there are other factors besides the levels of FFA that might affect the growth of *P. acnes*.

The present study corresponds to an initial analysis performed aimed at evaluating the prevalence of acne vulgaris in the adolescent population of an urban area and its association with the level of FFA, thus providing a foundation for future studies in this field. Also, the authors included only a sufficient number of participants to obtain a valid result. However, because it is a preliminary analysis, the present study was performed in only one population, implying that the study population was homogeneous.

CONCLUSION

The outcomes of the present study shows that FFA levels affect the degree of acne vulgaris and that the increase in the level of FFA was associated with the intensification of the severity of acne. Thus, FFA levels can be used as one of the markers for determining the severity of acne vulgaris. ●

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DECLARATION OF PARTICIPATION:

Farida Tabri | ORCID 0000-0003-4913-0909
Conceptual development and planning of the research project; data acquisition (laboratory or clinical), analysis and / or interpretation; manuscript preparation and / or critical review; approval of the final version

Anis Irawan Anwar | ORCID 0000-0002-3124-4070
Conceptual development and planning of the research project; data analysis and / or interpretation; manuscript preparation and / or critical review; approval of the final version

Nasrum Massi | ORCID 0000-0002-3347-6529
Data acquisition (laboratory or clinical); data analysis and / or interpretation; preparation and / or critical review of the manuscript; approval of the final version

Ilhamjaya Patellongi | ORCID 0000-0003-0147-6345
Data analysis and / or interpretation, preparation and / or critical review of the manuscript; approval of the final version

Rahmawati Anwar | ORCID 0000-0002-3124-4070
Data acquisition (laboratory or clinical); approval of the manuscript's final version

Method for quantitative evaluation of the efficacy of treatments for hair loss using image analysis: preliminary study

Método para avaliação quantitativa da eficácia de tratamentos para queda de cabelo mediante análise de imagens: estudo preliminar

Original Articles

Autors:
Leila David Bloch[1]
Cassiano Carlos Escudeiro[1]
Fernanda Daud Sarruf[1]

[1] IPclin, Instituto de Pesquisa Clínica Integrada, Jundiaí (SP), Brazil.

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ABSTRACT

Introduction: The number of women seeking treatment for androgenetic alopecia has increased during the last decade. Likewise, a greater amount of therapeutic options and methods for evaluating treatment efficacy have also become available. In face of this, it is necessary to develop simple and objective methods to quantitatively evaluate the effectiveness of hair treatments.

Objective: To validate a quantitative method that evaluates the effectiveness of treatments for hair loss.

Methods: Comparison of standardized photographs obtained before and after the treatments, analyzed by a software that provides automatic calculation of the area of hair loss in square pixels. This calculation is based on the contrast perceived between bright (hair loss) and dark (normal amount of hair) regions of the scalp, and allows estimating the area that is not covered by hair, thus quantifying the effectiveness of the treatments.

Results: The method is effective for assessing the affected area in patients with both initial and advanced degrees of hair loss.

Conclusions: The proposed method allows evaluating the effectiveness of diverse types of treatments for telogen effluvium and androgenetic alopecia in a rapid, straightforward and cost effective manner.

Keywords: Alopecia; Hair; Methodology; Methods

RESUMO

Introdução: *O número de mulheres que buscam tratamento para alopecia androgenética tem crescido na última década, bem como as opções terapêuticas e os métodos para avaliar a eficácia de tratamentos. Nesse contexto, é necessário o desenvolvimento de métodos simples e objetivos para avaliar quantitativamente a eficácia dos tratamentos capilares.*

Objetivo: *Validar um método quantitativo para avaliar a eficácia de tratamentos para a queda de cabelos.*

Métodos: *Comparação de fotos padronizadas, obtidas antes e depois dos tratamentos, analisadas com auxílio de um software, que fornece o cálculo automático da área de falha, em pixels quadrados, a partir do contraste entre claro (região com perda capilar) e escuro (região com quantidade normal de cabelos), possibilitando estimar a área de couro cabeludo que não apresenta cobertura capilar e, assim, quantificar a eficácia dos tratamentos.*

Resultados: *O método é eficaz para a avaliação da área afetada pela perda capilar tanto em pacientes com grau inicial (Savin I-1a) quanto em quadros mais avançados (Savin III e avançada).*

Conclusões: *O método proposto permite avaliar de forma rápida, simples e com baixo custo a eficácia de diversos tipos de tratamentos para eflúvio telógeno e alopecia androgenética.*

Palavras-Chave: *Alopecia; Cabelo; Metodologia; Métodos*

Correspondence:
Leila David Bloch
Rua Dr. Leonardo Cavalcante, 314 – Centro
13201-013, Jundiaí, SP
E-mail: leilabloch@gmail.com

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This study was performed at IPclin - Instituto de Pesquisa Clínica Integrada - Jundiaí (SP), Brazil.

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INTRODUCTION

Hair loss causes psychological and emotional distress, with a significant negative impact on the patients' self-esteem, confidence, and body self-image.[1]

Physical, hormonal, and emotional factors, diseases and surgical interventions can be classified as triggering factors of telogen effluvium (TE).

The number of women seeking treatment for androgenetic alopecia (AGA) and TE has increased in the last decade, as well as therapeutic options and methods to evaluate their treatment efficacy.

Cosmetic products may have the function of just masking the appearance of hair loss by covering up the exposed scalp where there is visible hair loss, as is the case with some pigment sprays. Shampoos and other topical agents can deposit particles aimed at adding volume to the surface of the hair fibers and reduce the space between them, giving the sensation of a scalp with greater coverage. In AGA, the hair shaft´s diameter is reduced, increasing the susceptibility to fracture (breaking of the threads). Lubrication for external protection – aimed at minimizing friction – combined with agents that provide temporary adhesion in order to prevent damage to the cuticles, helps to reduce hair breakage and consequently, their falling.2 Also, there are some products containing active principles, in their formulations – such as Minoxidil –, that stimulate the cycle of capillary growth.[3]

With the growing market for products aimed at treating hair loss, it has become necessary to develop simple and objective methods to quantitatively evaluate their efficacy. This would allow the assessment of effectiveness before new products are released into the market and enable both physicians and patients to monitor the development of the treatments.

Traditional methods used to evaluate the effectiveness of treatments are normally based on manual counting of hair strands from an area marked and photographed with a common camera or on a phototrichogram. Both techniques are laborious, in addition to requiring specific technical training in order to be implemented, which adds additional costs for testing and evaluating the effectiveness of products and for controlling and treating hair loss.[4]

OBJECTIVE

The present study is aimed at proposing a quantitative method to evaluate the effectiveness of treatments against PCPF/AGA and TE, based on the analysis of an imaging software.

METHODOLOGY

The proposed method was based on the methodology described by Hung et al.5 Standardized photographs of the frontoparietal area, in the region of central hair loss, were obtained for the evaluation. The photographs were taken before and after topical treatments were performed.

The photographs were individually analyzed using the Image Pro Premier® software (Media Cybernetics, Rockville, USA). Correction of the exposure was performed in all photographs in order to emphasize the contrast between normal areas and hair failure areas. The analysis corresponded to the automatic calculation of the area with hair loss in square pixels, performed by the software based on the contrast between bright regions (hair loss region) and darker regions (area without hair loss), as shown in Figures 1 and 2. In this way, it was possible to estimate the area (in pixels^2) of the scalp that was not covered by hair and, thus, to quantify the efficacy of the treatments used for AGA and TE, by comparing photographs obtained before and after its application.

RESULTS AND DISCUSSION

The Savin scale (Figure 1) was used as a parameter for classifying the degree of AGA 6. This scale distributes female androgenetic alopecia in eight degrees of hair loss intensity: I-1 to I-4 (mild loss), II-1 to II-2 (moderate loss), III and advanced (more intense stages of hair loss, as well as more rare frontal loss).

Women with AGA – associated or not to TE – who underwent topical treatment with minoxidil lotion associated with anti-dandruff shampoo were evaluated. Analysis of Figures 1 and 2 suggests that the method is effective for the evaluation of the area affected by hair loss both in patients with initial degrees of hair loss (Savin scale I1-4) 6, and with more advanced cases of hair loss (Savin scale II 1-2 and advanced).[6]

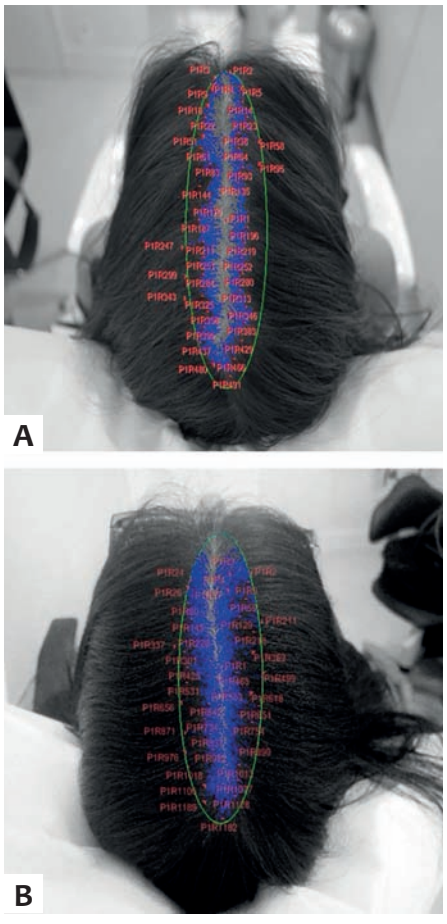

Figure 1: Female patient with hair loss (Savin scale I-3)
A - Before the treatment. **B** - After the treatment (Savin scale I-2)

Figure 1 depicts the effectiveness of a treatment for AGA (Savin scale I-3), with the area affected by hair loss measuring 31,564 pixel^2 before the treatment (Figure 2a) being reduced to 25,163 pixel2 after the 2-year therapy (Figure 2.b), which would clinically correspond to AGA - Savin scale I-2.[6]

The efficacy of a treatment for an AGA – Savin scale II-2 can also be observed in Figure 2. In this more severe case, the first image (Figure 2a) shows the area affected by hair loss prior to the treatment (440,529 pixel^2), with the second image (Figure 2.b) highlighting a reduction to 296,151 pixel^2 after 9 months of therapy, corresponding to the II-1 level in the Savin scale.

The proposed method stands out from those usually used for the straightforwardness of use, as it does not require specific technical training, yields results in a few minutes, is cost effective and allows to evaluate different degrees of hair loss. It is also possible to estimate the development of the AGA and worsening of the hair loss over time in percentage terms, as well as to evaluate the improvement caused by the treatment, rather than simply classifying patients according to scales.

On the other hand, it is not possible to evaluate the growth of hair strands or estimate the ratio of anagen to telogen fibers, as is the case with phototricograms.[4] However, concerning the coverage effect, as is the case with many cosmetic products that only mask the appearance of hair loss by filling or coloring the scalp, the proposed method is a better choice.

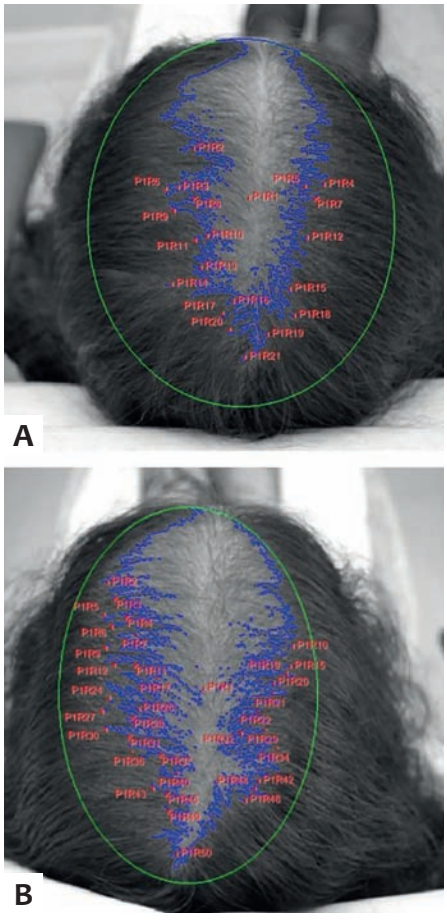

Figure 2: Female patient with hair loss (Savin scale II-2). **A** - Before the treatment. **B** - After the treatment (Savin scale II-1)

CONCLUSION

The proposed imaging software-assisted analysis method allows physicians and researchers to quantitatively evaluate the efficacy of products intended for the control and treatment of AGA and TE in a quick, efficient and cost-effective manner. It calculates the area of hair loss in the scalp caused by the decreased number and diameter of hair strands, which is more precise than just relying on visual observation, offering more accuracy and efficacy in the assessment of AGA severity. ●

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DECLARATION OF PARTICIPATION:

Leila David Bloch | ORCID 0000-0001-9596-9583
Conceptual development, oversight of the research project development, manuscript's final version preparation

Cassiano C. Escudeiro | ORCID 0000-0001-6637-3430
Research project development oversight, manuscript's final version review

Fernanda D. Sarruf | ORCID 0000-0003-4454-6323
Methodology development, research implementation, data analysis, manuscript's final version review.

Original Articles

Autors:
Claudia M. Duarte de Sá Guimarães[1]
Luciane Fachin Balbinot[1]
Marcos Leal Brioschi[1,2]

[1] Escola de Educação Permanente, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (EEP/HCFMUSP) – São Paulo (SP), Brazil.
[2] Department of Neurology, HCFMUSP – São Paulo (SP), Brasil, Brazil.

Correspondence:
Claudia Maria Duarte de Sá Guimarães
Av Nossa Sra. De Copacabana, 435
Sala 903
Copacabana, Rio de Janeiro - RJ
Email: doctorsa@uol.com.br

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This study was performed at the Graduate Program in Medical Thermology and Thermography, Universidade de São Paulo - São Paulo (SP), Brazil.

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Infrared images in the evaluation of the diabetic foot

Imagens infravermelhas na avaliação do pé diabético

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ABSTRACT

Introduction*:* Diabetes is a frequent pathology that has universal distribution. The incidence of the type 2 of this condition has been increasing with obesity. Early detection of dermatological, vascular, orthopedic and neurological origin pathologies helps the diagnosis and treatment of the diabetic foot.

Objective: To evaluate the feet of pre-diabetic and diabetic patients bearers of onychomycosis using thermography, aiming at identifying the vascular, neurological and orthopedic impairment, as well as following up the clinical development.

Methods: Capture of infrared images at baseline and after cold stimulus test, using an infrared sensor in a controlled environment.

Results: This examination allowed the suspicion of peripheral neuropathy of fine fibers to be raised, as well as to verify areas of footwear pressure and to evaluate the progression of Charcot foot.

Conclusions: Infrared imaging associated with dermatological examination can be a propaedeutic tool for the early identification of vasomotor alterations in the soles, even in asymptomatic patients.

Keywords: Diabetic foot; Diabetes Mellitus; Thermography

RESUMO

Introdução*: O diabetes é patologia frequente, de distribuição universal cuja incidência do tipo 2 vem aumentando com a obesidade. A identificação precoce das patologias de origem dermatológica, vascular, ortopédica e neurológica auxilia o diagnóstico e o tratamento do pé diabético.*

Objetivo: *Avaliar por termografia os pés de pacientes pré-diabéticos e diabéticos portadores de onicomicose, com o intuito de identificar o comprometimento vascular, neurológico e ortopédico, bem como acompanhar a evolução clínica.*

Métodos: *Captação de imagens infravermelhas basais e após teste de estímulo ao frio com sensor infravermelho em ambiente controlado.*

Resultados: *Esse exame possibilitou a suspeita de neuropatia periférica de fibras finas, áreas de pressão de calçados e avaliação da progressão do pé de Charcot.*

Conclusões: *O exame por meio de imagens infravermelhas associado ao exame dermatológico pode ser instrumento propedêutico para a identificação precoce de alterações vasomotoras nas plantas dos pés, também em pacientes assintomáticos*

Palavras-Chave*: Diabetes Mellitus; Pé diabético; Termografia*

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease that affects 18.6% of the elderly population in Brazil. Due to its high incidence, this disease is used as a model for the study of foot diseases.[1] Dermatological changes affecting the feet are precocious and precede hyperglycemia, arising in the phase when there is an increase in the peripheral insulin resistance or in cases of obesity. Among them, the following stand out: dryness and desquamation, fissures in the heels, plantar intertrigo, callosities, onychomycosis and edema of the toes. These dermatological clinical

signs, common in the early forms of the diabetic foot, may also be part of other diseases, such as hypothyroidism and chronic intoxication by alcohol and drugs. The detailed clinical history assists in the diagnostic elucidation, as well as the dosage of glucose, insulin, glycated hemoglobin, TSH, free T4 and other complementary tests. Since dermatological alterations in the feet may develop into serious problems despite the fact that they start in an apparently benign way, the dermatologist has the opportunity to diagnose the disease early on through dermatological examination and the use of a non-invasive technique aimed at identifying the presence of vasomotor and vascular changes. The presence of several degrees of neurological and vascular diseases, ulcers, infection and necrosis can be observed in the more advanced stages of the disease. Diabetic foot is one of the most common of non-traumatic causes of amputation in the lower limbs, accounting for 80% of the amputees. Treatment requires the intervention of a multidisciplinary team in order to control infections, pain, metabolic disorders, nutritional deficits, as well as comorbidities and implementing surgical interventions. The assessment and classification of cases according to the intensity of the impairment are important strategies for the treatment and reduction of the risk of amputation.[1]

Peripheral neuropathy is a common complication in DM and affects more than 30% of patients. It is described as a set of alterations in the fine nerve fibers that affect both the vascular sympathetic reflex's and the sensory and neurovegetative peripheral nervous system's responses, with reduction of pain sensitivity and sweating. These changes precede the emergence of symptoms such as burning sensation in the feet, metatarsalgia and leg weakness, which may be aggravated by consumption of alcoholic beverages, vitamin B12 deficiency, hypothyroidism, difficulty in controlling blood glucose and peripheral resistance to insulin.[2]

Its clinical appearance is progressive, leading to the involvement of the thick fibers responsible for motor innervation, and resulting weakening of the lower limbs' musculature, with gait alterations and biomechanical problems. Patients experience frequent falls and osteoarticular changes that characterize the Charcot foot, with progressive flattening of the plantar arch and Morton's neuroma development.

On the other hand, the neurological and orthopedic alterations favor traumatisms in areas of greater pressure, leading to the formation of callosities and ulcerations. Examination of the skin reveals dried feet due to reduction of sweating, cracks in the calcaneus region, desquamation, onychocryptosis, chronic onychomycosis, plantar intertrigo, plantar hyperkeratosis, blisters and even ulcers. Identifying this process early on can prevent the clinical development of alterations in the foot, which have great impact in the patients' quality of life.

Noninvasive examination by capturing images of infrared rays emitted between 8 and 12 μm by feet can be used to quantify and map skin temperature changes and define certain diseases. Its use as a diagnostic method is based on the fact that various types of organic processes are manifested by changes in the production of heat and changes in blood flow patterns in organs and tissues. Neurovegetative nervous system controlled thermoregulation of the skin governs the capillary and arteriovenous flow through central and peripheral activity. In the case of DM, sympathetic neurovegetative neuropathies result in the opening of these shunts and increased blood flow to the skin.[3]

Plantar vasomotor alterations can be observed as they are influenced by the sympathetic neurovegetative system and the room temperature with assistance of thermography, performed with cameras or thermographic sensors, which record the patterns of the emitted heat through images termed thermograms. The goal is to thermally map the soles of the feet.

This mapping observes the concept of angiosomes, which are anatomical functional units grouped by regions that coincide with a particular vasculo nervous territory.[4-6] The six angiosomes of the feet and ankles are supplied by three main arteries: 1) the posterior tibial artery, which irrigates the plant of the foot (through the medial and lateral plantar branches) and part of the calcaneal region; 2) the anterior tibial artery, which irrigates the dorsum of the foot through the dorsal artery of the foot; and 3) the fibular artery, that irrigates the lateral border of the ankle. Only the dorsal plantar artery can be palpated in the clinical examination.

The objective of thermography is to capture infrared images emitted by the skin in order to record changes in the vasomotor control of the microcirculation and the arterial circulatory system, in this way mapping the area according to the distribution of angiosomes and plantar vasomotor reaction.[7-10] Plantar morphological patterns are described according to the vascular anatomy of the lower limbs.

Infrared images also assist in the evaluation of infectious and traumatic intercurrences, among others. Diabetic foot ulcer is one of the most severe complications and early detection of its risk is crucial to preserve the foot. Thermography is used both to measure hyper-radiant areas with an acute increase in the plantar temperature, as well as chronic increases due to intensified arteriovenous flow. [11-17] On the other hand, a chronic decrease in plantar temperature might indicate peripheral vascular disease, and instability in thermoregulation might lead to the suspicion of diabetic neuropathy.[18] This variation can be assessed using the provocative cold stress test, performed with the exposure of the feet at 15°C, where thermal reheating can be observed after 10 minutes, promoted by reactive hyperemia in the plantar region. Analysis of the images performed by a specialized digital imaging software makes it possible to measure the reheat reaction with a 0.2°C accuracy, yielding a comparative curve between the feet.[19]

METHODS

In this retrospective study, medical records and infrared images (thermograms) of 9 patients with onychomycosis and DM Wagner's Grade 0 were evaluated (the Wagner Grading System for Diabetic Foot Ulcers classifies diabetic foot ulcerations according to increasing degrees of severity from I to V).[20] Seven patients had DM type 2, and two had DM type 1. They were treated at a private practice between May 2016 and January

2018. The study complied with the ethical criteria of the Helsinki Declaration. The capture of infrared images (thermograms) was performed in a controlled environment (room temperature at 23°C, and air circulation < 0.2 m/s) using a hypersensitive infrared sensor (18mm, 320x240 pixels resolution), Flir T420® (Flir Brasil, Sorocaba, São Paulo, Brazil). The baseline thermograms of the plant and dorsum of the feet were evaluated with a cold stress test, with immersion of the feet in water at 15°C for one minute and subsequent plantar registration after 10 minutes. The images were analyzed with assistance of the software Flir Tools® (Flir Brasil, Sorocaba, São Paulo, Brazil), with the measurement of the maximum, medium and minimum temperatures of the demarcated areas. Initially, the thermal pattern of the feet's dorsa and plants was observed, which should follow a thermal gradient pattern with hyper-radiation in the plantar arch and reduction of this radiation in the periphery, characterizing the butterfly pattern (Figure 1). Next, the forefoot, midfoot and hindfoot areas were measured according to the vascular territory of the anterior and posterior tibial arteries and their ramifications. Finally, the measurement of the toes was performed aimed at verifying the difference in temperature (ΔT), which is expected to be ≤ 0.4 °C, even after the cold stress test.

RESULTS

Four male and 5 female patients with DM and chronic onychomycosis, aged between 39 and 88 years, without history of foot ulcer (Wagner's ulcer Grade 0) were included in the present evaluation. Two patients (one with DM1 and one with DM2) underwent cold stress tests, aiming at enhancing the vasomotor reaction through cold stimulus. All evaluated patients were considered positive for abnormal sympathetic vasomotor instability in the feet, as they presented breakage of the transverse lines of the distal thermal gradient of the feet, as well as interdigital anisothermy ≥ 0,4°C – with or without the cold stimulus test (Figures 1 and 2). The patterns of plantar thermography varied according to the classification based on the anatomical units (angiosomes). A large increase in the area of plantar hyper-irradiation was observed in two T2 DM and Charcot foot bearer patients (aged 68 and 88 years), with one of the cases presenting recurrent paronychia, lymphedema and erysipelas, confirmed with ΔT above 3°C as compared to the contralateral limb (Figures 3a, 3b, 3c). The cases evaluated by thermography did not present poor vascular perfusion or ischemia – even in the hypothetic presence of those conditions, Nd:YAG laser would be contraindicated in the treatment of onychomycosis.

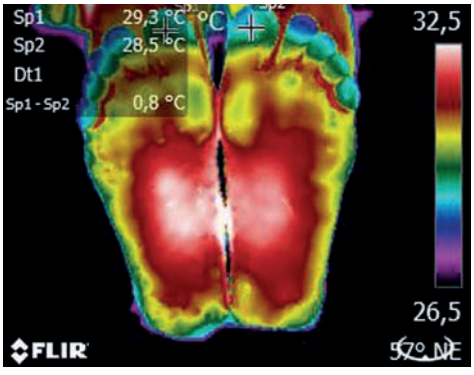

Figure 1: Seventy-five year-old male patient bearer of DM2, hyperglycemia, hyperinsulinemia, digital anisothermy with ΔT > 0.4°C, butterfly pattern with hyper-radiation to the calcaneus region

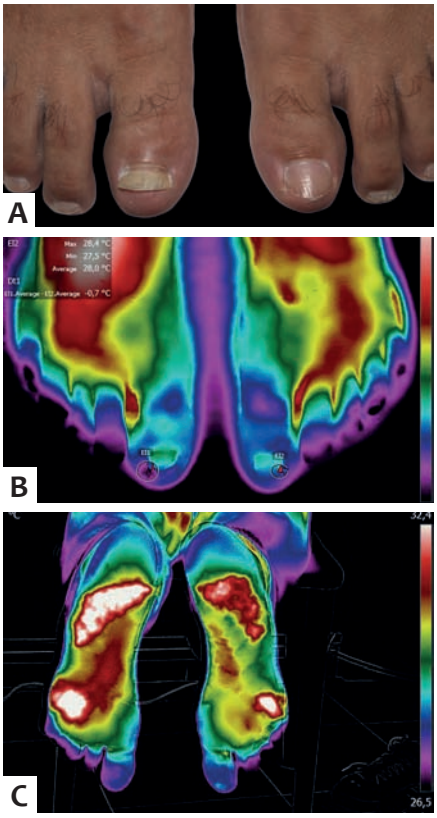

Figure 2: A - Fifty-nine year-old male patient, bearer of DM1, hypertension; onycholysis in the right hallux (coinciding with the jogging shoes' pressure area); dryness and fissures in the calcaneal region, which might have occurred due to peripheral neuropathy of fibers (reduction of sweating), **B -** Hyporadiant area in the right hallux (region of vascular suffering, coinciding to the jogging shoes' pressure area); breaking of the transverse lines of the thermal distal of the feet and digital anisothermy with hyper-radiation in the fifth metatarsus. **C –** Breakage of the transverse lines of the distal thermal gradient of the feet and digital anisothermy (ΔT > 0.3 °C, between the distal phalanges of the toes and hyper-radiation in the fifth left and right metatarsus); clinical history of L5-S1 lumbar hernia treatment, presents hypo-radiation bilaterally in the calcaneal region, characteristic pattern of neural root involvement at S1

DISCUSSION

Peripheral neuropathy is a common complication in diabetic patients, affecting more than 50% of that population.[1] This condition increases the risk of ulcerations that can lead to lower limb amputation. The patients examined did not had ulcers in the lower limbs, having therefore been considered grade 0 both by the Wagner's and the University of Texas' classification systems, used in the evaluation of the diabetic foot.[1,8] Infections or ischemia increase the risk of amputation, which suggests that diagnosis and regular follow-up decrease the morbidity and mor-

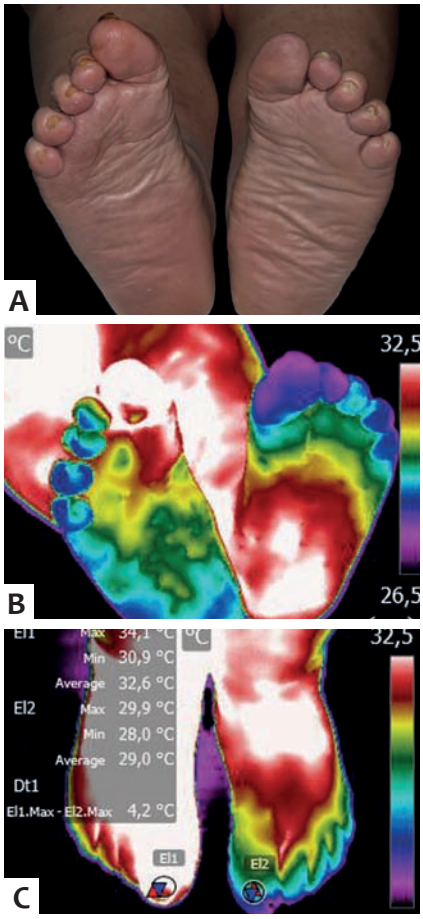

Figure 3: A – Sixty-eight year-old woman, bearer of DM2, hypothyroidism; clinical examination indicated a chronic lymphedema in the lower limbs and paronychia in the right hallux, drop in the plantar arch, loss of ankle dorsiflexion, ankle contracture, which are alterations commonly found in the Charcot's foot, confirmed by the radiological alterations found (subluxation of distal articulation of the right hallux, increase of soft parts, among others); thermography. **B –** Breakage of transverse lines of the distal thermal gradient of the feet with hyper-radiation throughout the soles, more pronounced in the left foot; pattern observed in cases of plantar circulatory and / or vasomotor alterations (peripheral neuropathy of fibers). **C –** Presence of hyper-radiation with ΔT > 4.2 °C when compared to the right and left halluces, with ascending pattern suggestive of lymphangitis; the infrared image accompanied by clinical examination confirmed the diagnosis of paronychia

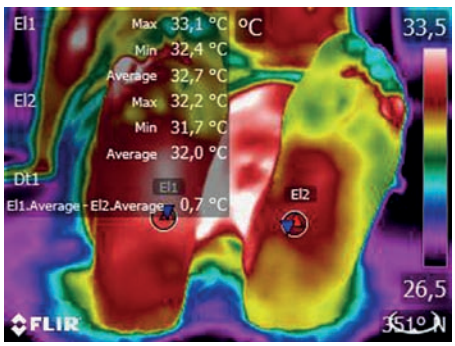

Figure 4: Eighty-eight year-old female patient, bearer of DM2, bilateral plantar callus more prominent on the right side, steppage gait, right plantar arch drop, with hyper-radiation of right fifth toe; breakage of the transverse lines of the distal thermal gradient of the feet and interdigital anisothermy with ΔT > 0.4°C

tality of diabetic patients with and without ulcers. In addition, diabetic patients with mild neuropathies are more prone to trauma and infection due to the fact they have reduced protective sensitivity, this being a factor to be considered.[2] Diabetic patients are more likely to have proximal and distal occlusive arterial vascular diseases, and may course with other intercurrences of superficial and deep venous origin, lymphatic occlusive diseases, in addition to posttraumatic vascular disorders or due to exposure to cold, meaning that clinical examination combined with thermography based propaedeutic examination may help in the differential diagnosis.[3,6,14,17]

The cold stimulus test followed by infrared imaging is used due to the fact it significantly increases the sensitivity of the method, and is indicated in tandem with ambulatorial exams performed when there is complaint of burning feet, signs of increased peripheral insulin resistance or of increased glucose tests in asymptomatic patients, or still when there are cutaneous signs of neurovegetative neuropathy.[19] The reactive hyperemia response can be measured and depicted on a graph used to monitor treatment. However, it is important to note that loss of fine nerve fibers can occur in other diseases, such as fibromyalgia syndrome, motor neuron disease, Ehlers-Danlos syndrome and Parkinson's disease, among others,[19] isolated or associated with diabetes. The clinical examination of the feet in the studied group showed areas of plantar dryness and desquamation, hyperkeratosis and plantar arch drop (Charcot's foot in two cases), in addition to steppage gait, associated with the results of basal thermography, evidencing areas of plantar hyper-radiation in the regions where there was frequent contact with footwear and inadequate tread (Figure 4). In diabetic patients, fine fibers neuropathy may gradually combine with that of large fibers in type 2 diabetes patients, and generally affect the distal extremities in the upward direction.[19] Patients may experience burning sensation, stinging, pruritus in the lower limbs in addition to cramps and restless legs during the night.[2] It may be accompanied by other neurovegetative symptoms, such as changes in sweating, diarrhea, constipation, dry eyes, palpitation, hot flashes, sensitive skin, burning feet and heat intolerance. Other tests may be necessary to confirm the diagnosis of diabetic peripheral neuropathy, by applying neurological protocols and performing skin biopsy with 3mm punch followed by histological examination with special stains, aiming at assessing adnexa and quantifying nerve fibers in the dermis.[2]

CONCLUSION

Infrared imaging of the feet may be a useful propaedeutic tool alongside ambulatorial clinical examination, as it provides assistance in the mapping of the lower limbs – in special the plantar region – in the preliminary and early diagnosis of fiber neuropathy and in the identification of areas of infection and poor blood perfusion, aiding in the preparation of differential diagnoses and aggravating risk factors already in the first ambulatorial clinic visit or at the dermatologist's practice. ●

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DECLARATION OF PARTICIPATION:

Claudia Maria Duarte de Sá Guimarães | ORCID 0000-003-4635-5897
Examination of patients, acquisition of infrared images, manuscript write up

Luciane Fachin Balbinot | ORCID 0000-0003-2762-393X
Oversight of the manuscript and image reviews according to the method validated in her doctoral thesis on the use of infrared images in the evaluation of peripheral neuropathy of thin fibers of the diabetic foot

Marcos Leal Brioschi | ORCID 0000-0003-4822-8314
Review of the manuscript and infrared images, rectification of diverging points

Prospective study for the treatment of rosacea flushing with botulinum toxin type A

Estudo prospectivo para tratamento do rubor da rosácea com toxina botulínica tipo A

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ABSTRACT

Introduction: Rosacea is a chronic facial condition characterized by erythema, edema, telangiectasias, papules and possibly pustules and nodules. There are four subtypes: erythematous-telangiectatic rosacea (I), papulopustular rosacea (II), phymatous rosacea (III) and ocular rosacea (IV). Its pathogenesis is multifactorial, and the treatments, diverse.

Objective: To demonstrate the effect of botulinum toxin in the improvement of flushing and erythema in patients with erythematous-telangiectatic rosacea.

Methods: Six patients with Subtype I rosacea were selected in the Dermatology Department's outpatient clinic of a university medical service. The patients received applications of botulinum toxin type A (dilution of 100 units to 5 ml of saline solution), with intradermal injections of 0.2 to 0.5 units per point in the affected region. Evaluations were carried out after one, two, three and six consecutive months.

Results: There was improvement of the facial erythema and flushing during the three months following the application, with symptoms returning around the sixth month after the treatment, in line with the estimated duration of toxin effectiveness.

Conclusions: There was improvement of the patients' symptoms and satisfaction, and it was deemed a treatment of easy application, associated with a low index of adverse effects and prolonged duration of outcomes.

Keywords: Botulinum Toxins, Type A; Erythema; Quality of Life; Rosacea

RESUMO

Introdução: *Rosácea é afecção crônica da face caracterizada por eritema, edema, telangiectasias, pápulas e eventualmente pústulas e nódulos. Existem quatro subtipos: rosácea eritêmato-telangiectásica (I), rosácea papulopustulosa (II), rosácea fimatosa (III) e rosácea ocular (IV). A patogênese é multifatorial, e os tratamentos são diversos.*

Objetivo: *Demonstrar o efeito da toxina botulínica na melhora do flushing e eritema, em pacientes com rosácea eritêmato-telangiectásica.*

Métodos: *Foram selecionadas seis pacientes com rosácea do subtipo I, no ambulatório do Departamento de Dermatologia de um serviço universitário. As pacientes receberam aplicações de toxina botulínica tipo A, em diluição de 100 unidades para 5ml de solução salina, com aplicação intradérmica de 0,2 a 0,5 unidades por ponto de aplicação na região acometida, tendo sido avaliadas após um, dois, três e seis meses consecutivos.*

Resultados: *Observou-se melhora do eritema facial e do flushing nos três meses consecutivos à aplicação, com retorno dos sintomas por volta do sexto mês após o tratamento, adequado ao tempo estimado de atuação da toxina.*

Conclusões: *Houve melhora dos sintomas e satisfação das pacientes, sendo um tratamento de fácil aplicação, com baixo índice de efeitos adversos e duração prolongada do resultado.*

Palavras-Chave: *Eritema; Qualidade de vida; Rosácea; Toxinas botulínicas tipo A*

Original Articles

Autors:
Luciana Couto e Silva[1]
Isadora Lopes Oliveira Ferreira[1]
Marina Leite da Silveira[1]
Denise Steiner[1]

[1] Department of Dermatology, Universidade de Mogi das Cruzes - Mogi das Cruzes (SP), Brazil.

Correspondence:
Luciana Couto e Silva
Rua Dom Antônio Cândido Alvarenga, 70
Centro, Mogi das Cruzes – SP, Brasil.
08780-070
E-mail: lucouto_fmit@hotmail.com

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INTRODUCTION

Rosacea is a chronic condition of the face characterized by erythema, edema, telangiectasia and papules, which may be accompanied by pustules and nodules.[1] Despite the fact that it is a relatively common dermatosis, the clinical and histological parameters of the disease are still poorly defined.[2]

In 2002, the USA National Rosacea Society Expert Committee issued a consensus establishing a classification for rosacea aimed at standardizing subtypes and variants, having been since widely accepted and used.

Four subtypes were defined based on clinical characteristics: Subtype I, or erythematous-telangiectatic rosacea, includes individuals prone to flushing, associated with persistent facial erythema and sometimes telangiectasias; Subtype II, or papulopustulosa rosacea, characterized by central facial eruption of multiple small erythematous papules (<3mm), sometimes topped by a pustule, isolated or in groups; Subtype III, or phymatous rosacea, in which there is thickening of the skin with irregular contours covering ears (otophyma), eyelids (blepharophyma), mentum (gnatophyma), forehead (metophyma) and nose (rhinophyma), with the latter being the most common manifestation, predominantly occurring in males; Subtype IV, or ocular rosacea, which may occur without cutaneous manifestation or may still be seen in patients with any of the other Subtype of the disease; is characterized by nonspecific complaints, such as pruritus, tearing, dryness, as well as frequent blepharitis.[1-3]

Subtype I – or erythematous-telangiectatic rosacea – will be the focus of the present study. It can be clinically graded by frequency and intensity (0 = fair skin with no signs of erythema, 1 = slight erythema, 2 = slight erythema with defined redness, 3 = moderate erythema with marked redness, and 4 = persistent and pronounced erythema with intense redness) according to the Clinician's Erythema Assessment (CEA). [5-7] Redness episodes can occur without provocation or in response to emotional stress, alcohol, hot drinks, spicy foods, physical exercise, cold or hot weather, and hot baths [5,8]

The prevalence of rosacea in the last few years varied between 1 and 22%, depending on the methodology used and the population analyzed. The most recent rates, obtained from retrospective study databases, range from 1.3% to 2.1%. These low rates are due to the fact that only data from patients with more severe symptoms of the disease is recorded, overlooking a significant portion of patients with milder symptoms.[3,9,10]

It affects more women than men, and Subtype I is the most prevalent, followed by Subtype II. Phymatous rosacea is seen mainly in males of over 40 years of age.[11] Ocular rosacea arises with nonspecific symptoms, being therefore of difficult diagnosis, with incidence rates varying between 6% and 72%, affecting both genders equally.[12] Taking all these factors into account, rosacea is a more common dermatological entity than previously suspected.[3]

The exact pathogenesis of rosacea is still unknown, however some factors are deemed relevant for its occurrence, such as: dysfunction in the innate immune system; exposure to ultraviolet radiation, which causes increased angiogenesis and the production of reactive oxygen species; vascular changes, increasing the expression of vascular endothelial growth factor and lymphatic endothelial markers; epidermal barrier dysfunction; neurogenic inflammation (sensory nerves release neuromediators at the site of inflammation resulting in vasodilation); recruitment of inflammatory cells; extravasation of plasma proteins; and microbial action - *Demodex foliculorum* and *Demodex brevis*, and intense perifollicular inflammatory infiltrate. Such factors lead to a persistent inflammatory state that becomes chronic.[2,3]

The treatments proposed for this pathology are diverse, including topical and oral therapies, and associations with lasers and other technologies. Some casual outcomes of reduction of erythema and acne with the use of botulinum toxin for cosmetic purposes inspired a study by Dayan et al., conducted in 2012 with 13 rosacea patients. Patients received microinjections of botulinum toxin in the affected areas over two years, with results indicating a significant reduction of erythema and redness of the treated area between 2 and 4 weeks after the application. [13]

Since its initial approval for the treatment of strabismus, spasms and hemifacial blepharospasm, botulinum toxin has become one of the most broadly used products for rejuvenation worldwide.[14] After years of successful use and proven safety, treatment with botulinum toxin has expanded to many other indications.[13] The application of botulinum toxin in dermatology currently mainly consists of smoothing dynamic facial and cervical region wrinkles, and treating localized hyperhidrosis (axillary, palmoplantar and craniofacial).[14,15] Nevertheless, new studies have been proposed aimed at expanding indications: trigeminal and post-zoster neuralgia, dyshidrosis, Hailey-Hailey's disease, inverted psoriasis, congenital pachyonychia, cutaneous texture improvement and oiliness control, healing, keloids, notalgia paresthetica, Raynaud's phenomenon, and anal fissure among others.[16]

Botulinum toxin is produced by the culture of *Clostridium botulinum*, a gram-positive anaerobic bacterium. There are seven immunologically distinct neurotoxin serotypes (from A to G), with type A (BTX-A) being the strongest and most frequently used. Its mechanism of action corresponds to the blockade of the release of the neurotransmitter acetylcholine from the peripheral nerves. It has been proposed that acetylcholine plays a role in cutaneous vasodilation and consequently in rosacea reactive erythema.[5,13,17] Several botulinum toxin presentations are available in the market on five continents. There are five presentations of BTX-A available in the Brazilian marketplace: Botox (ONA - onabotulinum toxin A), Dysport (ABO - abobotulinum toxin A), Prosygne (BTA - botulinum toxin A), Xeomin (INCO - incobotulinum toxin A), and Botulift (BTA - botulinum toxin A), according to their introduction precedence in Brazil.[17,18]

The objective of the present study is to observe the efficacy of Botulinum toxin type A injections in the treatment of erythema-telangiectasic rosacea redness or erythema. This is a treatment of straightforward application and low side effects rates.

METHODS

A prospective, interventional study of a case series evaluated 6 female patients aged from 20 to 70 years, selected at the Outpatient Dermatology Clinic of the Universidade de Mogi das Cruzes, located in the city of São Paulo, in Southeast Brazil. The patients had Fitzpatrick's phototypes ranging from I to IV, and clinical diagnosis of erythematous-telangiectatic rosacea. The study was appropriately inserted in the Plataforma Brasil base and approved by the Ethics and Research Committee of the University de Mogi das Cruzes. One hundred units of botulinum toxin type A (BTA - Botulift®, Medy-Tox Inc., South Korea, represented in Brazil by Laboratório Bergamo) were diluted in 5ml 0.9% of saline solution (2 units / 0.1 ml), with 0.2 to 0.5 units being injected per application point. Intradermal injections were performed in the malar regions, with an interval of 0,5cm per application point, totaling a volume ranging from 6 to 15 units per affected malar region (a total of 12 to 30 units, equivalent to 0.6 to 1.5ml of the dilution). The following tools were used for evaluating patients: photographic records taken before, during and after the treatment; assessment of the clinical improvement through the Clinician's Erythema Assessment (CEA); satisfaction questionnaire (DLQI-Dermatology Quality of Life Index); and objective visual evaluation of the improvement of the redness using the CR-300® colorimeter (Konica Minolta Brazil, São Paulo, Brazil), which is a compact color analyzer for measuring reflective surface colors. This device consists of a measuring tip and a DP-301 data processor. The tip's measuring area is 8mm in diameter, and uses diffuse lighting and zero angle viewing (specular component included) for the accurate measurements of a wide variety of surfaces. A pulsed xenon arc lamp in a mixing chamber provides lighting on the sample's surface. Six high-sensitivity silicon photocells, filtered to match the observer's standardized response (Commission Internationale de l'Eclairage - CIE standard), are used by the meter's dual-beam feedback system to measure incident and reflected light. The meter thus detects any slight deviation in the extra light beamed by the pulsed xenon arc lamp and compensates it automatically. The absolute measurements can be shown as tristimulus values of Yxy, L*a*b*, L*C*Ho, Hunter Lab or XYZ. The data can be converted between color systems or between absolute and difference measurements by the data processor. The authors of the present study used the system L*a*b*, in which *L** is the luminosity, which varies from black (0) to white (100); *a** is the gradation from green to red; and *b** is the gradation from blue to yellow. The results were statistically analyzed using the Friedman, Wilcoxon and equality of two proportions tests, confidence interval for the mean value and p-value. The following statistical softwares were used: SPSSV20, Minitab 16 and Excel Office 2010.

RESULTS

The non-parametric Friedman and Wilcoxon tests were used to verify whether the treatments applied to the patients were effective or not. It was possible to conclude that there is a statistically significant difference between the times for the three parameters of the Colorimeter (Table 1).

For the analysis of the improvement in rosacea erythema, the parameter A was predominantly used. For instance, there were higher values of A in the sixth month (mean = 24.23), while they are lower in the second (19.76) and third (18, 08) months, as shown in Table 1. Thus, it was inferred that in months two and three of the study there were statistically significant improvements ($p < 0.001$) in the erythema (Figures 1, 2 and 3), which coincides with the longer duration of the botulinum toxin's action, meaning a better control of the rosacea's malar redness. The higher mean value in the sixth month is also compatible with the fact that the botulinum toxin's effect is already reduced in the site, entailing the worsening of the erythema. The second parameter evaluated was the clinical improvement regarding the reduction of redness, erythema and inflammation based on the Clinician's Erythema Assessment (CEA): 0 = fair skin with absence of signs of erythema, 1 = slight erythema, 2 = slight erythema with defined redness, 3 = moderate erythema with marked redness, and 4 = persistent and pronounced erythema with intense redness. For instance, the result for the distribution of the answer "Moderate erythema with marked redness", which corresponded to 67% in before the treatment, was decreased to zero in the first three months (Table 2, Figures 4 and 5), with statistical significance (Table 3). Six months after, the time lapse necessary for the drug to have effect on the erythema's mechanisms, the percentage increased to 33%. Finally, the progression of the results of the distribution for the ten questions (DLQI questionnaire) was analyzed using the test for equality of two proportions. It was possible to conclude that there are no statistically significant differences between the months of treatment regarding the baseline, meaning that the frequencies vary, but not significantly, since the findings are pulverized due to the small sample size.

Table 1: Development according to the colorimeter's parameters

Colorimeter		Mean	Median	Standard deviation	N	IC	*p-value*
	Before	21.70	21.38	2.67	12	1.51	
	Month 1	22.71	22.80	1.88	12	1.06	
A	Month 2	19.76	19.66	1.69	12	0,95	< 0.001
	Month 3	18.08	20.63	7.03	12	3.98	
	Month 6	24.23	24.43	2.03	12	1.15	
	Before	12.58	12.82	2.44	12	1.38	
	Month 1	12.19	12.69	2.27	12	1.28	
B	Month 2	13.83	14,82	2,03	12	1.15	0.002
	Month 3	10.25	12.03	4.15	12	2.35	
	Month 6	12.51	11.48	3.56	12	2.02	
	Before	61.55	55.06	16.32	12	9.23	
	Month 1	58.36	59.23	2.84	12	1.60	
L	Month 2	55.52	55.56	1.54	12	0.87	< 0.001
	Month 3	68	63.45	13.47	12	7.62	
	Month 6	59.75	58.98	3.72	12	2.10	

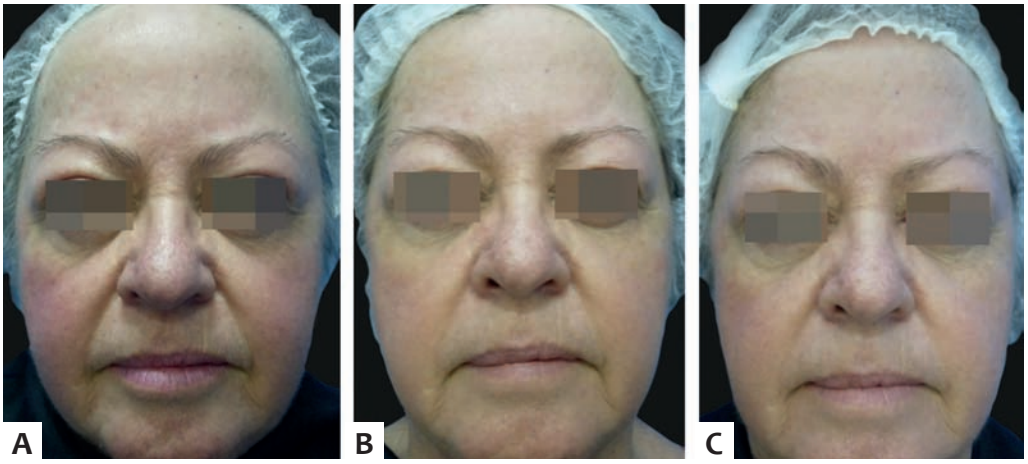

Figure 1: A - Pre-treatment; **B -** Two months after the application of the toxin; **C -** Three months after the application

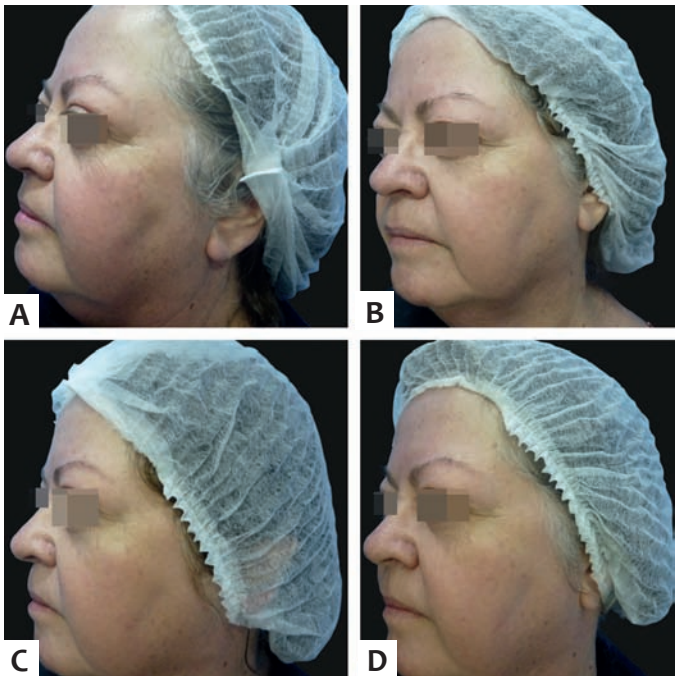

Figure 2: A- Pre-treatment; **B -** One month after the application; **C -** Two months after; **D -** Three months after the toxin application

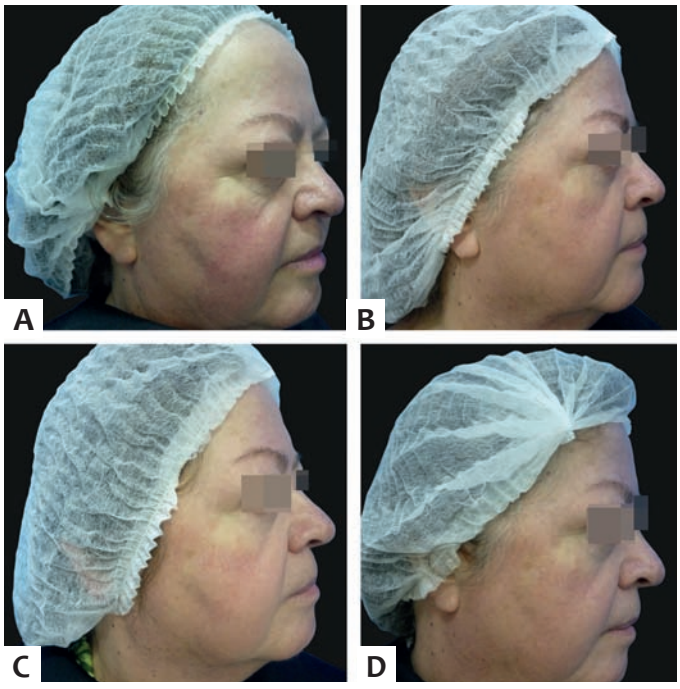

Figure 3: A - Pre-treatment; **B -** One month after the application; **C -** Two months after; **D -** Three months after the toxin application

DISCUSSION

Rosacea is an inflammatory cutaneous disease whose main manifestations include facial erythema, papules, pustules, telangiectasias and recurrent flushing, with heat and burning sensation, and local dryness. Facial erythema can cause discomfort, reduced self-esteem, anxiety and depressive symptoms, leading to a major impact on the patient's quality of life.[1,2,19] There are some treatments proposed for erythema / rosacea flushing, including topical brimonidine, oral beta-blockers, and laser and intense pulsed light based therapies.[19] Botulinum toxin has been recently studied as a therapeutic modality for these patients. Its mechanism of action is the transient blockade of presynaptic acetylcholine receptors at the neuromuscular junction. Since the 1980s, it has been used for dystonias, hemifacial spasms, strabismus correction, treatment for migraine and, more recently, has been applied in cases of sialorrhea, hyperhidrosis and aesthetic treatments.[14,15,20] Its application in cases of rosacea is recent, with few studies published.[2,3,13,20] A study carried out in 2012 by Dayan et al. analyzed 13 patients with erythematous-telangiectatic rosacea for over two years. Patients received botulinum toxin microinjections (7ml saline solution per 100 units of botulinum toxin) with 0.5cm spacing between the application points, in the affected areas, averaging eight to 12 units per area. Results indicated a significant reduction of erythema and flushing of the treated area between the second and fourth week after, with a sustained outcome for up to three months after the treatment.[13] Later on (in 2015), Bloom et al. demonstrated a similar

Table 2: Progression of the erythema's distribution

Erythema	Before		Month 1		Month 2		Month 3		Month 6	
	N	%	N	%	N	%	N	%	N	%
Fair skin with no signs of erythema	0	-	2	33	0	-	0	-	0	-
Slight erythema	0	-	2	33	4	67	1	17	1	17
Mild erythema with defined redness	1	17	2	33	2	33	5	83	3	50
Moderate erythema with marked redness	4	67	0	-	0	-	0	-	2	33
Erythema persistent and pronounced, with intense redness	1	17	0	-	0	-	0	-	0	-

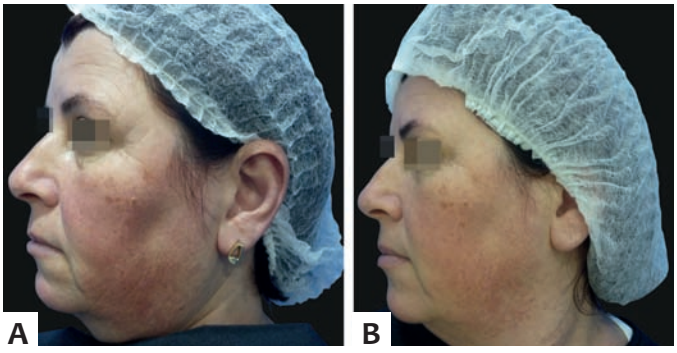

Figure 4: A - Pre-treatment**; B -** Three months after the application of botulinum toxin

Table 3: Table 2 p-values

Erythema	Month 1	Month 2	Month 3	Month 6
Fair skin with no signs of erythema	0.121	1	1	1
Slight erythema	0.121	0.014	0.296	0.296
Mild erythema with defined redness	0.505	0.505	0.021	0.221
Moderate erythema with marked redness	0.014	0.014	0.014	0.248
Erythema persistent and pronounced, with intense redness	0.296	0.296	0.296	0.296

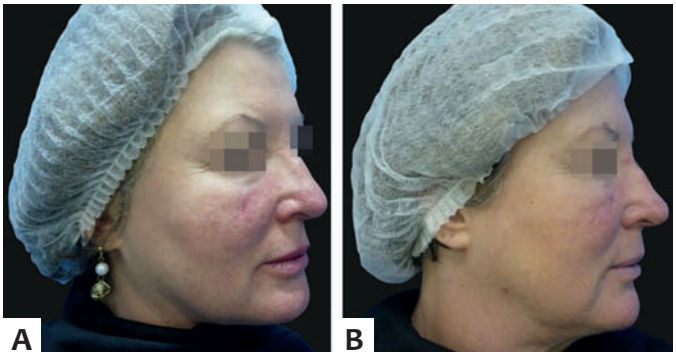

Figure 5: A - Pre-treatment; **B -** Two months after the application of botulinum toxin

treatment with a statistically significant outcome in the patients studied, showing improvement in erythema scores in the first three months after the treatment.[5] The present study employed botulinum toxin in a dilution of 100 units per 5ml saline solution, with intradermal application of 0.2 to 0.5 units per application point, which observed a spacing of 0.5cm between them, yielding results aligned with those of the reviewed literature, and statistical significant improvement of facial erythema in the first three months following the application, as well as reappearance of symptoms by the sixth month after the end of the treatment. As in other treatments for hyperhidrosis and hyperkinetic disorders, diverse amounts of the toxin were applied to each patient according to the area affected by erythema. A greater dilution and intradermal application of the drug in certain points allow better spreading of the product and less possibility of muscular involvement, which could lead to impairment in the facial mimicry's muscles.

CONCLUSION

It was possible to conclude that intradermal injections of botulinum toxin have been showing effectiveness and safety as an option for the treatment of rosacea-related facial erythema, offering straightforwardness in the application, a low rate of adverse effects and prolonged duration of outcomes. These results prevent the use of daily topical and oral therapies, making it easier for patients to adhere to the treatment, thus improving their quality of life. It has been proposed that acetylcholine, an important neuromediator linked to the mechanism of neurogenic inflammation through peripheral nerves, plays a role in cutaneous vasodilation – and consequently in rosacea-reactive erythema. The precise mechanism of action in the improvement of erythema has not yet been fully elucidated, however the action in the blocking of acetylcholine is one of the main evidences. Limitations of the present study include the reduced number of sample patients and the absence of a placebo group for controlling the outcomes. Further studies with larger groups of patients are necessary for determining the optimal dose and better estimating the duration of the treatment. ●

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DECLARATION OF PARTICIPATION:

Luciana Couto e Silva ORCID 0000-0002-0516-130
Clinical evaluation, bibliographic review, writining and manuscript correction.

Isadora Lopes Oliveira Ferreira ORCID 0000-0002-6119-8415
Clinical evaluation, bibliographic review, writining and manuscript correction.

Marina Leite da Silveira ORCID 0000-0002-1430-190X
Clinical evaluation, and manuscript review

Denise Steiner | ORCID 0000-0001-6450-9234
Clinical evaluation, and manuscript review

Pilot-study of photodamaged skin and melasma using reflectance confocal microscopy

Estudo-piloto da pele fotodanificada e do melasma pela microscopia confocal de reflectância

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ABSTRACT

Introduction: Photoaging and melasma are frequent dermatological complaints. Confocal reflectance microscopy (CRM) is a recent technique that can be used for diagnostic evaluation of these dermatoses.

Objectives: To evaluate the characteristics of the epidermis and dermis containing pigmentary alterations caused by photodamage and melasma with the assistance of CRM, and compare the findings linked to these changes with the perilesional region.

Methods: A pilot study was conducted with eight female individuals (aged 38 to 50 years, Fitzpatrick phototypes from II to IV) with clinical diagnoses of photodamage (n = 4) and melasma (n = 4) in the facial malar region. The perilesional and lesional regions were compared regarding the thickness of the stratum corneum and viable epidermis, the depth of the interpapillary crests, and the presence of hyper-refractive structures.

Results: The pigmentary alterations in the photodamaged skin revealed a morphological pattern – such as an increase in the depth of the interpapillary ridges in the lesion region – typical of solar lentigo. In the lesional region of volunteers bearing melasma, it was possible to observe the presence of dendritic cells in the epidermis and melanophages in the dermis. All volunteers had hyper-refractive keratinocytes in the lesional epidermis region.

Conclusions: Considering the number of patients evaluated, it was possible to characterize and compare cutaneous pigmentary alterations caused by photodamage to those cause by melasma.

Keywords: Aging; Microscopy, confocal; Diagnosis

RESUMO

Introdução*: O fotoenvelhecimento e o melasma são queixas dermatológicas frequentes. A microscopia confocal de reflectância (MCR) é técnica recente que pode ser usada para avaliação diagnóstica dessas dermatoses.*

Objetivos: *Avaliar as características da epiderme e derme nas alterações pigmentares da pele fotodanificada e do melasma pela MCR e comparar os achados dessas alterações com a região perilesional.*

Métodos: *Foi realizado estudo-piloto com oito participantes do sexo feminino, com idades variando de 38 a 50 anos, fototipos de II a IV, com diagnóstico clínico de fotodano (n = 4) e melasma (n = 4) na região malar da face. Foram comparadas a espessura do estrato córneo e da epiderme viável, a profundidade das cristas interpapilares e a presença de estruturas hiper-refrativas na região perilesional e lesional.*

Resultados e Discussão: *As alterações pigmentares da pele fotodanificada revelaram padrão morfológico característico do lentigo solar, como aumento na profundidade das cristas interpapilares na região da lesão. Nas voluntárias com melasma, foi possível observar a presença de células dendríticas na epiderme e melanófagos na derme na região da lesão. Todas as voluntárias apresentaram queratinócitos hiper-refrativos na epiderme da região lesional.*

Conclusões*: Considerando o número de pacientes avaliados, foi possível caracterizar e comparar as alterações pigmentares na pele fotodanificada e no melasma.*

Palavras-chave: *Envelhecimento da pele; Microscopia confocal; Diagnóstico*

Original Articles

Autors:
Francine Celise Siqueira César[1]
Ana Paula Martins Martini[2]
Maria Claudia Almeida Issa[3]
Patrícia Maria Berardo Gonçalves Maia Campos[1]

[1] Department of Pharmaceutical Sciences, Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo (USP) - São Paulo (SP), Brazil.
[2] Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo (USP) - São Paulo (SP), Brazil.
[3] Department of Dermatology, Universidade Federal Fluminense (UFF) - Niterói (RJ), Brazil.

Correspondence:
Patricia M. B. G. Maia Campos
Av. do Café, s/n - Ribeirão Preto (SP), Brasil
14040-903
E-mail: pmcampos@usp.br

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INTRODUCTION

Photoaging and melasma are frequent complaints in dermatological practices.[1-3] From a clinical point of view, photodamaged skin has wrinkles, changes in texture and pigmentation, and loss of elasticity and firmness.[3-5] Patients with melasma typically have brown spots with irregular borders and clear delimitation, located in areas exposed to the sun, especially in the face and in women. Both dermatoses can have impacts on the patients' quality of life.[5-9] In Brazil, roughly 8.4% of the population have some pigmentation disorder, while 10% of the Latino population living in the United States have melasma.[7,10]

Solar lentigo, also known as senile lentigo or aging spot, is a benign pigmentary disorder that arises with the process of photoaging. This hyperchromia occurs in areas exposed to the sun, especially in the dorsum of the hands, forearms and face.[11-14] It affects more than 90% of the Caucasian population over 50 years of age.[15] Factors linked to its onset would be related to exposure of the skin to external factors, such as ultraviolet (UV) radiation, polycyclic aromatic hydrocarbons (pollution), and the expression of growth and inflammatory factors.[12,16,17]

Melasma is a pigmentary disorder characterized by the presence of macules located mainly in the central, malar and / or mandibular regions of the face.[1,7,16-18] Ultraviolet (UV) radiation, female hormones (pregnancy, endocrine dysfunction, use of oral contraceptives) and inflammatory processes are involved in its pathogenesis as triggering factors, associated with genetic predisposition.[1,7,19,20] This disorder's pathophysiology has not yet been fully elucidated, however some theories suggest that its emergence would be linked to the increase in the expression of melanogenic factors and specific receptors such as estrogen.[1,19] The increase in the number and caliber of blood vessels in the affected region, as well as the increase in the expression of vascular endothelial growth factor, is also involved.[16,20]

The diagnosis of pigmentary changes of the face is predominantly performed by clinical examination and / or histological examination, when there is suspicion of malignancy. A new noninvasive technique, such as confocal reflectance microscopy (CRM), can assist in the clinical diagnosis and also contribute to increase therapeutic efficacy.[21-23] In addition, CRM can be applied in the quantification of epidermal pigmentation, [24] since this methodology's principle consists of the emission of infrared light on the skin and its subsequent selective capture when reflected by cutaneous structures that have different refractive indices, yielding black and white images. Keratin, melanin, and collagen fibers of the dermis are hyperrefractive structures, being visualized in a lighter color. [25-28]

Methods for instrumental evaluation of photodamaged skin and melasma

There are currently a variety of techniques for instrumentally evaluating the skin, assisting clinical diagnosis.[29] Among the methods available for evaluating melasma and photodamage, reflectance spectroscopy and high-resolution image analysis stand out in the investigation of skin color and melanin distribution.[30,31] The Cutometer® device (Courage-Khazaka, Germany) evaluates the mechanical properties (changes in the elasticity and firmness) of the photodamaged skin. In addition, the analysis of epidermis' and dermis' thickness using high frequency ultrasonography substantially contributes to the evaluation of the therapeutic efficacy.[32,33]

Confocal reflectance microscopy (CRM) is an advanced technique that allows examination of the epidermis and papillary dermis with a resolution close to that of histological examination, with the ability of identifying structures and cells with high resolution.[2,34] This technique's basic principle involves beaming infrared light on the skin and the selective capture of this light, after being reflected by cutaneous structures such as keratin, melanin and collagen fibers, whose refractive indexes are diverse.[26] Confocal reflectance microscopy is considered a tool for diagnostic confirmation of pigmentary changes in the photodamaged skin and melasma, in this manner avoiding cutaneous biopsy in the face.[2]

In light of this, the objective of the present study was to evaluate the characteristics of the epidermis and papillary dermis caused by pigmentary alterations linked to melasma and cutaneous photodamage using CRM, and to compare the findings related to these alterations with the characteristics of the perilesional region.

METHODS

Recruitment

This pilot study was performed after approval by the Research Ethics Committee of the Faculdade de Ciências Farmacêuticas de Ribeirão Preto (CEP / FCFRP, Protocol No. 1,418,673 / 2015). The study sample corresponded to 8 female participants aged 38-50 years, Fitzpatrick phototypes II to IV, with alterations of hyperpigmentation in the malar region, diagnosed with pigmentary skin alterations (n = 4) and melasma (n = 4).

Instrumental evaluation

Images of the malar regions were obtained in triplicate (lesional and perilesional) using a confocal reflectance laser microscope VivaScope 1500 (Lucid, USA), having been standardized using the coupled software Vivastack (Lucid, USA). The images were obtained at every 1.5μm, starting from the stratum corneum up until the depth of 37.5μm, and at every 3μm up until the depth of 132.5μm. Based on the obtained images, the thickness of the stratum corneum, the viable epidermis (granulosum, spinosum and basal layers), and the depth of the interpapillary ridges were evaluated quantitatively and objectively. Likewise, the presence and absence of hyperrefractive structures in the perilesional and lesional region were evaluated qualitatively and subjectively. These evaluations were performed all volunteers.

Statistical analysis

The data had normal distribution, meaning that the t-test was used to compare the morphological alterations between the lesional and perilesional regions. Results were expressed as mean

values and standard deviations. A significance level of $p < 0.05$ was used. The Origin8Pro® software (OriginLab, USA) was employed to evaluate the distribution of the data, while GraphPad Prism 5® software (GraphPad Software, USA) assisted in the statistical analysis.

RESULTS

The quantitative and objective analysis of the data obtained from the volunteers diagnosed with photodamage showed a non-significant increase in the values of the thickness of the stratum corneum and viable epidermis in the lesional region as compared to the perilesional region. Also, a significant increase ($p < 0.05$) in the depth of the interpapillary ridges of the lesional region was observed as compared with the perilesional region. These findings were not observed among volunteers bearers of melasma (Table 1).

Based on the qualitative and subjective analysis of the images, it was possible to observe the presence of hyperrefractive structures in the lesional region of all volunteers (Table 2 and Figures 1L.e, 2L.e and 3L.e).

In all volunteers diagnosed with photodamage, it was possible to observe a disorganized pattern for the interpapillary ridges and accumulation of hyperrefractive keratinocytes in the lesional region when compared to the perilesional region (Table 2 and Figure 1 L. JDE).

Two volunteers diagnosed with melasma presented hyperrefractive keratinocytes in the perilesional region (Table 2). In addition, it was possible to observe the presence of dendritic cells in the lesional region of a volunteer diagnosed with melasma (Table 2 and Figure 2L.e) and of melanophages in the lesional region's dermis of another volunteer who was also diagnosed with melasma (Table 2 and Figure 3 L.d).

In a third volunteer bearer of melasma, it was possible to observe a disorganized pattern for the interpapillary ridges in the perilesional region (Table 2).

Table 1: Comparison of the CRM findings related pigmentary changes caused by photodamage and melasma in the lesional (L) and perilesional (P) regions

Pigmentary disorder	Stratum corneum's thickness (µm)	Viable epidermis' thickness (µm)	Interpapillary ridge's depth (µm)
Melasma			
perilesional	25 +/- 4.5	32.9 +/- 3.5	30.12 +/- 6.8
lesional	24.5 +/- 1.47	33.6 +/- 5.8	35.7 +/- 10.1
Photodamaged skin			
perilesional	21.6 +/- 2.6	30.8 +/- 4	23.5 +/- 6.4
lesional	25.2 +/- 7.6	46.3 +/- 12.2	58.6 +/- 16.2*

* $p < 0.05$ related to the perilesional region. Values are expressed as mean values and standard deviations.

DISCUSSION

The images obtained by CRM evidenced the presence of hyperrefractive keratinocytes in the epidermis of the regions with benign pigmentation disorders. This outcome indicates the accumulation of melanin in keratinocytes, which is one of the

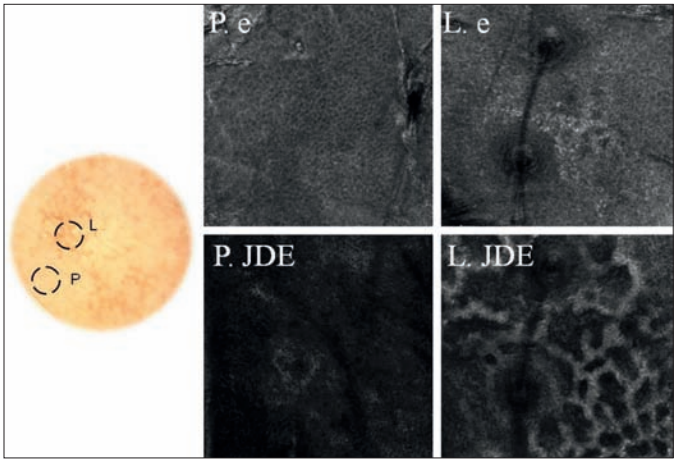

Figure 1: Lentigo solar: P - perilesional region; L - lesional region; Pe - perilesional region's epidermis; P. JDE: perilesional region's dermoepidermal junction; L. e: lesional region's epidermis; L. JDE: lesional region's dermoepidermal junction

Table 2: Comparison of the CRM findings related to the pigmentary changes caused by photodamage and melasma in the lesional (L) and perilesional (P) regions

Pigmentary disorder	Hyperrefractive keratinocytes		Dendritic cells in the epidermis		Melanophages in the dermis		Disorganized pattern of interpapillary ridges	
Melasma	L	P	L	P	L	P	L	P
1	+	+	-	-	-	-	-	-
2	+	-	-	-	-	-	-	+
3	+	-	-	-	+	-	-	-
4	+	+	+	-	-	-	-	-
Photodamage	L	P	L	P	L	P	L	P
5	+	-	-	-	-	-	+	-
6	+	-	-	-	-	-	+	-
7	+	-	-	-	-	-	+	-
8	+	-	-	-	-	-	+	-

L: hyperpigmented region; P: perilesional region; +: presence; -: absence

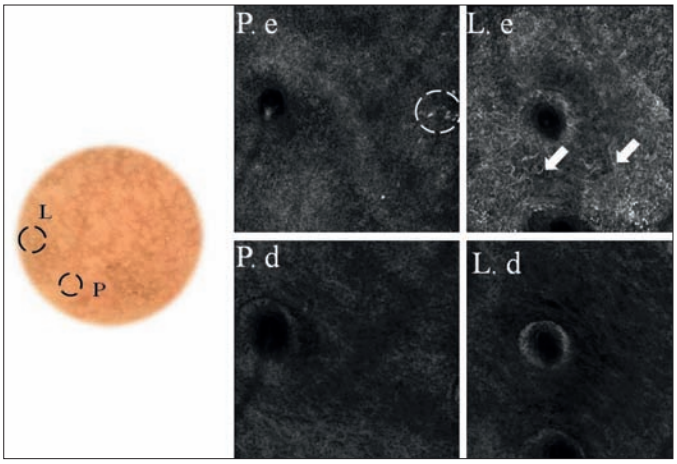

Figure 2: Melasma: P - perilesional region; L - lesional region; P.e - perilesional region' epidermis with ovoid cells suggesting inflammatory infiltrate; P.d: perilesional region's dermis; L.e: lesional region's epidermis with dendritic cells indicated by the arrows; and L.d: lesional region's dermis

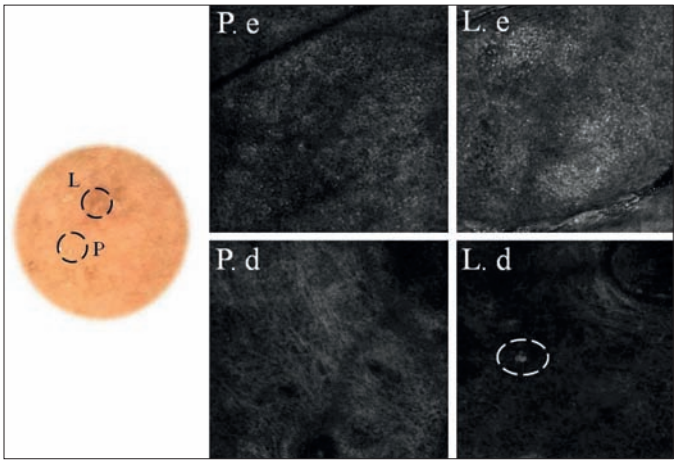

Figure 3: Melasma: P - perilesional region; L - lesional region; Pe - perilesional region' epidermis; P.d - perilesional region' dermis; L.e: lesional region's epidermis; L.d: lesional region's dermis with melanophages identified by the dotted circular region, characteristic appearance of the dermal melasma; Lentigo solar: P - perilesional region; L - lesional region; Pe - perilesional region' epidermis; P. JDE - perilesional region's dermoepidermal junction; Le - lesional region's epidermis; L. JDE - lesional region's dermoepidermal junction

morphological consequences of photoaging.[36] Irregular deposition of melanin in the skin has been reported in CRM studies and is characterized by the observation of bright structures due to the high refractive index of melanin.[21, 36,37]

The disorganized pattern of the interpapillary ridges – represented by a modification in the shape of the papillae, which become polygonal – associated with irregular alignment, was observed at the dermoepidermal junction in the lesional region of the volunteers with pigmentary alterations due to photodamage. These changes are characteristic of solar lentigo, as described in the literature.[21,37,38] A significant increase ($p < 0.05$) in the depth of the interpapillary ridges of the lesional region and a non-significant increase in the thickness of the viable epidermis were observed in the volunteers who presented photodamaged skin with solar lentigo. To date, according to histological studies, the increase in the keratinocytes' thickness in solar lentigo might be related to hypertrophy or increased cell proliferation.[39,40]

According to the literature, the presence of dendritic cells, commonly observed in melasma, might correspond to active melanocytes.[19] In another volunteer diagnosed with melasma, the presence of ovoid contrast cells located in the dermis was observed, which, according to reports in the literature, could be melanophages.[41,42] The outcomes obtained are aligned to those observed in previous investigations, suggesting a possible morphological difference between these pigmentary disorders, that are detectable by CRM.[19,21,36-24]

CONCLUSION

Considering the number of patients evaluated, it was possible to characterize the pigmentary alterations in the photodamaged skin and in the melasma. Based on the analyses performed with assistance of CRM, it was possible to identify differences between pigmentary alterations and the perilesional areas in the malar region, both in melasma and in photodamaged skin. ●

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DECLARATION OF PARTICIPATION:

Francine César | ORCID 0000-0002-3748-1341
Instrumental evaluation, image acquisition and manuscript write up

Ana Paula Martini | ORCID 0000-0003-3705-4339
Image interpretation, manuscript development and write up

Maria Cláudia Issa | ORCID 0000- 0003- 1031- 7370
Structural organization of the manuscript and final review

Patrícia Maia Campos | ORCID 0000-0001-6678-1207
Study coordination, manuscript development and final review

Original Articles

Autors:
Andressa Miléo Ferraioli Silva[1]
Wanessa Cardoso Praia[1]
Caroline da Silva Alves Palheta[1]
Rodrigo Paracampo Couteiro[1]
Andrew Moraes Monteiro[1]
Luciana Mota Silva[1]
Ismari Perini Furlaneto[2,4]
Josie Eiras Bisi dos Santos[3,4]
Miguel Saraty de Oliveira[4]

[1] Universidade do Estado do Pará – Belém (PA), Brazil.
[2] Faculdade Metropolitana da Amazônia – Belém (PA), Brazil.
[3] Instituto de Previdência e Assistência do Município de Belém (Ipamb) – Belém (PA), Brazil.
[4] Núcleo de Medicina Tropical do Pará, Universidade Federal do Pará – Belém (PA), Brazil.

Correspondence:
Andressa Miléo Ferraioli Silva
Avenida Senador Lemos, 500.
Apt 2801
66050-000 Umarizal - Belém (PA), Brasil
E-mail: andressa_ferraioli_@hotmail.com

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The effect of microneedling on scars resulting from induced cutaneous injuries in rats

Efeito do microagulhamento na cicatriz de ferida cutânea induzida em ratos

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ABSTRACT

Introduction: Being healthy corresponds to a state of absolute well-being. Scars are examples of con- ditions that endanger patients' emotional integrity, compromising their quality of life. Consequently, there are several therapeutic alternatives aimed at alleviating aesthetic disorders. Microneedling stimu- lates collagen production, improving the healing effect in the induced cutaneous injury.

Objective: to evaluate the effect of microneedling in the scars of surgically induced cutaneous wounds in rats.

Methods: Twenty-four male rats were distributed in five study groups. A surgically induced incision was inflicted on the animals' dorsa in all study groups, with the healing processes being followed up until completion. The study groups GC-14 and GC-30 served as controls for the groups GCM-14 and GCM-30, respectively.

Results: Reepithelialization and absence of granulation tissue were identified in 100% of the groups. Regarding the proportion of fibrosis, mean reductions of 19% and 4% were observed in GCM-14 and GCM-30, respectively. There was a stimulus to the production of type I and III collagen in the groups that underwent microneedling, with a greater amount of type I collagen in GCM-14 (62.1%) as compared to its control (37.8%).

Conclusions: Microneedling was effective in stimulating increased production of collagen fibers in 14 days, suggesting this treatment tends improve scars.

Keywords: Cicatrix; Collagen; Models, animal

RESUMO

Introdução: *A saúde representa estado de completo bem-estar. As cicatrizes são exemplos de afecções que colocam em risco a integridade emocional do paciente, comprometendo sua qualidade de vida. Existem diversas alternativas terapêuticas visando amenizar distúrbios estéticos. O microagulhamento estimula a produção de colágeno, melhorando o efeito cicatricial da lesão provocada.*

Objetivo: *avaliar o efeito do microagulhamento na cicatriz de ferida cutânea induzida cirurgicamente em ratos.*

Métodos: *Foram utilizados 24 ratos, machos, distribuídos em cinco grupos de estudo. Em todos os grupos realizou-se a incisão cutânea induzida cirurgicamente no dorso do ani- mal, aguardando-se a cicatrização completa. Os grupos GC-14 e GC-30 foram controles para os grupos GCM-14 e GCM-30.*

Resultados: *Foi identificada reepitelização e ausência de tecido de granulação em 100% dos grupos. Com relação à proporção de fibrose, observou-se redução média de 19% no grupo GCM-14 e de 4% no grupo GCM-30. Houve estímulo à produção de colágeno tipo I e III nos grupos submetidos ao microagulhamento, observando maior quantificação de colágeno tipo I no grupo GCM-14 (62,1%) em relação a seu controle (37,8%).*

Conclusões: *o microagulhamento mostrou-se eficaz ao estimular maior produção de fibras colágenas em 14 dias, sugerindo tendência à melhora da cicatriz.*

Palavras-Chave: *Cicatriz; Colágeno; Modelos animais*

INTRODUCTION

There are currently several therapeutic alternatives intended to repair damages resulting from elective surgical procedures or trauma, which have left aesthetic disorders, such as normotrophic scars. Consequently, there is a trend towards the indication of non-invasive procedures, isolated or in association, aimed at alleviating these disorders, with a view to reducing the risk of complications and allowing earlier return to work activities.[1]

Orentreich et al. (1995) 2 described the term "subcision" as a means of stimulating connective tissue underneath scars and retracted wrinkles. Based on this idea, collagen induction therapy (CIT) or microneedling was developed as a technique performed using a device containing a variable number of microneedles, with different lengths, that cause cutaneous microtrauma with multiple perforations in the skin, resulting in the formation of microchannels. This device is rolled on the skin in multiple cross directions several times, causing minimal bleeding, which is replaced by serous exudate, edema and erythema.[3]

The microneedling principle proposes the stimulation of collagen production, without causing total de-epithelization, in a fast, minimally invasive and effective manner, with promising results of the technique having been observed in a number of studies.[4-6] This procedure generates a healing wound response by releasing growth factors and cytokines, which in turn lead to the formation of new collagen and elastin in the papillary dermis.[7] The mechanism of action centers on the dissociation of keratinocytes, which results in the release of cytokines (mainly interleukin-1α, in addition to interleukin-8, interleukin-6, TNF-α and GM –CSF - granulocyte and macrophage colony stimulating factor), resulting in dermal vasodilation and migration of keratinocytes in order to restore epidermal damage. The healing process resulting from the trauma caused by the needles can be divided into 3 phases.

In the first phase (injury phase) - presence of platelets and neutrophils (responsible for the release of growth factors that act on keratinocytes and fibroblasts), transforming growth factors α and β (TGF-α and TGF-β), platelet derived growth factor (PDGF), connective tissue activator protein III, and connective tissue growth factor.[8]

In the second phase (healing phase), neutrophils are replaced by monocytes, and angiogenesis, epithelization and proliferation of fibroblasts take place, followed by the production of collagen type III, elastin, glycosaminoglycans and proteoglycans. Concomitantly, fibroblast growth factor, TGF-α and TGF-β are secreted by monocytes. Approximately five days after the injury has been inflicted, the fibronectin's matrix is formed, allowing the deposition of collagen just beneath the basal layer of the epidermis.

In the third phase (maturation phase), type III collagen, which was predominant in the early stage of the healing process, is slowly replaced by type I collagen, which is more durable, and lasts for a period ranging from 5 to 7 years.[5]

Therefore, the microneedling technique would act to stimulate the production of collagen, consequently improving the cicatricial effect of the lesion inflicted. This technique would be an alternative that would enable and potentialize the treatment of normotrophic scars.

OBJECTIVE

To evaluate the effect of microneedling on surgically induced cutaneous wounds in Wistar lineage rats.

METHODS

Sample

In the present experimental study, 24 male *Rattus norvegicus* (Wistar), aged 100 days, weighing on average 250 to 300g, were made available by the Instituto Evandro Chagas' bioterium after the approval by the Ethics Committee on Animal Use – CEUA of the Universidade do Estado do Pará, Belém do Pará (UEPA), Pará, Brazil. Rats bearing active infectious processes or wounds that could compromise the cutaneous site where experiments would be carried out were excluded from the study. The animals were kept in a temperature-controlled environment before and after the procedure, with 12 hours of light cycle, water and rat-specific feed, offered *ad libitum*.

The animals were randomly assigned to five study groups. In all groups, the skin incision was surgically induced on the animals' dorsa (described in the surgical technique section). Subsequently, a period of 3-week waiting period was observed in all groups for the complete healing of the surgical wound by second intention. From that moment on, differentiation in the procedures took effect according to the protocol established for each experimental group.

Group 1 - Pilot Group (Gp)

Four animals were used in this group after having undergone the pre-operative and anesthesia procedures, surgical technique and postoperative procedures specific to each of the four groups described below. They were not included in the research's casuistry, having been used to improve the study researchers' surgical technique.

Group 2 – Group Scar 14 days (GS-14)

Five animals were used in this group. Once the incision was performed and the complete healing period of the surgical wound elapsed (3 weeks), the animals underwent euthanasia 14 days after complete healing. The microneedling technique was not performed in this group, since it served as a control for comparisons with the other groups.

Group 3 – Group Scar and Microneedling 14 days (GSM-14).

Five animals were used in this group. Once the incision was performed and the complete healing period of the surgical wound elapsed (3 weeks), the animals underwent microneedling technique in the healing wound's site, and euthanasia 14 days after the procedure.

Group 4 – Group Scar 30 days (GS-30)

Five animals were used in this group. After the incision was performed and the complete healing period of the surgical wound elapsed (3 weeks), the animals underwent euthanasia 30 days after complete healing. The microneedling technique was not performed on this group, which served as a control for comparison with the other groups.

Group 5 – Group Scar and Microneedling 30 days (GSM-30)

Five animals were used in this group. Once the incision was performed and the complete healing period of the surgical wound elapsed (3 weeks), the animals underwent microneedling technique in the healing wound's site, and euthanasia 30 days after the procedure.

PROCEDURES

Preoperative and anesthesia

The animals were anesthetized with ketamine (70mg / kg) and xylazine (10mg / kg), by intraperitoneal route, with confirmation of anesthesia based on the absence of the podalic reflex, through interdigital pressure, as well as absence of the paw pinch reflex.

Microneedling

Dr. Roller® devices with 2.5mm long micro-needles, which are recommended when deep skin injury is required therefore being used to treat depressed scars, were used for the microneedling technique in GSM-14 and GSM-30 groups. In order to perform the technique, the device was positioned between the index finger and thumb, with moderate force being applied while moving it in four directions (horizontal, vertical and diagonals, ten passes in each), up until a uniform petechiae pattern was obtained. Aiming at minimizing a possible bias, the procedure was performed on all animals by the same person. When necessary, hemostasis was performed by tamponage with sterile gauzes.[5]

Surgical technique

The animals were anesthetized and fixed with a surgical tape (20x30cm) in the ventral decubitus position. Trichotomy of the dorsal region and subsequent antisepsis of the surgical area were performed with 2% chlorhexidine.

A cutaneous incision of 4cm in length was surgically induced in all animals using a cold scalpel on the right dorsa. The incision extended from the most superficial layer of the skin to the limit of the subcutaneous cellular tissue, having as anatomical references the distance of 2cm from the spine and 4cm from the tail of the animal.

After this surgical incision, 3 weeks were awaited up until second intention healing was complete. This period was based on the observation of the animals in the Pilot Group, which suggested this was the period necessary for epithelialization and contraction of the wound.[9] No suture or other synthesis technique was performed allowing the formation of a visible scar that favor the visualizing the microneedling's effect. From this moment on, there were variations of the procedures according to the protocol established for each experimental group.

All groups (GS-14, GSM-14, GS-30 and GSM-30) underwent similar cutaneous incisions with second intention healing, as described above. After 3 weeks, all animals in GSM-14 and GSM-30 underwent microneedling. The euthanasia of the animals in GSM-14 was performed 14 days later, while in GSM-30 it was carried out 30 days after the microneedling procedure.

The animals in GS-14 and GS-30 did not undergo microneedling, with euthanasia being performed after 14 days in the first group and after 30 days in the second group, counting from the day it was performed in the other groups. In this manner, these groups were used as controls for comparison with the groups that underwent the microneedling technique.

The present study was aimed at analyzing and comparing the amount of collagen present in the cutaneous scar 14 days and 30 days after microneedling, since according to the literature, there is an increase in the levels of cytokines that induce formation of collagen in the period of 2 weeks after the procedure.[10] Diversely, other studies demonstrate that the maximum production of connective tissue occurs 30 days after microneedling 2, justifying the use of the GSM-30 group. Thus, the study sought to analyze by comparison the period when collagen production occurred more effectively after microneedling, based on the count of new collagen fibers induced by the technique.

Post-operative care

The wound was cleansed with 0.9% saline solution daily for 7 days in order to prevent possible infections throughout the initial healing process.[11]

Histology

A sample of the skin of each animal was harvested for histological analysis using cold scalpel biopsy, leaving a margin of 1cm between the scar and the biopsy's incision. The fragments were removed and immediately placed in 10% formalin.

After preparation of the specimens on slides for microscopic study, they were stained with hematoxylin / eosin and Picrosirius, which evidenced the newly synthesized collagen fibers.

Morphological analysis of the samples was performed using optical microscopy by a specialized dermatopathologist. Likewise, the quantification of collagen fibers was carried out by a qualified professional from the Morphofunctional Laboratory of the Universidade do Estado of Pará (UEPA).

The slides for studying the collagen were visualized in a Zeiss microscope with 100x magnification and polarized light. Three photographs were taken of the area of fibrosis of each slide with assistance of the Axion Vision software. The microphotographs were analyzed using the Image J software, aided by the Threshold Color plugin. The percentage of collagen was computed based on the analysis of the colors of particles, selection and measurements of areas. The matrices 0-40 and 45-120 were respectively used for the red (type I collagen) and green (colla-

gen type III) colors, with 0-255 saturation and 5-225 brightness, according to the protocol standardized by Bedoya et al. (2016).[12]

The microscopic findings were observed and classified regarding the presence or absence of reepithelialization and granulation tissue in a semiquantitative way in the samples as follows 0 - absent, 1 – scarse, 2 - discrete, 3 – moderate, and 4 - marked.[13]

STATISTICAL ANALYSIS

The results of the present study were obtained through statistical analysis using the Fisher's exact test for qualitative morphological variables (reepithelialization, granulation and inflammation). The quantitative variables were in turn evaluated using the Student's t-test and Mann-Whitney test, with a significance level of $p < 0.05$. The Microsoft Office Excel and Microsoft Office Word softwares (version 2010), were used for preparing tables, graphs and texts.

RESULTS

The presence of reepithelialization and absence of granulation tissue were similar in GS and GSM groups – both at 14 and at 30 days after the microneedling procedure –

without statistical difference.

The rate of fibrosis was reduced in GSM by 19% on average, as compared to the GC at 14 days, while in GSM-30 that reduction was 4% as compared to GS-30. Nevertheless, both reductions were not statistically significant.

Taking into account the analyzed medians, the concentration of type I collagen increased GSM-14 and in GSM-30 when compared to their respective controls (GS-14 and GS-30), however this increase was not statistically significant. Type III collagen concentration also increased in GSM-14 regarding GS-14 when their medians were taken into account, however this increase was not statistically significant. At the 30-day experimental time point, the median in GSM-30 was lower than in GS-30, with no statistical relevance.

Figures 1 and 2, obtained through histology, demonstrate the proliferation of collagen fibers in GS-30 and GSM-30, respectively. Fibers stained in green represent type III collagen, while those stained in red represent type I collagen. In this manner, it is possible to visualize a larger amount of type I (red) collagen fibers in GSM-30 (Figure 2), corroborating the outcomes found above.

In GSM-14, 75% of the animals had a maximum of 62.1% of type I collagen, whereas in GSM-30 this figure was 64.5%, without statistical difference. Regarding the control groups, 75% of the animals in GS-14 had a maximum of 37.8% of type I collagen, whereas in GS-30 this value was 63.4%.

As for type III collagen, 75% of the animals in GSM-14 had a maximum of 19.8% collagen III, while in GSM-30 this value was equal to 20.8%, with no statistical difference. Regarding the control groups, 75% of the animals in GS-14 had a maximum of 18.4% type III collagen, whereas in GS-30 this value was equal to 13.8%.

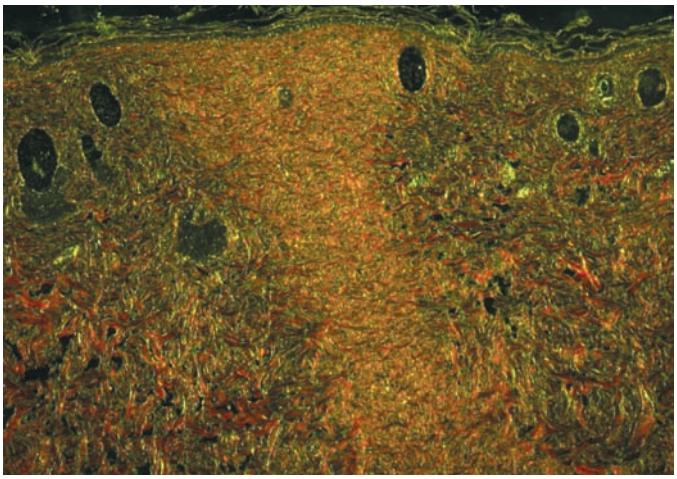


Figure 1: GS-30 slide stained with Picrosirius, x50 magnification

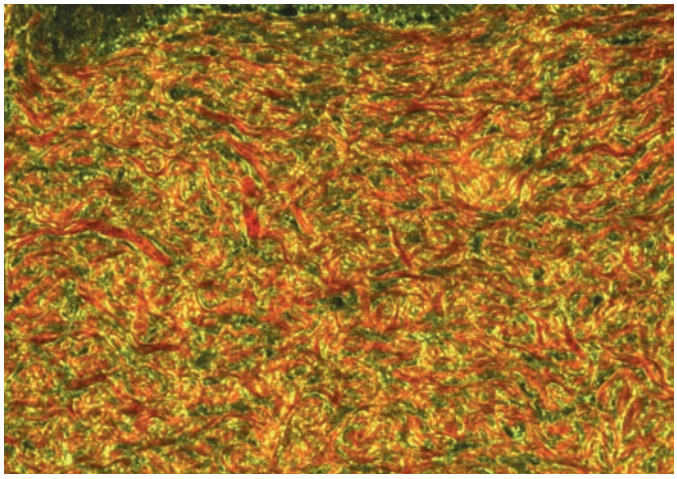


Figure 2: GSM-30 slide stained with Picrosirius, x100 magnification

Figures 3 and 4 represent the proliferation of collagen fibers in GS-14 and GSM-14, respectively, with green fibers and red fibers corresponding to type III and type I collagen.

DISCUSSION

Microneedling is currently emerging as a highly effective alternative for the correction of cutaneous scars as compared to classic ablative treatments, such as chemical peels, dermabrasion and lasers.[5] Unlike these, the microneedling technique is aimed at stimulating the production of collagen without causing the total removal of the epidermis, having been termed collagen induction therapy (CIT), since the inflicted microtraumas favor the release of chemical mediators, with a view to replace the damaged tissue with scar tissue.[14]

Among the variables analyzed in the present study, reepithelialization in the scars was taken into account. According to Campos et al.,[15] reepithelialization occurs early during the healing process, meaning this tales place still in the proliferative

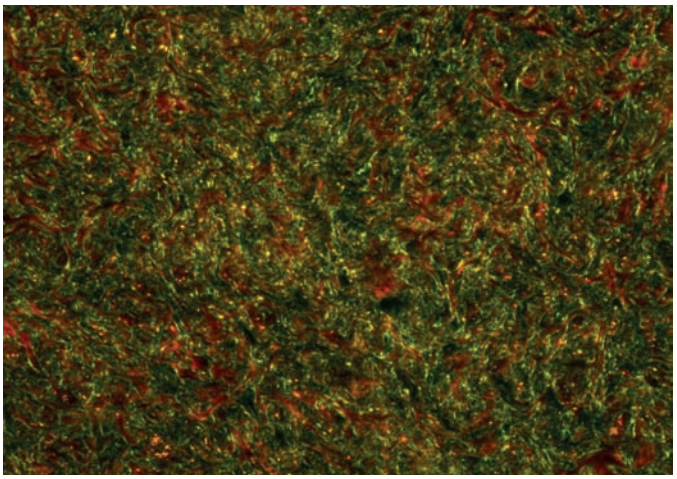


Figure 3: GC-14 slide stained with Picrosirius, x100 magnification

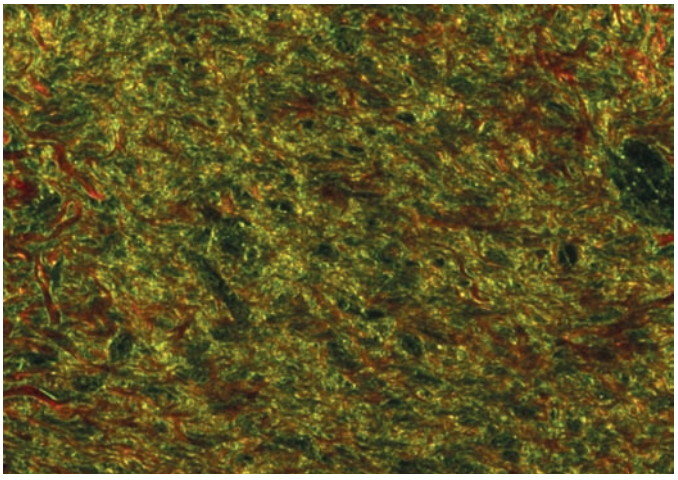


Figure 4: GSM-14 slide stained with Picrosirius, x100 magnification

phase, which comprises the first weeks of the cicatricial mechanism. The findings of the present study are in line with those of Campos et al.,[15] since all animals experienced complete reepithelialization of the induced lesion, since the time necessary for the completion of the natural reepithelialization process had already elapsed.

On the other hand, the animals that underwent microneedling had a small loss of integrity of the skin barrier at the time of the procedure, since the technique's principle consists of puncturing the epidermis without removing it, in order to trigger the cicatricial regeneration process proposed by microneedling. Thus, reepithelialization following the use of microneedles occurs more rapidly (within roughly 5 days), since the epidermis is not totally removed, but rather only perforated.[9]

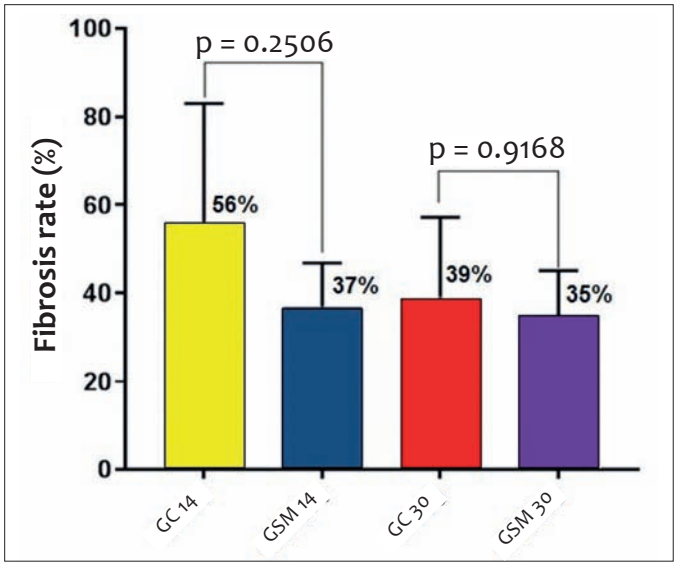
In light of this, the animals of the control groups (GS-14 and GS-30) experienced reepithelialization of the lesion in the first weeks, while the animals that underwent microneedling (GSM-14 and GSM-30) had a new reepithelialization after this procedure. However, no statistically significant difference was observed within the groups (p = 1), since reepithelialization had already been completed at the time of the histologic analysis due to the fact it is an early mechanism both in physiological healing and after the use of microneedles.

Another variable analyzed was the presence of granulation tissue. The production of this tissue originates at the beginning of the healing process (proliferative phase). It is predominantly composed of fibroblasts, which in turn will give rise to collagen, the main constituent of the final scar. The granulation tissue therefore undergoes a remodeling process during the healing process, meaning that it is progressively replaced by collagen fibers up until the point the latter predominate in the scar.

In this manner, the results obtained in the present study corroborate those of the literature, since all animals did not present granulation tissue at the end of the experiment, thus proving that the healing process had been completed.[17-19]

Regarding the proportion of fibrosis in the scars analyzed, the groups that underwent microneedling had fibrosis reduction as compared to the control groups. GSM-14 presented a mean reduction of 19% in the proportion of fibrosis regarding the total area of the wound, while in GSM-30 the fibrosis was reduced by 4% on average (Graph 1).

According to Fergunson et al.,[20] the TGF- β3 molecule induces a scar regenerative response, whereas TGF- β1 and TGF- β2 induce fibrotic scarring. Despite the fact that the effects of microneedling have not been analyzed in the present study, it can be inferred that the procedure provided reduction of fibrosis, corroborating the research of Aust et al.,[10] which proved that the microneedling technique is capable of inducing the expression of TGF-β3 – which is maintained over the following 2 weeks – as well as of decreasing the expression of TGF-β1 and TGF-β2. In light of this, the largest fibrotic reduction in GSM-



Graph 1: Percentage (%) of fibrosis in the scars of the groups evaluated at 14 and 30 days after microneedling.
Student's t-test: p = 0.2506 (GS-14 *versus* GSM-14) and p = 0.9168 (GS-30 *versus* GSM-30)
Source: Research protocol

14 is justified, since the scars in this group were analyzed exactly 2 weeks after the microneedling procedure.

In addition, the more modest degree of fibrosis reduction in GSM-30 might be justified by fact that a single microneedling session was performed in this study, given that other studies recommend microneedling sessions with monthly intervals for better outcomes.[21-23] As a conclusion, further research should be performed aimed at assessing the proportion of fibrotic tissue in the scars after monthly microneedling sessions, thus elucidating whether an increase in the number of sessions leads to a more effective reduction of fibrosis.

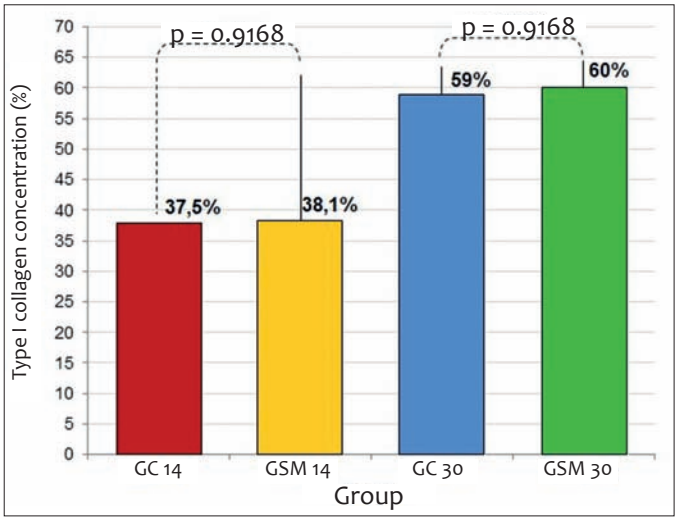
According to several studies – such as those by Cunha et al.,14 Tizzato et al.,[24] and Negrão et al.,[25] all of which performed in 2015, as well as that by Palheta et al.,[26], performed in 2016 – describe the action of microneedling on the stimulation of the production of collagen fibers and on the reconstruction of cicatricial tissue in the normal skin. Consequently, this technique improves the quality of scars. In this way, this study was expected to lead to outcomes that indicated a greater amount of collagen in the groups that underwent microneedling (GSM-14 and GSM-30).

In this sense, there was a numerical increase of both type III and type I collagens concentrations in GSM-14 as compared to GS-14, which did not undergo the technique. Taking into consideration the median percentage of type I collagen, it is possible to reaffirm the induction of the collagen production capacity generated by the microneedling technique. Although this increase was not statistically significant, there is a tendency to the expected result (Graph 2).

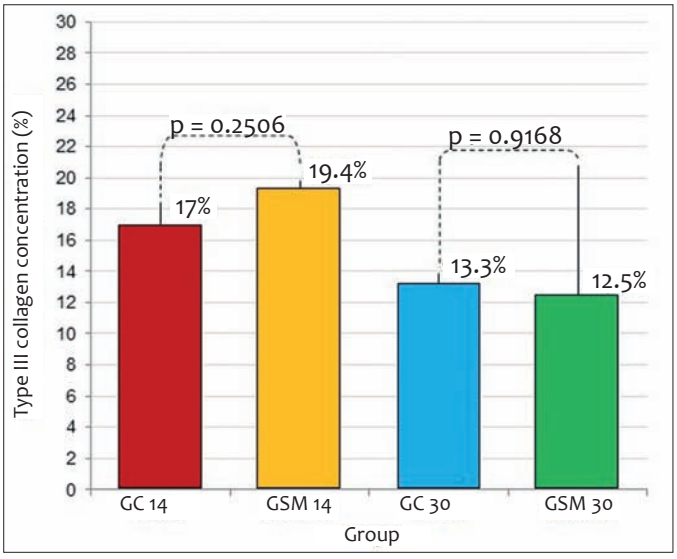
Based on the literature, CIT generates an increase in type I collagen – which is stronger and more resistant – and a decrease in the expression of type III collagen. In face of this, when analyzing the group with the longest experimental duration (GSM-30), type III collagen was lower when compared to the median of the group that did not undergo microneedling (GS-30). This fact suggests that the decrease in type III collagen is seen later on, after the procedure, since after 14 days the group that underwent microneedling (GSM-14) had a greater number of type III collagen fibers as compared to its control (Figure 4), although both groups did not present statistically significant differences (Graph 3).

Important data were derived from the comparative analysis of collagen type I concentration's percentiles between groups in both periods (Graph 4). The progression in GSM groups (14 and 30 days) revealed high rates of type I collagen as early as 14 days (GSM-14) following the microneedling session when compared to GS-14 (Graph 4), which did not undergo the technique. This number then remains almost constant for up to 30 days (GSM-30). This result is in line with studies that indicate the presence of induction of collagen production by the technique, suggesting promising results already within a period of 14 days after the procedure.

Nevertheless, doubts may arise regarding the number of subsequent sessions, in the optimization of this outcome based on the repetition of sessions for enhancing results within the



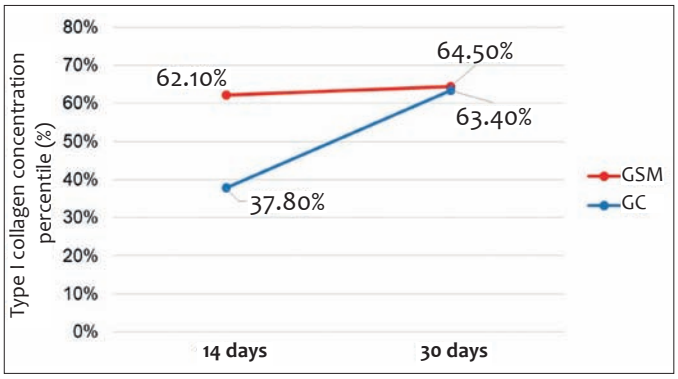
Graph 2: Median concentration of type I collagen in the groups evaluated at 14 and 30 days after microneedling
Mann-Whitney test.: p = 0.9168 (GS-14 *versus* GSM-14) and p = 0.9168 (GS-30 *versus* GSM-30)
Source: Research protocol



Graph 3: Median concentration of collagen type III in the groups evaluated at 14 and 30 days after microneedling
Mann-Whitney test.: p = 0.2506 (GS-14 versus GSM-14) and p = 0.9168 (GS-30 versus GSM-30)
Source: Research protocol

30-day post procedure period, as suggested by Zeitter et al. in a recent study. These authors found more effective results with 4 sessions as compared to the group that underwent only 1 session in atrophic scars. Therefore further studies should be carried out aimed at establishing the ideal number of sessions for normotrophic scars.[22]

Regarding type III collagen, a different trend was observed in the comparison of groups. Although GSM-14 and GSM-30 maintained an almost constant pattern, there was a decrease in type III collagen in GS-14 and GS-30. These data



Graph 4: Concentration percentile of collagen type I in GSM (scar + microneedling) and in GC (control groups), evaluated at 14 and 30 days after the microneedling procedure;
Kruskall-Wallis analysis of variance (results expressed in percentiles): *p* = 0.5410 (GSM-14 *versus* GSM-30) and p = 0.5410 (GS-14 *versus* GS-30).
Source: Research protocol

can be attributed to the natural replacement of collagen type III by type I collagen, a phenomenon already described in the literature. Other studies using microneedling with microneedles of various lengths focusing on the evaluation of the frequency of and interval between treatments for enhanced effects would be the next appropriate step to further confirm the effectiveness of the microneedling technique.[28]

While outcomes in GC14 and GC30 were not constant, it was possible to observe low values of type I collagen in 14 days (GS-14) as well as an exponential increase from 14 to 30 days (GS-30) – which occurs physiologically in the healing process – without, however, statistical significant difference between the groups. It was also observed that at 14 days the group that underwent previous microneedling had greater amounts of type I collagen fibers than the one that did not. In contrast, at the end of the 30-day period, both had similar amounts of this collagen, which suggests the necessity of further studies with larger samples and their respective long-term outcomes, aiming at defining the ideal number of sessions.[27]

CONCLUSION

Therefore, based on the outcomes of the present experimental study, it was possible to conclude that the microneedling technique was proven effective in stimulating collagen fibers in scars resulting from induced lesions. Although there was no statistical difference in the analyzes performed, it can be inferred that there was a tendency for improvement of the scars as a result of the decrease in fibrotic tissue, as well as greater production of collagen fibers, which have been shown to promote scar regeneration caused by the use of microneedles.

Regarding the studied experimental time lapses, it can be inferred that the production of both types of collagen (I and III) is more intense during the 14 day-period following microneedling, as compared to the control, with greater expression of type I collagen fibers. Regarding the 30-day post procedure period, it was observed that the animals that underwent microneedling had an effective replacement of type III collagen with type I collagen – a necessary and beneficial event in the cicatricial regeneration process.

In this manner, microneedling acts by stimulating a greater production of collagen fibers – especially type I – in a shorter period (14 days), and that remain constant on subsequent days. In the 30-day period after the procedure, the replacement of collagen fibers is more effective.

Align with these findings, further experimental studies should be performed aimed at elucidating whether monthly microneedling sessions – rather than a single session – would promote better outcomes, both by stimulating increased production of type I fibers and promoting the effective replacement of type III collagen with type I collagen in the long run. ●

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DECLARATION OF PARTICIPATION:

Andressa Miléo Ferraioli Silva | ORCID 0000-0001-8276-0676
Conceptual development, initial write up of the manuscript, data acquisition and analysis, final conceptual and methodological review of the research project, approval of the manuscript's final version

Wanessa Cardoso Praia | ORCID 0000-0003-1912-695X
Conceptual development, initial write up of the manuscript, data acquisition and analysis, final conceptual and methodological review of the research project, approval of the manuscript's final version

Caroline da Silva Alves Palheta | ORCID 0000-0001-8989-9101
Conceptual development, final write up, conceptual and methodological review, general oversight of the research project, approval of the final version

Rodrigo Paracampo Couteiro | ORCID 0000-0003-2854-159X
Data analysis, manuscript write up, final conceptual and methodological review of the research project, final approval of the manuscript

Andrew Moraes Monteiro | ORCID 0000-0002-3549-881X
Conceptual development, initial write up of the manuscript, data acquisition and analysis, final conceptual and methodological review of the research project, approval of the final version

Luciana Mota Silva | ORCID 0000-0002-4417-7401
Preparation of histological material and analysis, data analysis, final conceptual and methodological review of the research project, approval of the final version

Ismari Perini Furlaneto | ORCID 0000-0001-9941-0162
Data analysis, statistical analysis of results, approval of the final version

Josie Eiras Bisi dos Santos | ORCID 0000-0001-8512-3920
Conceptual development, histological data analysis, final conceptual and methodological review of the research project, approval of the final version

Miguel Saraty de Oliveira | ORCID 0000-0002-0971-8671
Conceptual development, initial write up of the manuscript, data analysis, final conceptual and methodological review of the research project, approval of the final version

Original Articles

Autors:
Raissa de Lima Gadelha[1]
Daniele Loureiro Mangueira Paiva[1]
Carla Wanderley Gayoso[1]
Juliana Nunes Maciel Cilento[1]

[1] Dermatology Service, Hospital Universitário Lauro Wanderley, Universidade Federal da Paraiba - João Pessoa (PB), Brazil.

Correspondence:
Raissa de Lima Gadelha
Rua Carlos Ulisses de Carvalho, Número: 25, Apartamento: 901, Brisamar
58033-130, João Pessoa, PB
Brasil.
E-mail: raissalimagadelha@hotmail.com

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Pulsed radiofrequency for periorbital sagging: a comparative study

Radiofrequência pulsada para flacidez periorbitária: estudo comparativo

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ABSTRACT

Introduction: Wrinkles, sagging, changes in texture and skin pigmentation in the periorbital region are common complaints in dermatologic practices. Several treatment options, including fractional radiofrequency, which has been shown safe and effective, have been described.

Objective: To compare outcomes and side effects after the use of two types of electrodes coupled to a radiofrequency device, used for rejuvenating the eyelid region.

Methods: A comparative, randomized and blind clinical trial was carried out with patients bearing aging in the periorbital region. The patients were treated with two different electrodes (called standard tip and Lima 8 tip), which can be coupled to the same radioelectrosurgery device. The variables investigated were sagging, wrinkles, texture and firmness of the treated skin, in addition to the presence of adverse effects. Thirty days after the last session, patients answered to a satisfaction questionnaire, having been photographed for clinical assessment.

Results: The patients treated with both tips experienced considerable satisfaction with the improvement of sagging and wrinkles. The variable firmness presented worse satisfaction indices, with a disadvantage for the standard tip. Important edemas emerged after the use of both tips; nevertheless ecchymosis occurred most frequently and lasted longer with the Lima 8 tip. Hyperpigmentation was more frequent and longer lasting with the standard tip, however without statistically significant difference.

Conclusions: The two tips were equally effective for the treatment of sagginess, wrinkles and skin texture in the periorbital region. The patients treated with the Lima 8 tip had higher satisfaction indices regarding the skin's firmness, experiencing a higher incidence of ecchymosis, as well as a longer duration of that side effect.

Keywords: Eyelids; Pulsed radiofrequency Treatment; Skin aging

RESUMO

Introdução: *Rugas, flacidez, alterações da textura e da pigmentação da pele da região periorbitária são queixas comuns nos consultórios dermatológicos, para as quais têm sido descritas várias opções terapêuticas, entre elas a radiofrequência fracionada, que se tem mostrado segura e eficaz.*

Objetivo: *Comparar os resultados e efeitos colaterais após o uso de dois tipos de eletrodos acoplados a um aparelho de radiofrequência, para o rejuvenescimento da região palpebral.*

Métodos: *Trata-se de ensaio clínico comparativo, randomizado e cego com pacientes portadores de envelhecimento da região periorbitária, tratados com dois eletrodos diferentes, que podem ser acoplados a um mesmo aparelho de radioeletrocirurgia, denominados ponteira-padrão e ponteira Lima 8. Os aspectos investigados foram flacidez, rugas, textura e tonalidade da pele tratada, além da ocorrência de efeitos adversos. Trinta dias após a última sessão, os pacientes responderam a um questionário de satisfação e foram fotografados para julgamento clínico.*

Resultados: *Os pacientes tratados com ambas as ponteiras apresentaram expressiva satisfação com a melhora de flacidez e rugas. O item tonalidade apresentou piores índices de satisfação, com desvantagem para a ponteira-padrão. O edema foi importante após o uso de ambas as ponteiras, mas as equimoses ocorreram em maior frequência e por maior duração com a ponteira Lima 8. Houve maior ocorrência de hiperpigmentação e com maior duração com a ponteira-padrão, mas sem diferença estatisticamente significativa.*

Conclusões: *As duas ponteiras mostraram-se igualmente eficazes para o tratamento de flacidez, rugas e textura da pele da região periorbitária. Os pacientes tratados com a ponteira Lima 8 apresentaram maiores índices de satisfação com relação à tonalidade da pele, com maior ocorrência de equimoses, bem como maior duração do evento.*

Palavras-Chave: *Envelhecimento da pele; Pálpebras; Tratamento por radiofrequência Pulsada*

INTRODUCTION AND OBJECTIVE

Skin aging is a complex biological phenomenon that comprises intrinsic and extrinsic processes, producing visible manifestations such as wrinkles, sagginess, dryness and heterogeneous pigmentation of the skin. These changes are histologically associated with the quantitative and qualitative changes in the elastic and collagen fibers, atrophy and reduction of the dermoepidermal junction.[1]

The periorbital region is one of the first to show the signs of aging. Due to their delicate nature and safety concerns linked to the proximity of the eyeball, treatment options are limited.[2,3]

The currently available methods for the rejuvenation of the periorbital region include blepharoplasty, botulinum toxin, hyaluronic acid based cutaneous filling, dermabrasion, 88% phenol or 35% trichloroacetic acid chemical peels, microneedling, diverse radiofrequency modalities and ablative and non-ablative laser therapy. Despite the efficacy of these methods, their costs, potential side effects, long recovery periods and prolonged inactivity after the procedure correspond to limitations to their application.[4-6]

Radiofrequency uses electromagnetic radiation to generate heat and reach deeper tissues, keeping the skin's surface cool and protected. This energy causes immediate contraction and denaturation of the existing collagen fibers in the dermis, leading to the stimulation of new collagen and elastic fibers synthesis. This reorganization lends increased efficiency to them for supporting the periorbital skin.[7,8]

Fractional radiofrequency is a procedure that uses a random energy fractioning system that respects the tissue's thermal relaxation time, similarly to what happens with fractional CO laser, although with a different energy source.[9] This technique has allowed cost effective rejuvenation, with a low rate of complications, thus becoming more accessible as compared to lasers, yet with very similar outcomes.[10] More recently, a pulsed radiofrequency system has been created using electrodes with microneedles that penetrate the epidermis to provide radiofrequency pulses directly into the upper dermis. This technique was proven equally effective and with fewer side effects when compared to traditional fractional ablation procedures.[11]

The objective of the present study was to compare the results obtained in the treatment of wrinkles, sagginess, texture and skin tone of the periorbital region after the use of two different fractional radiofrequency tips coupled to a radiofrequency device, as well as the occurrence of adverse effects in both procedures.

METHODS

A randomized, blind, comparative, non-placebo clinical trial was performed, in which patients at the Dermatology Outpatient Clinic of the Hospital Universitário Lauro Wanderley, with aging in the periorbital region's skin and who wished to undergo rejuvenation treatment were selected (April to June 2017).

The sample of 92 patients had the following characteristics: mild to moderate periorbital sagginess, absence of indication for blepharoplasty, older than 18, absence of comorbidities that prevented the use of the device, such as the use of pacemakers or collagen diseases.

The softwares employed to determine sample size were the R and PS, available for download at http://www.r-project.org/ and biostat.mc.vanderbilt.edu, respectively.

All patients were adequately informed about the procedures and risks of the research project, having signed a Term of Free and Informed Consent and authorized the publication of photographs. The study was approved by the Research Ethics Committee of the institution.

The patients underwent three sessions with the FRAXX® radiofrequency device (Loktal Medical Eletronics Industria e Comércio Ltda, São Paulo (SP), Brazil), with intervals of 30 and 60 days, in April - September 2017. Photographic records were prepared before and one month after the third session.

All sessions were performed by the same applicator physician under topical anesthesia with 4% lidocaine cream (Dermomax® Aché, Guarulhos (SP), Brazil) and injection of 2% lidocaine with epinephrine, followed by aqueous chlorhexidine cleansing, and skin moisturizing with gauze and sterile saline solution. The FRAXX® radiofrequency device with Wavetronic 5000 was used in CUT mode in the following ways:

1) Megapulse, 60% power, sequence 2, active for 60ms, 60ms of delay, coupled to the standard tip with 64 microneedles (8x8) (half of the patients);

2) Single pulse, 30% power, active for 30ms, coupled to the 2.5mm Lima 8 tip (in the other half of the patients).

The limit of the application area was 2mm from the ciliary border in the lower eyelid and the palpebral fold in the upper eyelid. In the post-procedure, the patients used micropore tape for 24 hours, Cicaplast Baume® regenerator (La Roche Posay, Rio de Janeiro (RJ), Brazil) twice daily for five days, and SPF60 sunscreen. The first return visit took place five days after, aimed at evaluating side effects such as edema, echymoses and ulcerations. Thirty days after the last session, patients answered the satisfaction questionnaire and were photographed for clinical assessment. The questionnaire classified the degree of satisfaction into: dissatisfied, satisfied, and very satisfied. The authors of the present study also evaluated the occurrence of adverse effects, such as edema, ecchymosis, hyperchromia and others.

From that point on, classic descriptive statistics techniques were used. The database was built and analyzed by the statistical software R 3.3.1 for Windows. The sample was obtained using a probabilistic, simple random sampling method for estimation of a population proportion. A confidence level of 95% and an estimation error of 6% were considered.

RESULTS

The sample with 92 patients was subdivided into two groups of 46: one of the groups, consisting of patients who underwent treatment with the standard tip, was denominated *Standard Group*, and the other group, with patients who underwent treatment with a Lima 8 tip, was denominated *Lima 8 Group*.

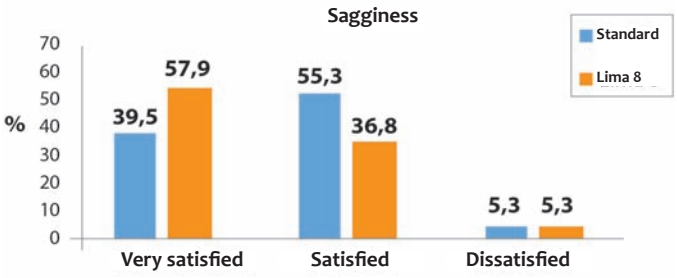
Of the 46 patients in the Standard Group, one dropped out of the study after the first session, while five followed suit after the second session. Of the 46 patients in the Lima 8 Group, four gave up after the first session, with three following suit after the second session. Three patients were excluded: two due to having been treated with botulinum toxin and one for having undergone cutaneous filling during the course of the study. After taking into account the exclusions, the final sample size was 76 patients – 38 in the Standard Group and 38 in the Lima 8 Group. The percentage of female patients was 92% in both groups. There was a higher prevalence of phototype III patients in both groups, with 60.5% in Standard Group and 47.4% in Lima 8 Group. Phototypes V and VI were found only in Lima 8 Group. Regarding the age, the groups had similar mean ages: 47.21 years in Standard Group, with a standard deviation of 9.19 years, and 47,55 years in Group Lima 8, with a slightly lower standard deviation (7.47 years).

Regarding the patient satisfaction results linked to the evaluated treatments, the investigated aspects were *sagginess*, *wrinkles*, *texture* and *tone* of the treated skin. The results are summarized in Graphs 1 to 4. For the aspect *sagginess*, 57.9% of the patients who underwent treatment with the Lima 8 tip reported being very satisfied, while in the Standard Group that ratio was 39.5%; 55.3% of the patients were satisfied with the outcomes of the treatment in Standard Group while 36.8% has the same opinion in Lima 8 Group. In general, both treatments presented expressive results regarding sagginess, since the aggregate percentages (very satisfied and satisfied) were 94.8% and 94.7% for the Standard Group and Lima 8 Group, respectively.

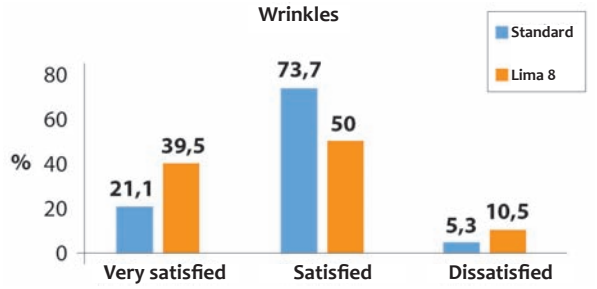
Regarding the aspect *wrinkles*, more than half of the patients were satisfied with both treatments, whose percentages were 73.7% for the Standard Group and 50% for Lima 8 Group. Evaluating the level of aggregate satisfaction, the percentages of very satisfied and satisfied patients were 94.8% (Standard Group) and 89.5% (Lima 8 Group).

Regarding the aspects *texture* and *tone*, the results indicated that the highest percentages of patients classified as very satisfied were found in Lima 8 Group – 50% and 44.7% for texture and tone, respectively. For the Standard Group, these percentages were 28.9% and 18.4%, respectively. In general, regarding texture and tone, the compared procedures yielded similar results, with the accumulated percentages for the category very satisfied and satisfied with the *texture* being 97.3% (Standard Group) and 97.4% (Lima 8 Group), and 65,8% (Standard Group) and 68.4% (Lima 8 Group) with the *tone*. The results also indicated that the item *tone* was associated with the worst satisfaction index when compared to the other items, for both treatments being compared.

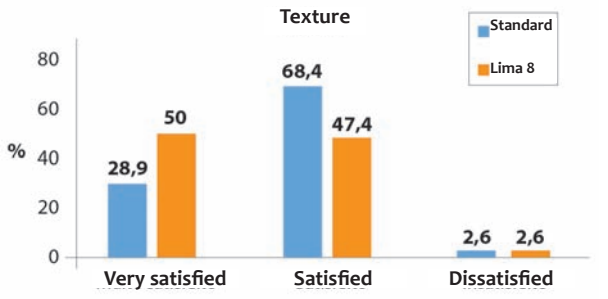
Comparison tests were applied using the chi-square homogeneity test aimed at comparing the patients satisfaction regarding the therapies being analyzed. The p-values of the tests for each investigated aspect were considered significant when $p < 0.05$. As shown in Table 1, the results showed that for the *sagginess*, *wrinkles* and *texture* there were no significant statistical differences (p-values > 0.05), meaning that both treatments yielded very similar results regarding the satisfaction with the results. Nevertheless, regarding the aspect *tone*, there was a significant difference between the treatment with the standard tip and that based on the tip Lima 8, at the specified significance level (p-value = 0.0272), according to Table 1.



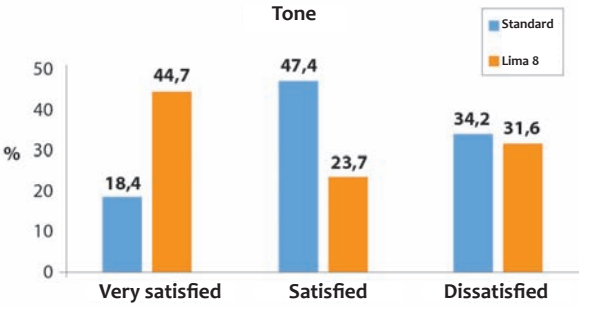
Graph 1: Percentage distribution of the patients' satisfaction regarding the aspect *sagginess*



Graph 2: Percentage distribution of the patients' satisfaction regarding the aspect *wrinkles*



Graph 3: Percentage distribution of the patients' satisfaction regarding the aspect *texture*



Graph 4: Percentage distribution of the patients' satisfaction regarding the aspect *tone*

Regarding the main side effects, edema, ecchymosis and darkening were evaluated (Table 2). Regarding the occurrence of edema, both treatments presented an equal and expressive percentage: 94.7%. Of the patients who underwent treatment with the Lima 8 tip, 86.8% had ecchymosis as an adverse effect – a higher frequency than that of the Standard Group (57.9%). Darkening was present in 63.2% of the patients in Standard Group and in less than half of those in Lima 8 Group.

Based on the evaluation of the significant differences between the treatments regarding adverse effects, it was possible to verify that only for ecchymosis there were significant differences between the treatments, with a p-value of 0.0094.

Considering the variable *days of edema*, it was possible to observe that the mean duration was 3.08 ± 1.05 days in the Standard Group and 3 ± 1.37 days in for Lima 8 Group. Regarding the *days of ecchymosis*, the mean value was 3.73 ± 1.7 days for the treatment with the standard tip, and longer with the Lima 8 tip, whose mean duration was 6.18 ± 3, 27 days. As for the *days of darkening*, it was longer for the standard tip than it was for the Lima 8 tip.

Aiming at observing the statistically significant differences between the duration of the adverse effects' persistence of the treatments, comparative tests were conducted. The non-parametric counterpart of the Student t-test and the U-Mann-Whitney test were used.

As can be seen in Table 3, it was possible to verify that at the specified level of significance for the variable *days of ecchymosis*, there were significant differences between the treatments being compared, indicating a longer duration of side effects for the Lima 8 tip. For the variables *days of edema* and *days of darkening*, the tests did not suggest significant differences (p-value > 0.05), although in the exploratory analysis it was evidenced that the treatment with the standard tip was associated with longer durations of side effects.

Figures 1 and 2 show some of the results obtained, while Figure 3 depicts some of the adverse events observed in this study.

Table 1: Frequency distribution regarding aspects and treatment

		Tip				
		Standard		Lima 8		*p-value*
Aspect		n	%	n	%	
Sagginess	Very satisfied	15	39.5	22	57.9	0.3187**
	Satisfied	21	55.2	14	36.8	
	Dissatisfied	2	5.3	2	5.3	
Wrinkles	Very satisfied	8	21.1	15	39.5	0.1199**
	Satisfied	28	73.6	19	50	
	Dissatisfied	2	5.3	4	10.5	
Texture	Very satisfied	11	28.9	19	50	0.1459**
	Satisfied	26	68.5	18	47.4	
	Dissatisfied	1	2.6	1	2.6	
Tone	Very satisfied	7	18.4	17	44.7	0.0272*
	Satisfied	18	47.4	9	23.7	
	Dissatisfied	13	34.2	12	31.6	

*** chi-square test value**
**** chi-square test permutation value**

Table 2: Percentage distribution of the occurrence of side effects for the Standard and Lima 8 treatments

		Tip				
Side effect		Standard		Lima 8		p-value
		n	%	n	%	
Edema	Yes	36	94.7	36	94.7	1**
	No	2	5.3	2	5.3	
Ecchymosis	Yes	22	57.9	33	86.8	0.0094*
	No	16	42.1	5	13.2	
Darkening	Yes	24	63.2	16	42.1	0.1072*
	No	14	36.8	22	57.9	

*** chi-square test value**
**** exact Fisher's test value**

Table 3: Descriptive measures for the variables days of edema, days of ecchymosis and days of darkening for the Standard and Lima 8 Groups

	Tip					
Statistics	Days of edema		Days of ecchymosis		Days of darkening	
	Standard	Lima 8	Standard	Lima 8	Standard	Lima 8
n	38	38	38	38	38	38
Nas	2	2	16	5	14	22
Mean	3.08	3	3.73	6.18	29.58	22.13
Median	3	3	3,5	7	30	30
Standard deviation	1.05	1.37	1.7	3.27	17.61	10.07
Minimum	1	1	1	2	2	3
Maximum	5	7	7	20	60	30
p-value	-	0.5837	-	0.0008	-	0.1640

DISCUSSION

Periorbital wrinkles mainly arise as a result of photoaging and repetitive muscle contraction over time. Treatment of the periorbital area is difficult due to its delicate nature and important function. To avoid eye lesions and complications, such as scars and ectropion, it is important to control the depth of treatment. A minimally invasive approach using microneedles is capable of accurately controlling the depth of treatment, meaning a lower risk is expected as compared to those of the other technologies. The positive therapeutic result is believed to result from a combination of the effects of radiofrequency and microneedling.[12]

Some studies on the thermal effects of fractional radiofrequency delivered by microneedles to *in vivo* skin have shown the formation of a confined zone of denatured collagen or radiofrequency thermal zone. The presence of superficial perivascular inflammatory cells infiltrates was described in these studies from the first day of the procedure, with a initial peak of neutrophils – that progress to lymphocytes – in 7 (and up to 30) days. The areas of denatured collagen were replaced by newly formed collagen fibers three months after a single session, which was evidenced by the increased presence of mucin in the treated area. There was also an increase in elastic fibers and a progressive

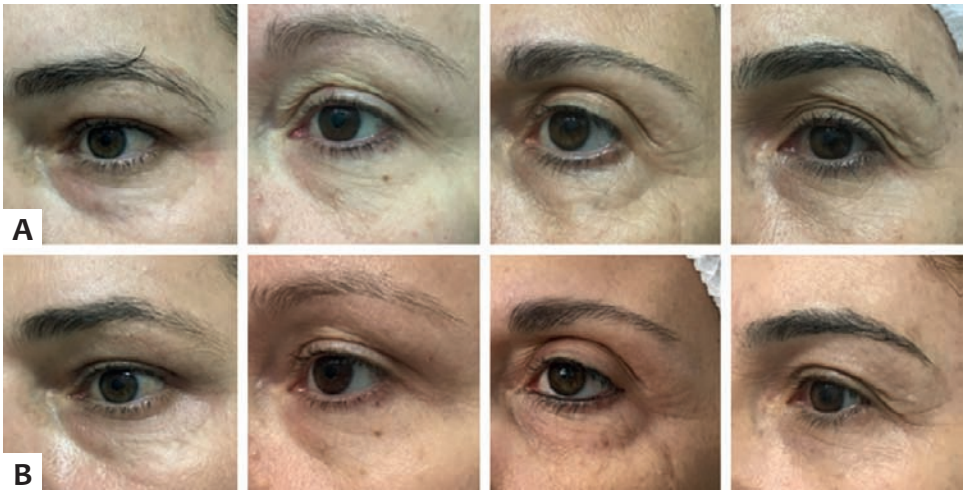


Figure 1: A - Pretreatment**; B -** Post treatment with Lima 8 tip

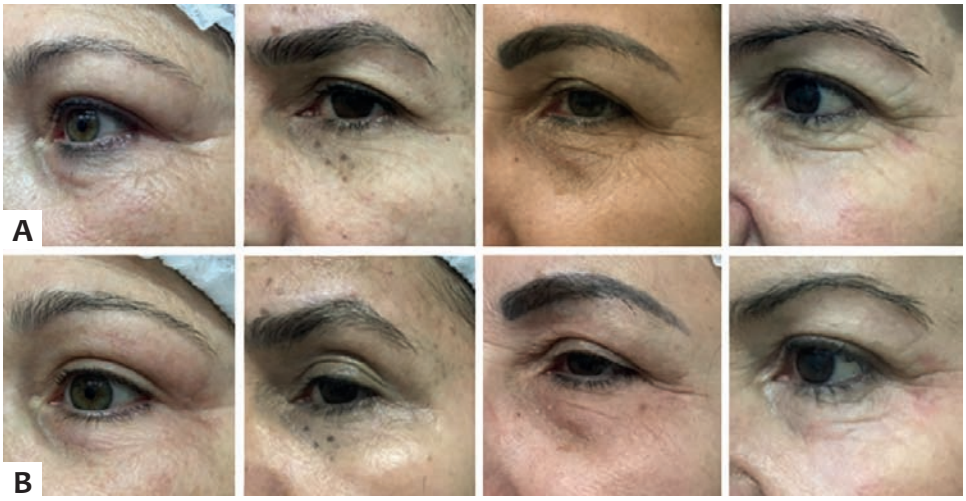


Figure 2: A - Pretreatment**; B -** Post-treatment with Standard tip

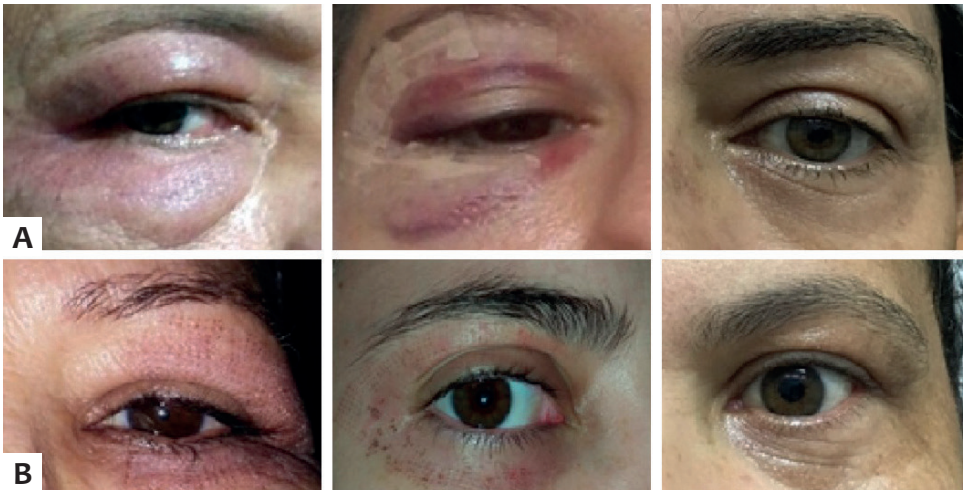


Figure 3: A - Adverse effects occurred with the use of the Lima 8 tip (edema, ecchymosis and post-inflammatory hyperchromia);
B - Adverse effects occurred with the use of the Standard tip (crusting, erythema, edema and post-inflammatory hyperchromia);

decrease in the density of melanin incontinence, with total disappearance after three months of follow-up.[13]

One study used fractional radiofrequency microneedling (RFXEL®) in the region of the eyes of 11 patients. The treatment's side effects were minimal as compared to those of conventional ablative and non-ablative lasers. Pain was minimal in almost all patients who used topical anesthetic creams, and bleeding was transient when compared to that of isolated microneedling or dermabrasion. The crusts disappeared within a week, and no patient reported post-inflammatory hypo or hyperpigmentation.[12]

In a comparative study between fractional radiofrequency with multineedles and botulinum toxin in the periorbital region, it has been demonstrated that radiofrequency treatment can better regenerate elastic and collagen fibers as compared with botulinum toxin, meaning that the first can be effective for the rejuvenation of static wrinkles. This study noticed prompt patient satisfaction with botulinum toxin type A, nonetheless the effect decreased in the 18-week follow-up. On the other hand, radiofrequency gradually and slowly improved the wrinkles, and provided greater satisfaction up until the 18th week of the follow-up.[14]

In the same study, fractional radiofrequency (INFINI®) was used with 49 microneedles, in three sessions (0, 3 and 6 weeks) in the periorbital area of 9 patients. In that study, three patients dropped out (25%) and the pain ranged from painless to intolerable. Hematomas improved within a week, and there was no crusting, hypopigmentation or infection. Two patients (22.2%) reported postinflammatory hyperpigmentation, which resolved spontaneously in two months.[14]

Another study used fractional radiofrequency (FRAXX®) with 64 microneedles (measuring 0.2mm in thickness and 0.8mm in length), in the megapulsed mode. Anatomopathological studies verified that epidermal (ablative) perforation measured 0.1mm and that the thermal effect on the dermis (non-ablative) was 0.1mm deep, meaning that it reached the papillary dermis, with negligible lateral thermal effect and total preservation of the tissue located between the perforations. In that study, a single session was performed with three passes in the lower eyelids of 20 patients, of which 18 were very satisfied (90%), and two (10%) were only satisfied with the outcomes. The edema lasted on average 3 days before disappearing; the erythema, 17 days; and the crusts, 10 days. Two patients (10%) had postinflammatory hyperpigmentation in the treated region, which was resolved after use of the topical combination of hydroquinone with tretinoin for 15 days.[15]

In the present study, three sessions were performed, with intervals of 30 and 60 days, in 38 of the 76 patients, using the same power, active and delay parameters, and methodology. A total of 39.5% of patients were very satisfied while 53.3% were satisfied with the outcomes obtained regarding the variable *sagginess*. Likewise, 21.1% were very satisfied and 73.7% were satisfied regarding the improvement in the variable *wrinkles*. Edemas lasted on average 3.1 days, while ecchymoses lasted 3.7 days, with postinflammatory hyperpigmentation occurring in 63.2% of the patients and lasting on average 29.6 days. Other side effects observed in the present study were: burning sensation (15.7%), pruritus (15.7%), crusting (13.1%), ulceration (5.2%), acneiform eruption (2.6%), and contact eczema (2.6%). On a diverse study, fractional radiofrequency (FRAXX®) was applied with 8 microneedles (Lima 8), this time in single pulsed mode. These needles are 0.1mm thick and 2.5mm long, and it is possible to reach the epidermis, dermis and, sometimes, the periorbital musculature, with them, causing contraction and intense stimulation of collagen. In that study, a single session was performed on the upper and lower eyelids of 19 patients, without overlap. The patients, who were between 42 and 67 years old, their Fitzpatrick's phototype ranging from II and IV, all reported satisfaction with the results (good and very good). The pain was considered tolerable, and the edemas and hematomas lasted between 5 and 7 days. Postinflammatory hyperpigmentation occurred in 11 patients (58%) and was resolved within 20 to 30 days with the use of whitening formulations. No infections, achromia, ectropion or unsightly scars were observed in this group.[16]

In the present study, 3 sessions were performed with intervals of 30 and 60 days, in 38 of the 76 patients included in the study, observing the same power and active parameters, and methodology. The ages in the sample varied between 30 and 61 years, with a mean value of 47.5 years, while the Fitzpatrick's phototypes ranged from II to VI, with phototype III being the statistical mode, with 47.4% of the patients. There was satisfaction with the results in *sagginess* among 94.7% of patients (aggregate satisfaction = very satisfied and satisfied), and 89.5% regarding *wrinkles*. Regarding the side effects, the authors of the present study obtained results in line with a study by Lima,[16] with a mean edema duration of 3 days, and mean ecchymosis duration of 6.2 days. Regarding postinflammatory hyperpigmentation, 42.1% of the patients had it – less than the 58% observed by Lima[16] – having experienced resolution in 22.2 days on average. There were no infections, hypochromia or scaring. Other side effects were pruritus (15.7%), increased local sensitivity (2.6%), acneiform eruption (2.6%), and contact eczema (2.6%).

When comparing the satisfaction with the results obtained with the standard tip and the Lima 8 tip regarding *sagginess*, *wrinkles*, *texture* and *skin tone*, there were significant differences between the treatments only in the variable *tone* (p-value = 0.0270), for a significance level of 5%, with an advantage in favor of the Lima 8 tip.

As for the occurrence of side effects, such as edema, ecchymosis and postinflammatory hyperpigmentation, there were significant differences between treatments only for ecchymosis, which was more frequently with the Lima 8 tip – a fact that can be justified by the different lengths of the needles (Lima 8 = 2.5mm and Standard = 0.8mm). As expected, there was also a significant difference in the duration of ecchymosis, with a mean value of 6.2 days for the Lima 8 tip, and 3.7 days for the Standard tip.

As is the case in other studies, the authors of the present study cannot state that the results obtained were the best possible. In addition, there is still no consensus on the ideal number of passes, or on the maximum or minimum number of sessions for an optimal outcome. There are also a large number of radiofrequency devices available worldwide operating in different pulse delivery modes, types of tips, and needle sizes, with variations in the used power level, making it difficult to compare the methodology, results and effects of radiofrequency devices.

In this way, this legitimates the comparison proposed by the authors of the present article, by analyzing the results obtained employing the 64 micro-needles tip and the Lima 8 tip, given that the same radiofrequency device (Wavetronic coupled to the FRAXX® fractional system) is used in both cases. ●

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DECLARATION OF PARTICIPATION:

Raissa de Lima Gadelha | ORCID 0000-0002-9531-1973
Critical review of the literature, research implementation, conceptual development and planning of the study; data acquisition, analysis and interpretation; statistical analysis, approval of the final version of the manuscript

Daniele Loureiro Mangueira Paiva | ORCID 0000-0001-7440-7127
Conceptual development and research planning, research project guidance, propaedeutic and / or therapeutic approach development, critical review of the manuscript, approval of the final version

Carla Wanderley Gayoso | ORCID 0000-0002-8031-4143
Conceptual development of the propaedeutic and / or therapeutic approach, critical review of the manuscript

Juliana Nunes Maciel Cilento | ORCID 0000-0002-4753-104X
Conceptual development of the propaedeutic and / or therapeutic approach, critical review of the manuscript

Profile of surgically treated lesions in toes and fingers, at a dermatology referral service

Perfil das lesões tratadas cirurgicamente em pododáctilos e quirodáctilos em um serviço de referência de dermatologia

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ABSTRACT

Introduction: Lesions in fingers and toes are frequent in the dermatological practice, and diagnosis is feasible in the majority of cases after a thorough anamnesis and physical examination.

Objective: To draw a profile of the most prevalent lesions in toes and fingers that were surgically approached by the dermatologic surgery team, at a dermatologic referral service, as well as to evaluate the classification of these lesions, their distribution among age groups and genders, and the correlation between clinical suspicion and anatomopathological diagnosis.

Methods: A retrospective observational study was performed with 344 patients, and the evaluation of 367 surgical procedures.

Results: The analysis showed that most of the procedures were performed in female adults, with the left hallux being the most affected location in the studied sample. It was also verified that the majority of the procedures were linked to lesions of traumatic nature, with biopsy/excision and canthoplasty/canthotomy being the most accomplished procedures.

Conclusions: The results of the present study contribute to the planning and design of future dermatological care.

Keywords: Ambulatory surgical procedures; Fingers; Toes

RESUMO

***Introdução**: As lesões em quirodáctilos e pododáctilos são frequentes na prática dermatológica, sendo possível diagnosticar a maioria após anamnese completa e exame físico.*

***Objetivo:** Traçar perfil das lesões mais prevalentes em pododáctilos e quirodáctilos abordadas cirurgicamente pela equipe de cirurgia dermatológica em um serviço de referência em dermatologia, bem como avaliar a classificação dessas lesões, sua distribuição nas faixas etárias, gêneros, locais de acometimento e a correlação entre a suspeita clínica e o diagnóstico anatomopatológico.*

***Métodos:** Estudo epidemiológico observacional retrospectivo transversal incluindo e avaliando 344 pacientes e 367 procedimentos cirúrgicos.*

***Resultados:** A análise demonstrou que a maior parte dos procedimentos foi realizada em adultos, do sexo feminino, sendo o hálux esquerdo a localização mais acometida na amostra estudada. Verificou-se também que a maioria dos procedimentos decorreu de lesões de natureza traumática, sendo a biópsia/exérese de lesões e a cantoplastia/cantotomia os procedimentos mais realizados.*

***Conclusões:** Os resultados deste estudo contribuem para o planejamento e dimensionamento de futuros atendimentos dermatológicos.*

***Palavras-chave**: Dedos; Dedos do pé; Procedimentos cirúrgicos ambulatoriais*

Original Articles

Autors:
Luisa Preisler [1]
Ludmilla Cardoso Gomes [1]
José Roberto Pereira Pegas [1]

[1] Complexo Hospitalar Padre Bento de Guarulhos, Guarulhos (SP), Brazil.

Correspondence:
Luisa Preisler
Ambulatório de Dermatologia
Av. Emílio Ribas, 1819, Bairro Gopouva
CEP 07051- 000 - Guarulhos (SP), Brasil
E-mail: luisapreisler@gmail.com

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INTRODUCTION

Lesions in fingers and toes are common in the dermatologist physician's routine. Despite their great importance, there is little information about this topic in the dermatological literature.[1] Many of these lesions, in addition to affecting productivity, cause limitations to daily activities.[2] It was estimated that in 2004, the cost of dermatological diseases was US$ 39.3 billion in the USA,[2] with a significant impact not only on the quality of life of those affected, [3] but also on health systems spending. Considering that epidemiological information is fundamental for directing health policies, [3] this paper is aimed at outlining the profile of the most prevalent lesions in toes and fingers that were treated by the dermatologic surgery team in a dermatology referral service, in addition to evaluating the classification of these lesions, their distribution by age groups, genders and body sites of occurrence, as well as the correlation between the clinical suspicion of lesions and their anatomopathological diagnosis.

MATERIALS AND METHODS

A cross-sectional retrospective observational epidemiological study was performed, in which dermatological surgeries performed on lesions located in chirodactyls and toes were analyzed in a period of 93 months (August 2009 to April 2017), as well as their histological evaluations, and the records of patients who underwent the surgical procedures, surgical records books and pathological anatomy reports, in the dermatology ambulatory of the Complexo Hospitalar Padre Bento de Guarulhos (CHPBG). Lesions operated by the hospital's plastic and oncological surgery teams were excluded, while lesions located in chirodactyls and pododactyls operated by the dermatologic surgery team during the period considered and ambulatorially followed up were included. The present study was approved by CHPBG's Research Ethics Committee (Opinion number: 2,300,429).

The lesions were classified by the authors into: tumoral, traumatic, inflammatory, infectious and others. The first group included tumors of vascular, cystic, fibroepithelial, neural, melanocytic, epithelial, and other origins. Traumatic lesions included nail plate alterations, onychocryptosis and callosities. Inflammatory lesions included ungual psoriasis, annular granuloma and chronic paronychia. In the studied sample, viral warts represented infectious lesions. The lesions resulting from deposition (gouty tophi), genetic alterations (rudimentary and supernumerary fingers) and actinic keratosis, were classified as "other".

The procedures performed were standardized and grouped into: biopsy of the nail apparatus; canthotomy / canthoplasty; biopsy / lesion exeresis; curettage associated or not to electrocoagulation, and others. Biopsies of the nail apparatus comprised those performed in the nail's bed, matrix or plate. Canthotomy and canthoplasty included the implementation of Haneke's techniques, [4] Fanti's surgery, [5] matricectomy, [4] reduction of the nail folds using the Dubois[4] or "super U" techniques, [4] in addition to phenolization of the nail matrix.[4] Exeresis / biopsy corresponded to procedures for complete removal of tumors and / or biopsies of lesions located outside the nail apparatus. Curettage and electrocoagulation were performed for the treatment of viral warts and pyogenic granulomas. The group "Others" consisted of the techniques of prolonged stay suture (mucosal cyst transfixation), oblique exeresis of the proximal nail fold, and osteotomy, used for the treatment of mucinous / myxoid cysts, chronic paronychia and osteochondromas, respectively.

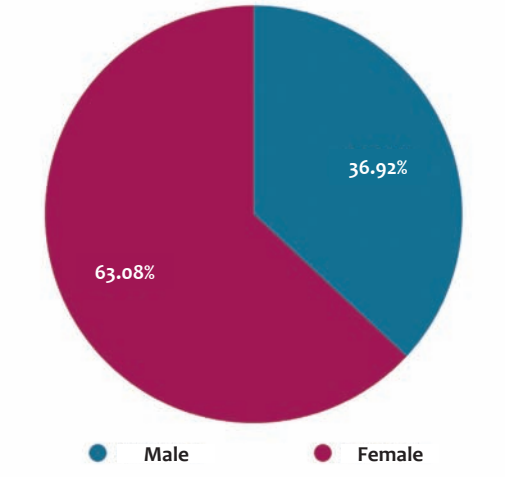
For concordance analysis between preoperative and post-operative diagnoses, two variables were established: "yes" and "no / inconclusive". The first variable includes the cases in which the preoperative diagnostic hypothesis was confirmed by anatomopathological analysis. The second refers to cases of disagreement between pre- and postoperative diagnoses, to those whose previous hypotheses were not identified in the analyzed records, or those with inconclusive results. The lesions studied were also grouped and classified as benign or malignant.

RESULTS

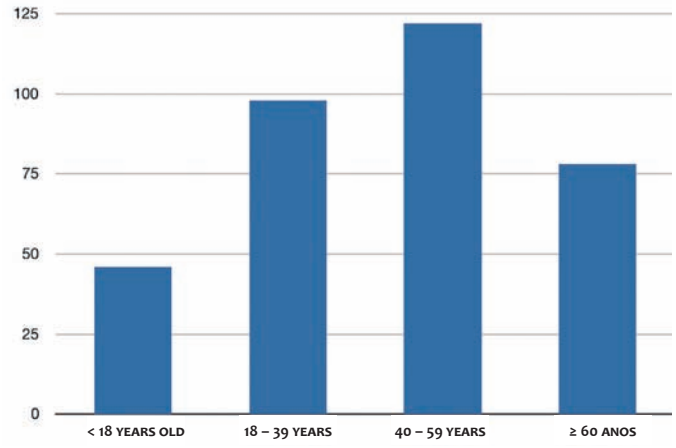
A total of 454 records of patients followed up by the dermatologic surgery team were analyzed, with 110 exclusions due to discordance of lesion location, incomplete data, missing medical records, or the non-surgical nature of the procedures, such as cryotherapy and infiltration of periungual medication.

A total of 344 patients were included in the study, of which 63.08% were female, and 36.92% were male (Graph 1). The age ranged from 5 to 89 years (mean value = 43.1 years, STD = 19.59 years). Of the patients evaluated, 13.37% were younger than 18 years old at the time of the procedure, 28.49% were between 18 and 39 years old, 35.47% were between 40 and 59 years old, and 22.67% were older than 60 years (Graph 2).

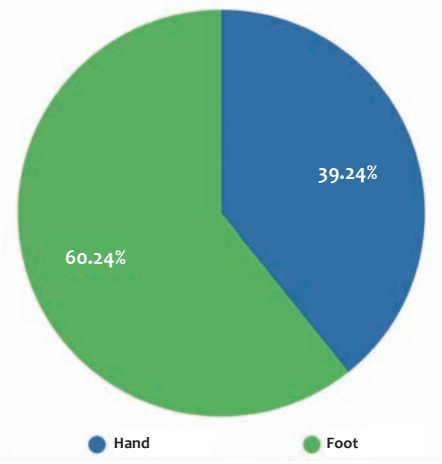
Regarding the location of surgically treated lesions, the study showed that they were more frequent in pododactyls (60.76%) than in chirodactyls (39.24%) (Graph 3), with the most frequently affected being the left hallux (22.07%) and the right hallux (19.89%) (Figure 1).



GRAPH 1: Gender



GRAPH 2: Age group



GRAPH 3: Chirodactyls and pododactyls that underwent procedures

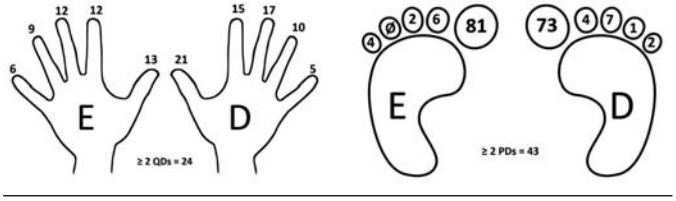
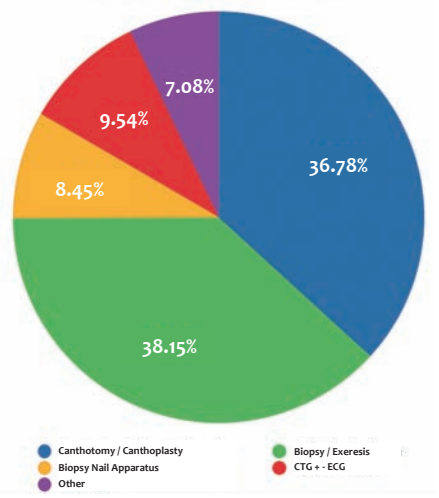


FIGURE 1: Number of lesions operated on each finger and toe

A total of 367 procedures were performed, with the most frequent being biopsy / excision of lesions in fingers and toes, corresponding to 38.15% of the total, while biopsies of nails comprised only 8.45% of the cases. Canthotomy / canthoplasty was the second most frequent procedure, with 36.78% of the total. Curettage, whether or not accompanied by electrocoagulation, accounted for 9.54% of the sample. Other less frequent procedures, such as oblique excision of the proximal nail fold, osteotomy and the prolonged stay suture technique (transfixation of mucosal cyst) corresponded to 7.08% of the total (Graph 4).



GRAPH 4: Procedure performed

Regarding the procedures performed, 141 lesions were sent for anatomopathological study. Taking into account only lesions that were sent for analysis, 55.32% were classified as having tumoral origin (Graph 5).

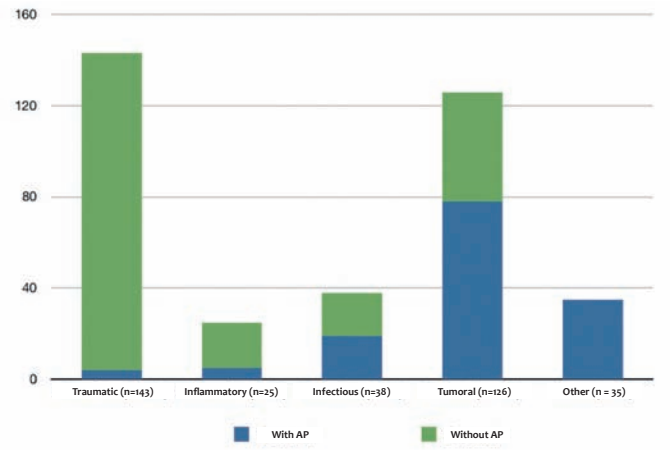
Evaluating all 367 procedures, it was possible to verify that the majority resulted from lesions of traumatic nature (Graph 5).

Of the lesions of tumoral origin, 92.31% were benign, and 7.69% malignant, the latter corresponding to five squamous cell carcinomas and one melanoma, totaling 6 malignant neoplasms in the sample. Graph 6 shows the proportion of benign lesions (95.74%) and malignant lesions (4.26%), as percentages of the total sent for anatomopathological analysis.

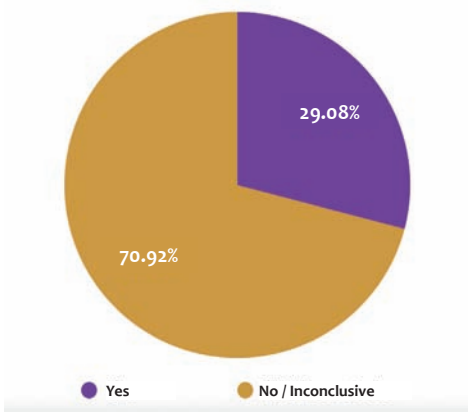
The concordance between the diagnostic hypothesis and the anatomopathological report was positive for 29.08% of the sample, with the remaining 70.92% coming out inconclusive or discordant (Graph 7).

DISCUSSION

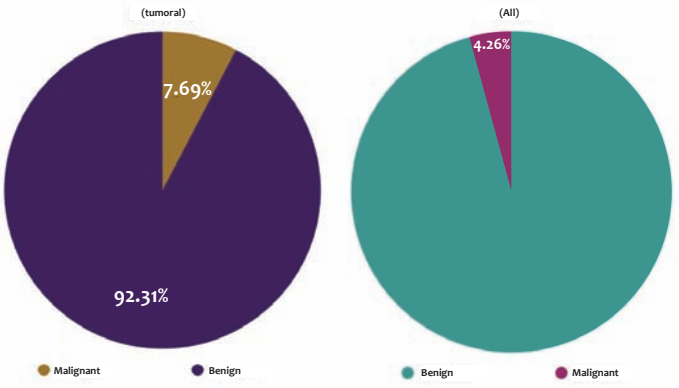
Lesions in toes and fingers can mostly be diagnosed by complete anamnesis and physical examination, and handled adequately by dermatologist physicians with training in dermatological surgery.[6] Epidemiological information about them is crucial for directing health policies, however they are unfortunately limited when taking into account all dermatological nosologies.[3] In the case of lesions in fingers and toes, the information is even scarcer. In a study carried out by the Brazilian Society of Dermatology in 2006 on the profile of diseases treated in dermatological consultations in Brazil, the main reason for consultation was acne, followed by superficial mycoses, pigmentation disorders and actinic keratosis. A subsequent study carried out in 2011 at a dermatology reference center in the Northern Brazilian State of Amazonas on the frequency of dermatoses, found STDs, allergic dermatoses, unspecified dermatoses, leprosy and acne, seborrhea and the like as the five most diagnosed groups.[7] Both studies evaluated only ambulatorial consultations



Graph 5: Nature of the lesions



Graph 7: Concordance between the hypothesis and the AP anatomopathology examination → sim



Graph 6: Benign lesions x malignant lesions

without information on the location of the lesions, also not contemplating non-surgical procedures, which probably was one of the factors that contributed to the discordance with the findings of the present study, where only lesions located on toes and fingers were evaluated. A study carried out from 2002 to 2007 in Curitiba, the capital of the Southern Brazilian State of Paraná, analyzed the surgical procedures performed in a medical residency service, verifying that the most frequent procedure was diagnostic biopsy.[8] Although this study did not describe the location of the lesions treated, it was possible to observe the presence of agreement with the findings of the present study.

Regarding the most frequently affected age group and gender, the present study is in line with the available literature regarding ambulatorial care, with the majority of patients being female and young adults.[2,3] No studies were found in the literature describing the frequency and types of surgical procedures performed in fingers and toes, nor the most frequent nature of the lesions or correlation between clinical and anatomopathological diagnosis.

CONCLUSION

Analysis of the results showed that most of the procedures were performed in adult female patients, with the left hallux being the most affected location in the sample studied. Based on the analysis of the data collected, it was also verified that most of the procedures resulted from lesions of traumatic nature, with biopsy / excision of lesions, and canthotomy / canthoplasty being the most frequently performed procedures, with prevalence of the benign lesions over malignant ones. The present study contributes to the planning and design of future dermatological consultations. ●

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DECLARATION OF PARTICIPATION:

Luisa Preisler | ORCID 0000-0002-1600-9953
Conceptual development and research project planning; preparation and write up of the manuscript; data acquisition, analysis and interpretation; approval of the final version of the manuscript

Ludmilla Cardoso Gomes | ORCID 0000-0002-8165-5345
Conceptual development and research project planning; preparation and write up of the manuscript; data acquisition, analysis and interpretation; approval of the final version of the manuscript

José Roberto Pereira Pegas | ORCID 0000-0002-2541-6008
Conceptual development and planning of the research project, review and approval of the final version of the manuscript

LA ROCHE-POSAY
LABORATOIRE DERMATOLOGIQUE

VIDA MELHOR PARA AS PELES SENSÍVEIS

TOLERIANE SENSITIVE

O CUIDADO DIÁRIO PREBIÓTICO
QUE HIDRATA, SUAVIZA
E REDUZ A SENSIBILIDADE.

FÓRMULA MINIMALISTA

73%
Anti-irritações
Água termal

10%
Ativos hidratantes
e suavizantes

17%
Ativos estabilizadores
conforto

ATIVOS

GLICERINA
Hidrata por 48h

CERAMIDA
Repara e protege
a barreira cutânea

VITAMINA B3
Acalma intensamente

ÁGUA TERMAL DE LA ROCHE-POSAY
Acalma, suaviza e
reduz os desconfortos

SEM SABÃO • SEM PERFUMES • SEM CONSERVANTES

Flap-plasty and closure by second intention: an option in the reconstruction of the ear and external auditory canal

Retalhoplastia e fechamento por segunda intenção: opção na reconstrução da orelha e conduto auditivo externo

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ABSTRACT

Non-melanoma skin cancer is the most common type of neoplasia. Basal cell carcinoma is the most common cancer of them, the incidence of which is steadily increasing, implying an important public and financial health issue. The authors present the case of a patient with an extensive basal cell carcinoma affecting part of the external auditory canal and auricular concha, treated with a combination of surgical techniques: flap-plasty associated with second intention closure of the external auditory canal. Due to the excellent aesthetic and functional outcomes, this technique should be considered as a therapeutic option for auricular lesions.

Keywords: Carcinoma, Basal cell; Dermatology; Ear neoplasms; Ear, external; Surgical flaps

RESUMO

O câncer da pele não melanoma é o tipo de neoplasia mais comum. O carcinoma basocelular é o mais frequente dos cânceres da pele, cuja incidência aumenta constantemente implicando uma importante questão de saúde pública e financeira. Apresenta-se o caso de paciente portador de carcinoma basocelular extenso, acometendo parte do conduto auditivo externo e concha auricular, que foi tratado por associação de técnicas cirúrgicas: retalhoplastia associada ao fechamento por segunda intenção do conduto auditivo externo. Devido ao excelente resultado estético e funcional, essa técnica deve ser lembrada como opção terapêutica para lesões auriculares.

Palavras-Chave: *Carcinoma basocelular; Dermatologia; Neoplasias da orelha; Orelha externa; Retalhos cirúrgicos*

INTRODUCTION AND LITERATURE REVIEW

Non-melanoma skin cancer is the most common form of cancer in humans. Basal cell carcinoma (BCC) is the most frequent skin cancers and has an ever growing incidence, meaning an important public health and financial issue for several countries.[1,2]

It is known that exposure to the sun is the most important risk factor for BCC, while sensitivity to the sun is the main predisposing factor related to the host. Intensely fair skin and presence of actinic keratoses are the personal risk factors most frequently related to the development of BCC. A study suggested that intermittent exposure to the sun is closely related to the occurrence of BCC, and that the risk of developing this condition is proportional to the incidence of ultraviolet (UV) radiation in the geographical area where the patient dwelled during his or her first 20 years of life. However, there was no increase in the risk of BCC regarding cumulative exposure – unlike what is observed in squamous cell carcinoma patients, which is another malignant keratinocytic neoplasia.[1]

New techniques

Autors:
Lais Lopes Almeida Gomes[1]
Bianca de Franco Marques Ferreira[1]
Mário Chaves Loureiro do Carmo[1]
Solange Cardoso Maciel Costa Silva[1]

[1] Dermatology Service, Hospital Universitário Pedro Ernesto, Universidade do Estado do Rio de Janeiro – Rio de Janeiro (RJ), Brazil.

Correspondence:
Laís Lopes Almeida Gomes
Av. Nelson Cardoso, 1149/310
Taquara – Rio de Janeiro-RJ – Brasil
E-mail: llag_3@hotmail.com

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The authors describe the case of a patient with extensive BCC affecting part of the external auditory meatus and auricular concha, whose treatment by association of surgical techniques – flap-plasty associated with second intention closure of the external auditory meatus – resulted in excellent esthetic and functional outcomes.

CASE REPORT

A 72-year-old, phototype III male patient sought care related to a lesion perceived 7 months earlier in the right ear. At the clinical examination, an ulcer vegetative lesion with pearly borders was observed spanning the entire auricular concha, external auditory meatus and part of the lobule (Figure 1). The patient also referred to progressive ipsilateral hearing loss. Following the clinical diagnosis of BCC, the authors chose to completely surgically excise the lesion. Surgery was performed with simultaneous histological analysis of borders and resulted in a large surgical defect (Figure 2).

The preparation of a transposition flap harvested from the area anteroinferior to the auricular pavilion was the procedure chosen for repairing the operative wound. The flap was elevated, positioned and sutured in the bloody area, covering the defect, leaving out the area of the external auditory meatus to heal by second intention. The flap's donor area was chosen due to its proximity to the primary defect (Figure 3). The transposed tissue was rotated about 90° aiming at covering the area of the wound resulting from the resection of the tumor, having been being sutured with 4-0 nylon thread (Figure 4). Careful measurement of the flap (width and height) was taken to ensure that the extensive defect would be fully covered. In the secondary operative defect, the primary closure was performed by means of a simple suture with 4-0 nylon thread, in order to reduce tension.

RESULTS

The patient treated the wound with daily hygiene and standard dressings in the postoperative period, when no inter-

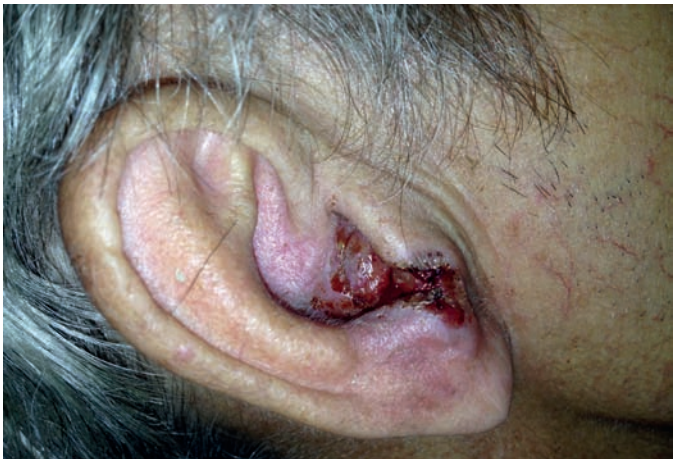

Figure 1: Preoperative BCC

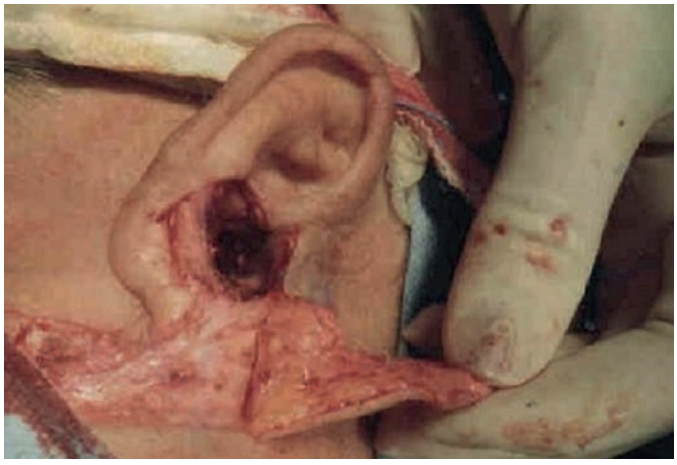

Figure 3: Donor area

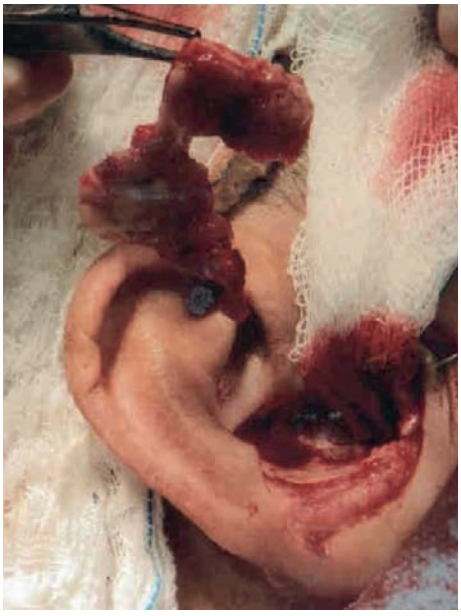

Figure 2: Primary defect

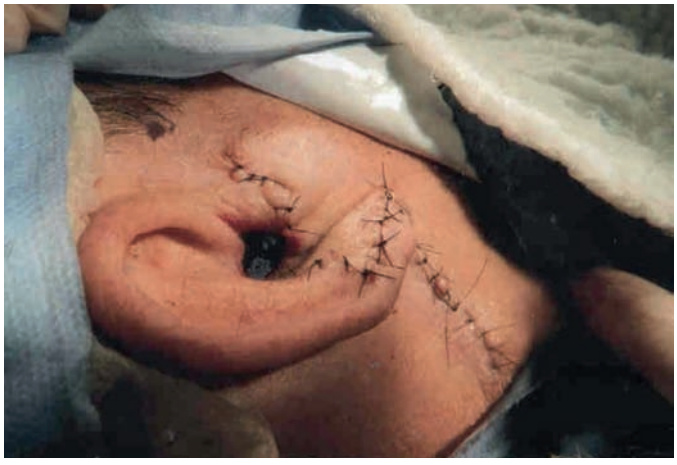

Figure 4: Immediate postoperative

currences were observed. Aiming at a better aesthetic outcome, 50% trichloroacetic acid was applied to the surgical scar in two sessions, (Figures 5 and 6). Three weeks after, the patient was evaluated at the Otorhinolaryngology Department, which confirmed the good healing of the external auditory meatus area by second intention.

DISCUSSION

Basal cell carcinoma accounts for about 90% of malignant cutaneous lesions of the head and neck region, being the most common type of ear carcinoma. The vast majority of cases occur in the ear helix and periauricular area, which are especially susceptible to exposure to the sun.[2,3] Nevertheless, 15% of these arise in the external auditory meatus, [2] with the most common BCC variant in this area being the ulcerative nodular, that arises as a slightly erythematous, desquamative, sometimes pigmented papule surrounded by a capillaries network, with pearly border, with possible central ulcer. Although metastases are extremely rare, the invasive character of the tumor can cause extensive local damage linked to cartilage infiltration.[2]

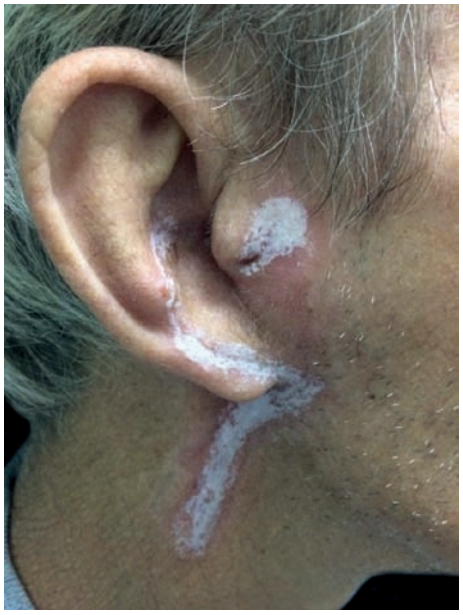

Figure 5: Application of trichloroacetic acid to the surgical site after 6 weeks

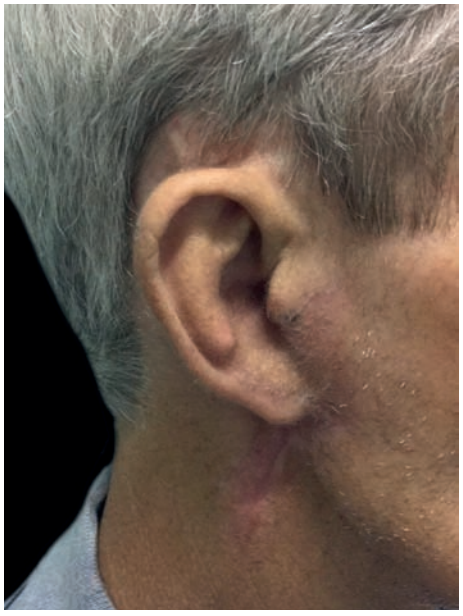

Figure 6: Scar after 13 weeks

The ear is susceptible to the effects of UV radiation due to its location, which causes extensive exposure and, consequently, susceptibility to neoplastic and pre-neoplastic skin lesions. In addition, the ear has the function of transmitting sounds and participating in the facial aesthetics. Depending on the affected site, lesions of the external ear can be easily perceived by the patient or by friends and relatives, meaning that the search for medical attention will most probably occur without delay.[2,3] On the other hand, when lesions occur in less exposed areas, as in the present case, the search for a dermatologist physician might be delayed, resulting in the development of the lesion over time. This fact embeds increased risk in cases of malignant tumors due to their invasive potential, associated to the small thickness of the skin in this area as compared to that of other regions.[2]

It is important to highlight that the physician should always perform the complete examination of the patient's body after diagnosis of the first BCC due to the high frequency of synchronous BCCs. Follow-up studies have shown that the emergence of new skin cancers occurs in roughly half of the patients in the following five-year time interval.[3,4]

The outer ear consists of the external auditory meatus and the auricular pavilion (Figure 7). Both are formed by elastic cartilage covered by skin, connected to the perichondrium, and poorly vascularized. The epidermis of its concave part covers a thin layer of dermis and subcutaneous, which is strongly attached to the pavilion's cartilage – in contrast to the skin in the outer ear's convex part, which rests over a thick subcutaneous fat layer that provides more laxity and mobility.[2]

Reconstruction of the ear can be challenging due to its complex topography. Post-surgical ear distortions and asymmetries can affect the patient's facial aesthetics. Several options for ear reconstruction are available and should be individualized,

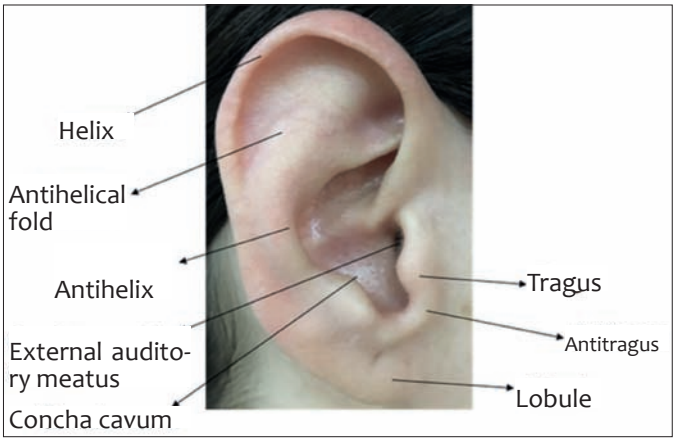

Figure 7: Anatomy of the ear

according to the surgeon's area of expertise and experience.[5] Among the options for auricular reconstruction, the authors of the present article highlight rotation, advancement and interpolation flaps, in addition to the transposition flap. It is important to note that despite the complex primary reconstruction alternatives, closure by secondary reepithelialization is also an option [3] to be used in concave areas.

Regarding the primary reconstructions of the ear, flaps are indicated for covering primary defects in the helix, lobe, anti-helix and cavum. The authors of the present article highlight the pre or retroauricular transposition flaps in these cases. It should be borne in mind that the transposed skin can not be excessively thin due to the risk of necrosis, nor excessively thick, which would cause an elevated scar.[5,6]

CONCLUSION

Reconstruction of auricular surgical defects with transposition of pre-auricular flaps and primary closure associated with second-intention closure of part of the external auditory meatus proved to be a viable and effective surgical technique, with absence of complications in the immediate and late postoperative periods. Due to the excellent aesthetic and functional outcomes, the technique described should be borne in mind as a therapeutic option for auricular lesions. ●

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DECLARATION OF PARTICIPATION:

Laís Lopes Almeida Gomes | ORCID 0000-0001-5396-4362
Participation in the procedure, patient postoperative follow-up, literature review, manuscript write up, photographic records

Bianca de Franco | ORCID 0000-0001-5997-4246
Participation in the procedure, patient postoperative follow-up, literature and manuscript review, photographic records

Mário Chaves | ORCID 0000-0003-2943-0322
Participation in the procedure and patient follow-up

Solange Maciel | ORCID 0000-0003-0812-908X
Conceptual development of the technique, procedure implementation

Factitious panniculitis mimicking chronic erythema nodosum

Paniculite factícia mimetizando eritema nodoso crônico

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ABSTRACT

Factitious panniculitis can be triggered by subcutaneous injections of substances linked to esthetic procedures. A case diagnosed and treated as chronic erythema nodosum manifested nodule five years later, with the anatomopathological study suggesting atypical lipomatous tumor. After resection of the lesion, histology showed steatonecrosis, compatible with lobular panniculitis. Magnetic resonance imaging examination revealed the presence of a liquid substance in the gluteal region, favoring the diagnostic suspicion of factitious panniculitis. The patient admitted to having undergone silicone injection in this region in the past, with additional findings arising from the histological review confirming this hypothesis. The late complication linked to injections of cutaneous filling material motivated the present study.

Keywords: Erythema chronicum migrans; Panniculitis; Silicones

RESUMO

A paniculite factícia pode ser desencadeada por injeções subcutâneas de substâncias com finalidade estética. Caso diagnosticado e tratado como eritema nodoso crônico, cinco anos após, manifestou nódulo, cujo estudo anatomopatológico sugeriu tumor lipomatoso atípico. Ressecada a lesão, o exame histopatológico mostrou esteatonecrose, compatível com paniculite lobular. Na ressonância magnética, imagens de líquido na região glútea favoreceram a suspeita diagnóstica de paniculite factícia. A paciente admitiu injeção pregressa de silicone nessa região, e os achados adicionais na revisão histopatológica confirmaram essa hipótese. A complicação tardia das injeções do material de preenchimento motivou nossa apresentação.

Palavras-Chave: *Eritema migrans crônico; Paniculite; Silicones*

INTRODUCTION

Panniculitides, a group of subcutaneous inflammatory conditions of septal or lobular predominance, with or without vasculitis, have multiple etiologies.[1]

Erythema nodosum (EN) migrans, Vilanova-Pinol Aguadé subacute panniculitis nodosa migrans (SPNM) and chronic EN, variants of classic EN, are now deemed as distinct phases of the same pathological process.[1] Described in 1956 by Vilanova and Pinol Aguadé, [2] SPNM is singular due to the fact it has few, unilateral and asymmetrical nodules, which converge to form indurated plates of up to 20cm, with active centrifugal lesions and concomitant central involution, acquiring different shapes and shades. There is predominance in females and it is not very symptomatic, developing during months to years in the knees, buttocks and thighs.[1]

The objective of the present report is to demonstrate a late complication (10 years after), due to a cutaneous filling, and represented by panniculitis symptoms.

Case Reports

Autors:
Ludmilla Luiza Libanio Guimarães[1]
Nurimar Conceição Fernandes[2]
Tullia Cuzzi[3,4]

[1] Clindes - Vitória (ES), Brazil.
[2] Universidade Federal do Rio de Janeiro - Rio de Janeiro (RJ), Brazil.
[3] Department of Pathology, Universidade Federal do Rio de Janeiro - Rio de Janeiro (RJ), Brazil.
[4] Instituto Nacional de Infectologia, Fundação Oswaldo Cruz – Rio de Janeiro (RJ), Brazil.

Correspondence:
Ludmilla Luiza Libanio Guimarães
Avenida Nossa Senhora da Penha no 699 – Torre B – sala 913, Santa Lúcia
29056-250, Vitória, ES
Brasil.
e-mail: ludlibanio@gmail.com

Received on: 07/07/2015
Approved on: 29/05/2018

This study was performed at the Hospital Universitário Clementino Fraga Filho (HUCFF). Universidade Federal do Rio de Janeiro (UFRJ) – Rio de Janeiro (RJ), Brazil.

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METHODS

The authors of the present study report the case of a 50-year-old, mulatto, not very assiduous female patient, who sought care at the Dermatology Clinic of a university medical service in the city of Rio de Janeiro, Brazil, in November 2001. She complained of an erythematous-infiltrated, indurated plaque measuring 25cm in length, with an increase in temperature, located in the anterior aspect of the right thigh (Figure 1), that had emerged four years before. In light of the hypothesis of panniculitis, a biopsy was performed with the anatomopathological study indicating an EN in its chronic phase. The possibly associated conditions (trichomoniasis, onychomycosis, paronychia, hidradenitis and scabies) were adequately treated in ambulatorially during the follow-up. The results of laboratory tests (blood count, biochemistry, thyroid function, serologies for hepatitis B and C, VDRL, anti-HIV, ASLO, alpha -1-antitrypsin, urinary sediment, parasitologic stool) and chest X-ray were normal. Non-hormonal anti-inflammatories, oral potassium iodide saturated solution (reaching only 15 drops / day due to gastrointestinal intolerance), potassium iodide in cream and systemic corticosteroid therapy during periods of more intense inflammation, were administered without significant change in the course of panniculitis.

In March 2006, the patient returned to the clinic reporting the emergence of a hardened painful nodule measuring 7cm on the lateral aspect of the left thigh one year before. Ultrasonographic evaluation described echogenic formations of imprecise limits on the subcutaneous external aspect of the left thigh, left inguinal region and the inner aspect of the right thigh. Subsequent incisional biopsy of the lesion was performed, with the anatomopathology revealing an atypical lipomatous tumor, negative for common germs, fungi and mycobacteria. In February 2012, the histological examination of the lesion's exeresis (Figure 2) revealed extensive steatonecrosis. Magnetic resonance imaging performed after surgery evidenced liquid infiltration in the subcutaneous area of the gluteal region, in addition to multiple non-specific lymph nodes in the iliac and femoral chains (Figure 3).

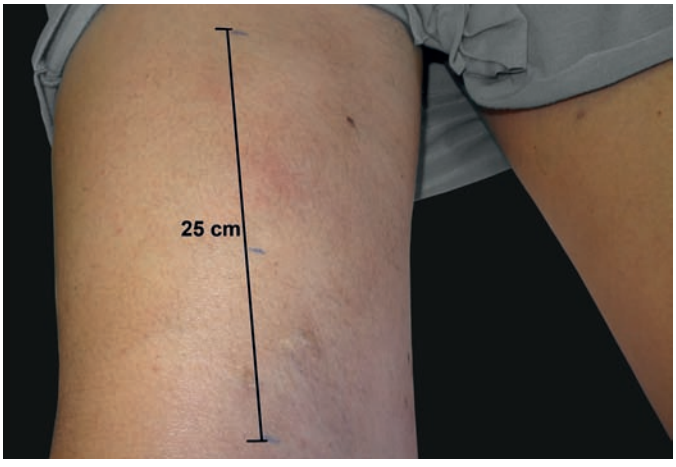

Figure 1: Plaque on the frontal aspect of the right thigh

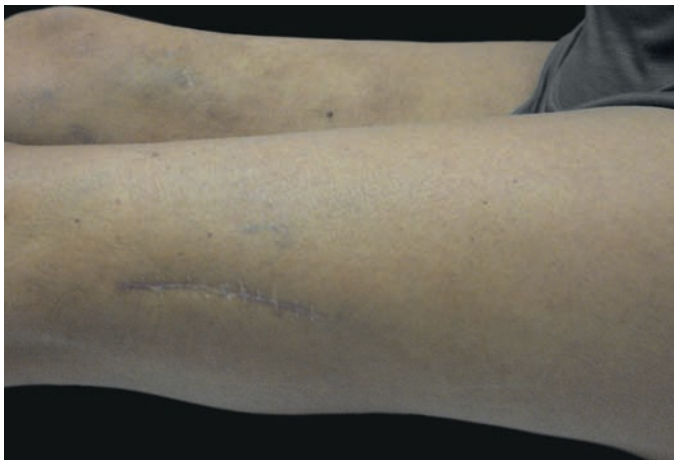

Figure 2: Surgical scar on the lateral aspect of left thigh

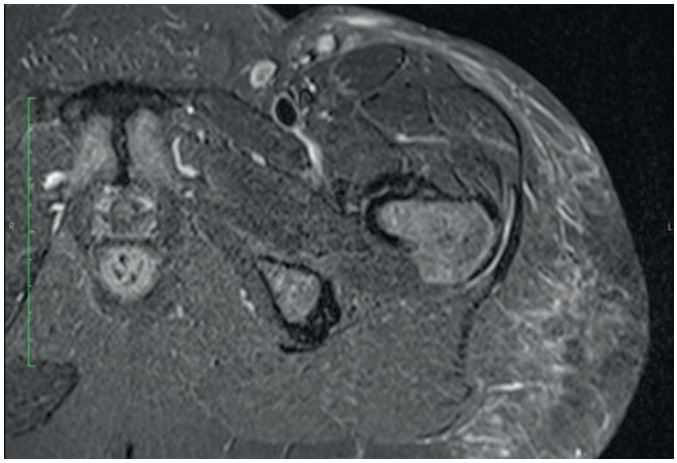

Figure 3: Magnetic resonance imaging showing liquid infiltration in the subcutaneous of the gluteal region

RESULTS

Taking into account the steatonecrosis (a finding that is present in the histology of some lobular panniculitis), the image of liquid infiltration in the gluteal region, and the clinical history review (information provided by the patient about the silicone injections applied in the gluteal regions at least 10 years before), the hypothesis of factitious panniculitis caused by exogenous substance was raised.

The review of the histological samples added the presence of microcystic spaces in the hypodermis to the finding of steatonecrosis. Some of these spaces were delimited by amphiphilic material, and foam cells, in line with the hypothesis of factitious panniculitis (Figures 4-7). The absence of refraction in polarized light was consistent with the type of material reported by the patient (silicone).

DISCUSSION

Factitious or artificial panniculitis are lesions of the subcutaneous tissue that are caused by external factors (mechanical,

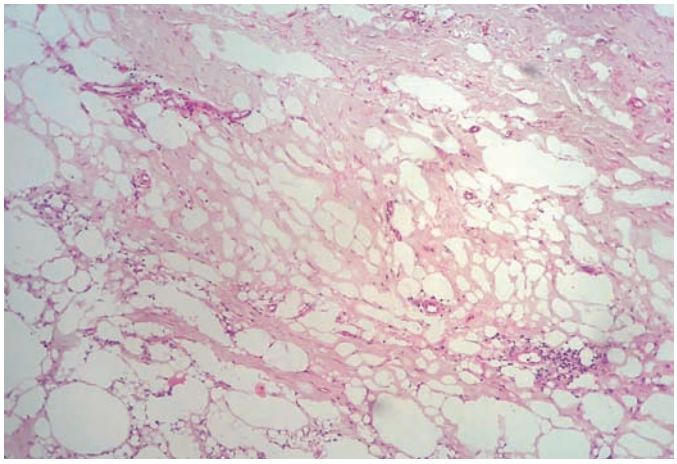

Figure 4: Steatonecrosis focus in the upper portion of the image, adjacent to the inflammatory infiltrate and microcysts

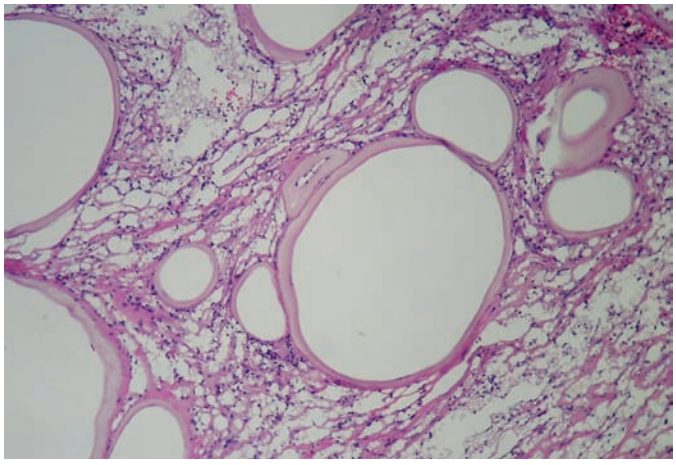

Figure 5: Cystic spaces of various sizes, lined with amorphous amphiphilic material, among inflammatory cells

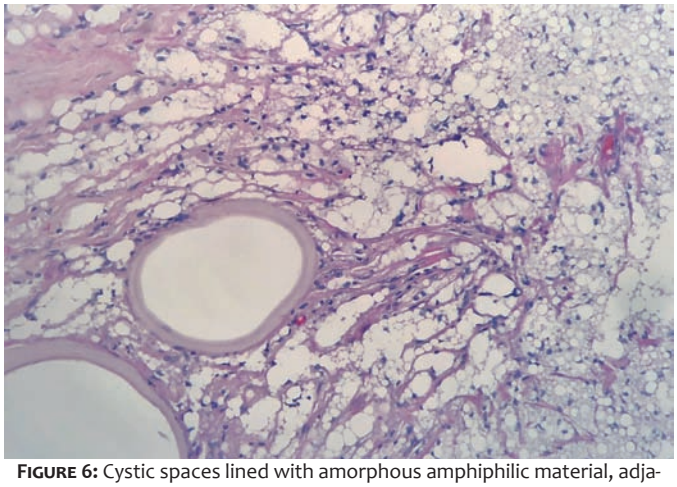

Figure 6: Cystic spaces lined with amorphous amphiphilic material, adjacent to foam cells

chemical and physical), and belong in the group of lobular panniculitides without vasculitis.[3,4] They can be self-induced, accidental, intentional, a manifestation of psychiatric disorder, or of the iatrogenic injection of substances. Although the etiopathogenic mechanism is unknown, vasoconstriction with ischemia at the sites of injection, inflammatory response to precipitated drugs and trauma by repeated injections have been implicated.[3]

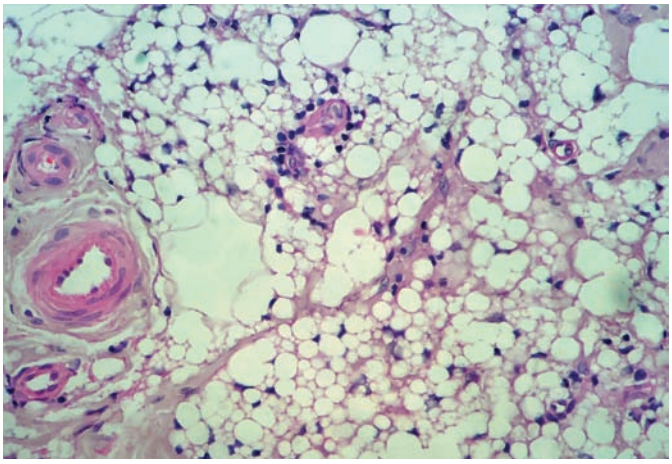

Figure 7: Detail of the foam cells making up most of the inflammatory infiltrate

Fillers can induce a range of adverse reactions – e.g. some may disappear spontaneously while others may lead to complications 30 years after the procedure, [3] at a time when the patient no longer remembers which material was injected.[5]

When the patient in question admitted to having undergone the filling procedure at a clandestine clinic before the 1990s, the authors of the present study hypothesized that the iatrogenic injection of nonabsorbable material in the past was responsible for the current manifestation. Omission of the procedure, often performed by professionals without the legally required qualification,[6] is the probable explanation for the late diagnosis of this type of panniculitis.

Silicone is a polymeric hydrophobic compound that can be found in the forms of oil, gel or solid implant. In its liquid form, it was widely used for cosmetic correction of fine wrinkles, scars and facial tissue volumization of HIV positive patients with lipoatrophy.[5,7]

The migration of non-biodegradable fillers, such as silicone, is often described to mimic malignant neoplasms and granulomatous diseases.[8] It is able to reach sites distant from the treated area, [5,7] causing local inflammatory reaction. The absence of a fibrous capsule involving large volumes allows gravitational migration of the implant towards undesired areas.[9] It is believed that the injection of excessive bolus volumes precipitates this process.[7] In the studied case, the authors suspected that the filling material previously injected in the buttocks migrated, via the subcutaneous plane, towards the thighs' topography.

The histological pattern generally observed in factitious panniculitis is that of acute lobular panniculitis associated with steatonecrosis and inflammatory infiltrate with neutrophilic predominance, coursing with granulomatous appearance.[3] Chronic lesions are characterized by foamy histiocytes and surrounding fibrosis.[3,4] The important dermal involvement also assists in differentiating the shape induced by injected substances from other types of panniculitis.[3]

The histological findings associated with the use of silicone are varied and correspond more frequently to cutaneous nodules. In general, there is diffuse infiltrate of macrophages and multinucleated giant foreign body cells that delimit empty spaces of varying sizes, in a pattern known as "Swiss cheese." The presence of cells with reactional cytological atypias – and even of lipoblasts – may justify the differential diagnosis *vis a vis* neoplastic processes.[5,6,10]

Due to the fact silicone is a permanent filler, the inflammatory response can occur at any time, constituting a therapeutic challenge.[9] The literature describes treatments with local and systemic corticosteroids, [11] minocycline, [5,7,11] 5% imiquimod, [5,7,11] isotretinoin and doxycycline.[7]

Morrondo et al.[11] reported a case of factitious panniculitis in gluteal regions caused by silicone and EN (associated with Löfgren's syndrome) in concomitant pretibial regions with good response to non-steroidal anti-inflammatory.

Intralesional corticosteroids are used in cases secondary to granulomatous reaction, [3,5] with removal of the implants in irresponsive cases, [3,7] which might require extensive resections and complex reconstructions.[8]

The loss of ambulatorial follow-up precluded therapeutic guidance after the review of this case.

CONCLUSION

The histological data, in addition to the previous cutaneous filling history, the migration potential of silicon, the chronic and atypical development, and the evidence of gluteal liquid infiltration, underpinned the conclusion of factitious panniculitis.

Adverse reactions to fillers can arise many years after the procedure has been carried out, and abundant documentation on migration of silicone to distant sites is available. A complete anamnesis, including information from the past and previous aesthetic treatments, should be especially performed in cases of chronic panniculitis. ●

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DECLARATION OF PARTICIPATION:

Ludmilla Luiza Libanio Guimarães | ORCID 0000-0002-6543-610X
Diagnostic suspicion, literature research and manuscript write up

Nurimar Conceição Fernandes | ORCID 0000 - 0002-1819-9630
Patient ambulatorial follow-up, oversight of the manuscript write up and final review

Tullia Cuzzi | ORCID 0000-0002-3331-5290
Histological reports preparation, histological findings analysis and discussion, histological photographic records, critical review of the manuscript

Melanocyte transplantation – a variation of the micrografting technique

Transplante de melanócitos – Variação da técnica de microenxertia

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ABSTRACT

Vitiligo is an acquired pigmentation disorder characterized by the development of well-defined achromic macules in the skin. It is deemed stable when no new lesion emerges or when pre-existing lesions do not undergo changes for at least one year. In these cases, surgical treatment is an important therapeutic option. Punch micrografting is the most commonly performed melanocyte transplantation technique, resulting in excellent repigmentation. The authors describe a variation of this technique using even smaller and finer grafts (consisting of epidermis and thin dermis), in order to achieve aesthetical outcomes that are better than those obtained with the traditional technique, especially when treating areas with significant aesthetic impairment.

Keywords: *Melanocytes; Transplantation; Vitiligo*

RESUMO

Vitiligo é desordem adquirida da pigmentação, caracterizada pelo desenvolvimento de máculas acrômicas bem definidas na pele. É considerado estável quando nenhuma lesão nova aparece ou quando lesões preexistentes não sofrem alterações ao longo de pelo menos um ano. Nesses casos o tratamento cirúrgico é importante opção terapêutica. A microenxertia por punch é a técnica de transplante de melanócitos mais comumente realizada, com ótima repigmentação. Descreve-se uma variação dessa técnica utilizando enxertos ainda menores e mais finos (que consistem de epiderme e derme fina), para buscar resultados esteticamente melhores do que os da técnica tradicional, principalmente ao tratar áreas com significativo acometimento estético.

Palavras-Chave: *Melanócitos; Transplante; Vitiligo*

INTRODUCTION

Vitiligo is an acquired pigmentation disorder, characterized by well-defined achromic macules on the skin with loss of epidermal melanocytes. Lesions are localized or generalized, and may coalesce into large depigmented areas. Given the contrast between the affected areas and normal skin, it is more disfiguring in high phototypes and has a profound impact on the patients' quality of life.[1]

Incidence of vitiligo is 1-2% in the world population, affecting genders equally, and all ethnic groups. Several theories have been proposed aimed at explaining its pathogenesis, including biochemical, neural and autoimmune hypotheses. A multifactorial etiology, known as convergence theory, is currently proposed.[2] Vitiligo is classified into two main clinical groups: segmental and non-segmental. According to its activity level, it can be stable or unstable. It is considered stable when no new lesion appears or when preexisting lesions do not change over at

Case Reports

Autors:
Carlos Roberto Antonio[1]
Lívia Arroyo Trídico[1]
Thalita Marçal Machado[1]
João Roberto Antonio[1]

[1] Dermatology Service, Hospital de Base, Faculdade de Medicina de São José do Rio Preto (Famerp), São José do Rio Preto (SP), Brazil.

Correspondence:
Lívia Arroyo Trídico
Rua Silva Jardim, 3114, Centro - São José do Rio Preto (SP), SP
Email: latridico@gmail.com

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This study was performed at the Faculdade de Medicina de São José do Rio Preto (Famerp) – São José do Rio Preto (SP), Brazil.

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least one year.[1,3,4] This fact is relevant since surgical treatment is a therapeutic option reserved for stable vitiligo.[5] Patients with segmental vitiligo, unlike those with the non-segmental variant, are more resistant to treatment, despite the fact they present good response to surgical treatment.

There are two important pre-requisites for surgical treatment with melanocyte transplantation: i) the vitiligo must be stable and ii) there must be lack of response to other modalities of clinical treatments available. In those cases, patients may benefit from surgical treatments, which correspond to the transplantation of melanocytes, and can be performed using two main techniques: transplantation of cutaneous tissue or cell suspension to the affected areas.[4,7,8]

Punch micrografting – a method for transplantation of cutaneous tissue – is the most frequently performed surgical technique. For its execution, the recipient area is prepared by performing multiple holes using punches that are 0.25 or 0.5mm smaller in diameter than the grafts harvested from the donor area, which measure up to 1mm for facial areas and up to 1.2mm for other regions.[3,4,9] Larger grafts may lead to a cosmetically undesirable effect, known as cobblestoning (the appearance of).[9] Punch micrografting assures an excellent repigmentation, with around 75% of treated patients reaching between 90 and 100% pigmentation.[10]

In the present study, the authors describe a variation of the punch micrografting technique, using even smaller and thinner grafts, aimed at achieving better aesthetical outcomes when compared to those obtained with the traditional technique in cases of stable vitiligo without response to clinical treatments.

METHODS

Two female patients bearing stable facial segmental vitiligo for more than two years without response to clinical treatment were selected (Figures 1 and 2). Both had been clinically treated with 1% hydrocortisone cream for 3 months and subsequently with 0.03% tacrolimus for another 3 months, totaling 6 months of treatment, during which they also underwent 2 weekly phototherapy sessions.

The selected donor area was the retroauricular region, from where fragments were harvested with 2mm punchs, after local anesthesia (Figure 3). Donor fragments are composed of epidermis, dermis and subcutaneous layers. After the removal, shaving was performed aimed at carefully separating the papillary dermis and epidermis from the reticular dermis and subcutaneous layer. Next, with the assistance of a magnifying glass, the grafts consisting only of dermis and epidermis were cut into ^{4}–^{6} smaller fragments (Figure 4).

After anesthetizing the recipient area, one of these small fragments was placed on the tip of an 18G needle and the anesthetized area pierced with the needle's bevel. With the aid of a forceps, the fragment was pushed into the orifice using the needle, which was carefully removed so as to leave the fragment at the perforated site (Figures 5 and 6). All the harvested fragments are implanted in the recipient area in this way, with an average distance of 1cm between them.

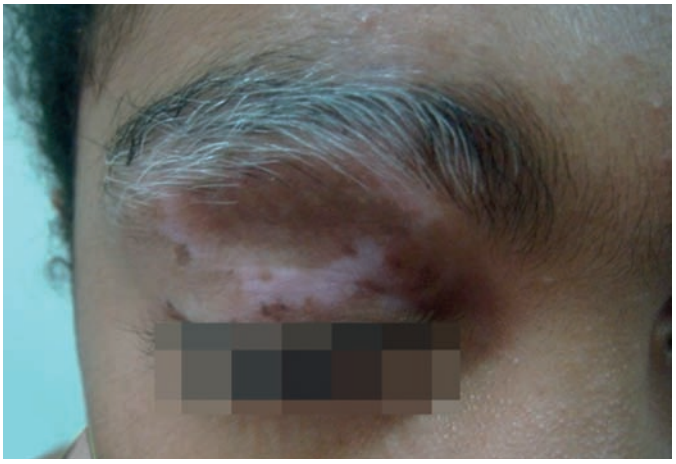

Figure 1: Stable vitiligo lesion before treatment – achromic macule in the left upper eyelid

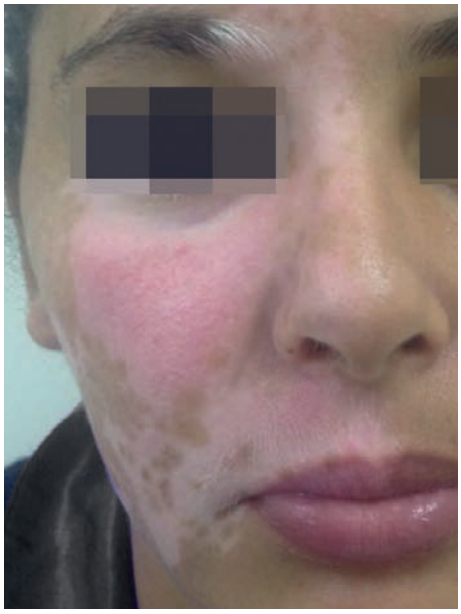

Figure 2: Stable vitiligo lesion before treatment - achromic macule in the regions of the glabella, cheek, upper lip's skin, right lateral nasal region and right mandibular region

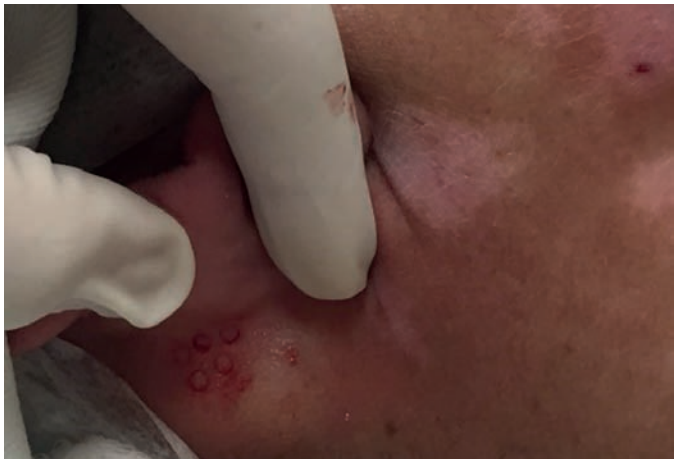

Figure 3: Fragments harvested from the donor area with the assistance of a punch

After the procedure, no local dressing was performed, as usual. Patients were instructed not to wash their face on the same day, not to remove hematic crusts nor rub with towels for 7 days. It is not necessary to use sunscreen, since the crusts themselves protect the micrografts. The treated patients underwent 2 weekly sessions of UVB phototherapy after the surgical stage: 27 sessions for the one who received the graft in the left upper eyelid region and 20 sessions for the other, who was treated in the regions of the glabella, cheek, upper lip's skin, right lateral nasal region and right mandibular region.

Figure 4: Donor fragment consisting of dermis and epidermis, cut into smaller fragments

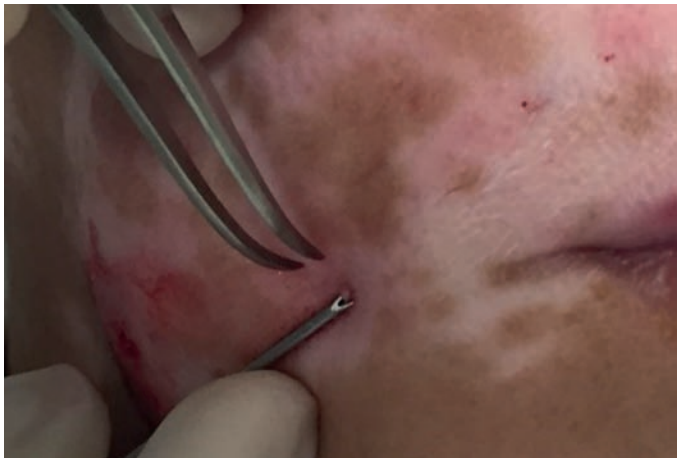

Figure 5: Graft implantation in the recipient area

RESULTS

Both patients experienced repigmentation in the treated area. The one who was treated in the left upper eyelid region underwent 3 surgical procedures, with an interval of 6 months between them, achieving 90% of repigmentation in the eyelid in the period of 6 months after the last surgery session (Figure 7). The other patient, who had vitiligo lesions in the regions of glabella, cheek, upper lip's skin, right lateral nasal wall and right mandibular region, underwent 2 surgical procedures with a 6-month interval between them, experiencing repigmentation in roughly 60% to 70% of the lesion up until 3 months after the last transplant of melanocytes (Figure 8).

With this technique, it was possible to observe that the donor fragment adapted to the recipient area in a simple and complete way, avoiding differences in the skin's surface that would otherwise evidence the grafted areas. The appearance of the treated area became smooth and aesthetically acceptable after the procedure, with repigmentation beginning close to the mini-grafts and spreading around. All implanted grafts promoted pigmentation. Both patients were satisfied with the treatment. There was no side effect in these cases.

DISCUSSION

Melanocyte transplantation is an important therapeutic option for patients with a stable disease that does not respond to classical treatment.[11] The surgical treatments available to treat vitiligo are aimed at promoting a reserve of melanocytes in order to stimulate repigmentation in refractory lesions.[12] In this manner, the authors used a variation of the micrografting technique of melanocyte transplantation to treat two female patients with facial lesions and suffering considerable psychological impact.

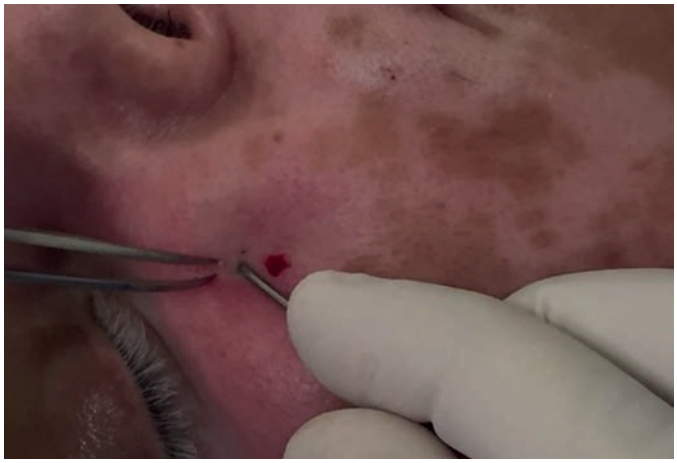

Figure 6: Graft implantation in the recipient area

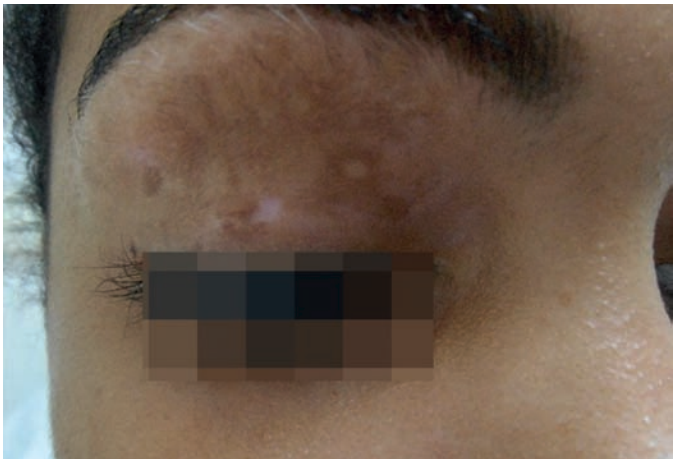

Figure 7: Repigmentation of the lesion after the treatment

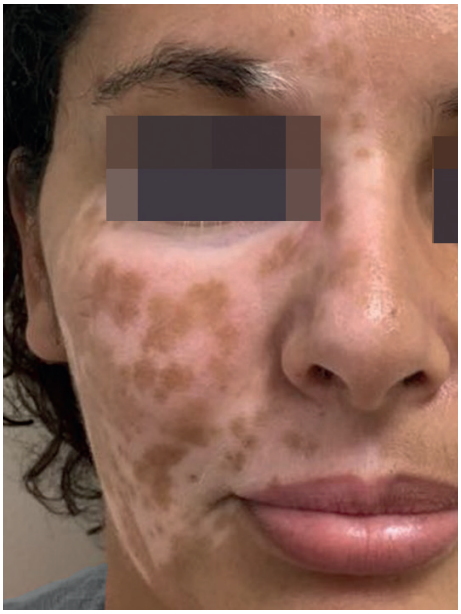

Figure 8: Graft implantation in the recipient area

Given that these are lesions affecting the face of women, it is crucial to take into account the aesthetic involvement. Therefore, the authors of the present article developed this technique, aiming at achieving better aesthetical outcomes than those obtained with the traditional punch micrografting technique, which may be associated with some adverse effects – such as static grafting (absence of spreading of the pigment), cobblestone effect, postinflammatory hyperpigmentation, graft failure and scar formation – considering it a variation of the traditional.[7,12]

By removing the subcutaneous layer and deep dermis from the graft, its possible to obtain a better fitting into the recipient area, preventing the graft from being more elevated than the surrounding skin. In addition, smaller fragments are associated with fewer local side effects and stimulate pigmentation as much as the traditional punch micrografting technique.

CONCLUSION

This variation of punch micrografting technique has proven effective in the repigmentation of two patients with stable vitiligo on the face. No side effects were observed, and there was good acceptance of the recipient area to the mini-grafts. The authors conclude that this variation of the traditional technique is promising in the treatment of stable vitiligo, in delicate areas that require considerable aesthetic concern. In addition, the technique is straightforward and inexpensive. Further studies are needed in order to verify these outcomes in a greater numbers of patients. ●

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DECLARATION OF PARTICIPATION:

Carlos R. Antonio | ORCID 0000-0001-9243-8293
Conceptual development of the technique, performed surgical treatment in one of the patients, final review of the manuscript

Lívia Arroyo Trídico | ORCID 0000-0002-7743-4195
Literature review, manuscript write up, performed surgical treatment in one of the patients

Thalita M. Machado | ORCID 000-003-2078-305X
Literature review, performed surgical treatment in one of the patients

João Roberto Antonio | ORCID 0000-0002-0268-5934
Final review of the manuscript

A-T flap for reconstruction of surgical wound in the nasal tip

Retalho A-T para reconstrução de ferida operatória na ponta nasal

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ABSTRACT

The nasal region is a frequent site of cutaneous tumors, and repairing defects in this region can be a great surgical challenge due to the need to restore their structural, functional and aesthetic properties. The present study describes the implementation of an A-T flap as an option for reconstructing surgical wounds secondary to the excision of basal cell carcinomas in the nasal tip.

Keywords: Carcinoma, Basal Cell; Nose; Surgical flaps

RESUMO

A região nasal é local frequente de tumores cutâneos, e reparar defeitos nessa região pode ser um grande desafio cirúrgico devido à necessidade do restabelecimento de suas propriedades estrutural, funcional e estética. Este estudo descreve a aplicação de um retalho A-T como opção para reconstrução de ferida operatória secundária à excisão de carcinoma basocelular na ponta nasal.

Palavras-Chave: *Carcinoma basocelular ; Nariz; Retalhos cirúrgicos*

INTRODUCTION

The reconstruction of surgical defects resulting from the excision of neoplasias in the nasal region poses a great challenge due to the anatomical site's characteristics, such as its stiff structure and low mobility. The authors of the present article describe the implementation of an A-T flap as an option for closing a surgical wound located in the nasal tip.

CASE REPORT

A 76-year-old Caucasian female patient had had an erythematous and infiltrative plaque at the nasal tip for 8 months, with prior incisional biopsy compatible with nodular basal cell carcinoma. Three-millimeter surgical margins were marked and the reconstruction was performed with an A-T flap, with incisions carried out in both nasal alar sulcus so as to allow bilateral advancement (Figure 1). The surgical defect resulting from the tumor's excision did not allow primary closure (Figure 2A), and the incisions planned for the A-T flap were then performed (Figure 2B). The flap was positioned and sutured with 5-0 mononylon thread, interspersed with 6-0 mononylon thread (Figure 3). Six months after, the patient had no signs of tumor recurrence, with an excellent aesthetic result (Figure 4).

Case Reports

Autors:
Théo Nicolacópulos[1]
Rogério Nabor Kondo[1]

[1] Department of Dermatology, Hospital Universitário Regional do Norte do Paraná, Universidade Estadual de Londrina (UEL), Londrina (PR), Brazil.

Correspondence:
Rogério Nabor Kondo
Hospital das Clínicas de Londrina (AEHU)
Rodovia PR 445, km 179 – Campus Universitário (UEL)
Londrina-PR – 86051990
E-mail: kondo.dermato@gmail.com

Received on: 12/11/2016
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This study was performed at the Dermatology Service of the Hospital Universitário do Norte do Paraná, Universidade Estadual de Londrina (UEL) – Londrina (PR), Brazil.

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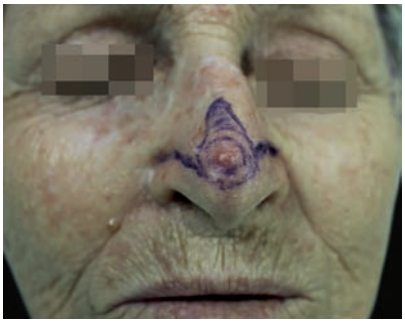

Figure 1: Marking of lesion with safety margins of 3mm and drawing of the A-T flap

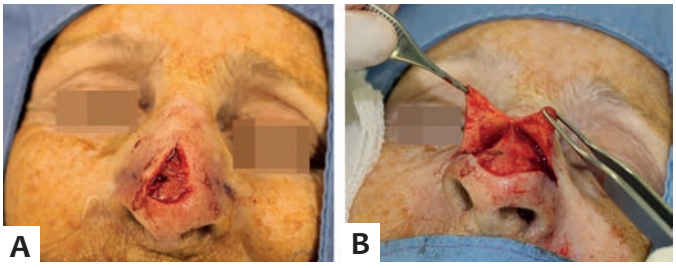

Figure 2: A - Appearance of the surgical defect after resection of the lesion, and **B –** flap's incision

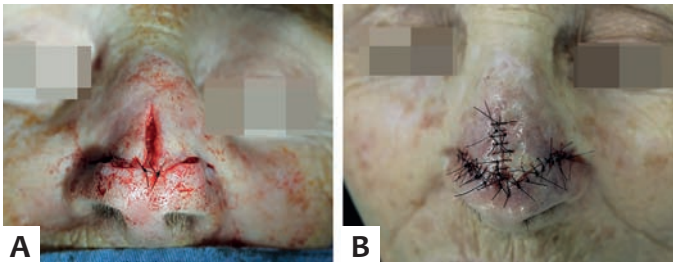

Figure 3: Flap positioned **(A)**, and sutured **(B)**

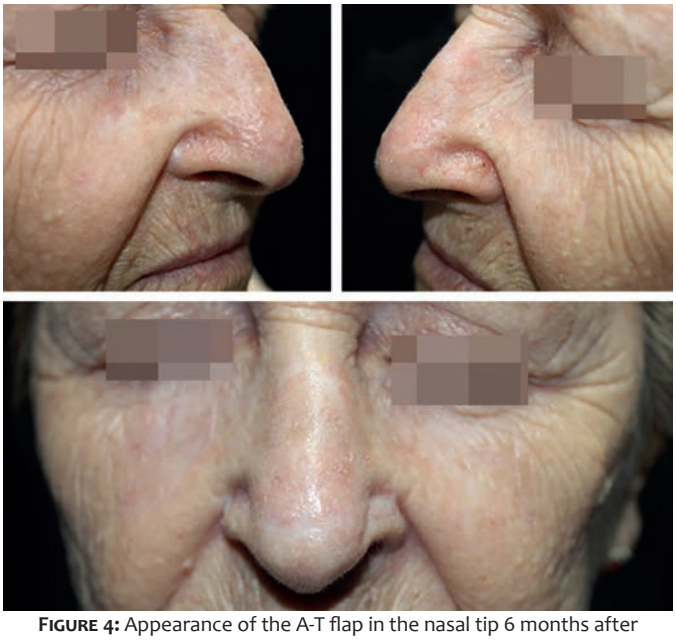

Figure 4: Appearance of the A-T flap in the nasal tip 6 months after

DISCUSSION

Cutaneous flap techniques may be required to close excisions of facial skin tumors.[1-4] At the same time, reconstructions in the nasal region might constitute a real challenge for the dermatological surgeon, due to the requirements of aesthetic and functional outcomes. Alternatives include primary closure, second intention healing, skin grafts or skin flaps. Nevertheless, several factors guide the surgical choice, and cutaneous flaps are an excellent option due to the similarity of the skin – in texture, color and thickness – used for the closure. Also, specifically in the nasal tip aesthetic subunit, the focus of attention should be directed to maintaining the shape, position, and contour, and to the scar.[5,6]

The A-T flap is classified as a bilateral advancement flap, according to its main motion towards the defect area.[2,4] It is an excellent method to solve a wide and deep defect whose adjacent tissue does not allow direct closure. It has the advantages of being able to be performed under local anesthesia and in a single surgical time.[4]

In the present case, the lesion in the nasal tip would correspond to the "A" shape and the bilateral incisions in the nasal alae folds, to the ceiling of the "T" shape', allowing bilateral advancement. Such technique observes the fundamental cosmetic principles, in a way that the incisions were strategically positioned at the junction of the nasal subunits, maximizing the camouflage of scars. There was good integration of the flap into the recipient area and excellent cosmetic appearance outcome (Figure 4).

CONCLUSION

The use of the A-T flap for the correction of surgical defects in the nasal tip observing fundamental cosmetic principles emerges as a surgical option with excellent aesthetic and functional outcomes. ●

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DECLARATION OF PARTICIPATION:

Théo Nicolacópulos | ORCID 0000-0001-7672-4337
Conceptual development and planning of the research project, manuscript preparation and write up, case dermatologic surgeon

Rogério Nabor Kondo | ORCID 0000-0003-1848-3314
Conceptual development, guidance and planning of the research project; preparation and write up of the manuscript; case dermatologic surgeon

Case Reports

Autors:
Ana Cláudia Cavalcante Espósito[1]
Angela Sanderson[2]
Jorge Ocampo-Garza[2]
Gustavo Alonso[1]
Carlos D'Apparecida S. Machado Filho[2]
Luiz Roberto Terzian[1]

[1] Department of Mohs Micrographic Surgery, Faculdade de Medicina do ABC, Santo André (SP), Brazil.
[2] Department of Dermatological Surgery, Faculdade de Medicina do ABC, Santo André (SP), Brazil.

Correspondence:
Luiz Roberto Terzian
Av. Albert Einstein, 627 - bloco A1 1º andar sala 122
Morumbi
05652-900, São Paulo, SP
E-mail: terzian@mohs.com.br

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This study was performed at the Faculdade de Medicina do ABC, Santo André (SP), Brazil.

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Necrosis of skin graft entailed by smoking habits

Necrose cutânea do tecido enxertado decorrente de tabagismo

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ABSTRACT

Adequate healing of surgical wounds is influenced by the operative technique, the presence of postoperative complications and the patient's life habits. We report the case of a patient submitted to excision of basal cell carcinoma by Mohs micrographic surgery and reconstruction with palpebral cutaneous grafting. In the postoperative period there was graft necrosis due to poor perfusion of the surgical bed imputed to smoking. Smoking interferes with plasma embolization and graft neovascularization, as well as promoting oxidative stress and endothelial dysfunction. The surgeon should counsel the cessation of smoking for at least four weeks prior to the procedure in order to avoid further risks of complications.

Keywords: Carcinoma, basal cell; Graft survival; Mohs surgery; Necrosis; Smoking

RESUMO

A cicatrização adequada das feridas cirúrgicas é influenciada pela técnica operatória, pela presença de intercorrências pós-cirúrgicas e pelos hábitos de vida do paciente. Relatamos caso de paciente submetido a exérese de carcinoma basocelular por cirurgia micrográfica de Mohs e reconstrução com enxertia cutânea palpebral. No pós-operatório houve necrose do enxerto devido má perfusão do leito cirúrgico imputada ao tabagismo. O tabagismo interfere na embebição plasmática e neovascularização do enxerto, além de promover estresse oxidativo e disfunção endotelial. O cirurgião deve orientar a suspensão do tabagismo por pelo menos quatro semanas antes do procedimento, a fim de evitar maiores riscos de complicações.

Palavras-Chave: *Carcinoma basocelular; Cirurgia de mohs; Hábito de fumar; Sobrevivência de enxerto; Necrose*

INTRODUCTION

Cutaneous tumors located in periorificial regions – periorbital, perioral, nasal tip and ala – should be treated with redoubled attention. Tissue retraction becomes more critical in areas of free borders and, consequently, there is a greater probability of functional impairment as a result from inadequate reconstructions.[1,2] Flaps and grafts can be used in these locations to close surgical defects, aiming at preserving function and aesthetics.

Adequate healing of surgical wounds is influenced by the technique performed by the surgeon, operative and postoperative complications, in addition to patient-specific factors and life style habits.

The authors of the present article describe and discuss the case of a patient who underwent palpebral cutaneous grafting, whose result was unsatisfactory in the immediate postoperative period due to poor tissue perfusion attributed to smoking habits.

CASE REPORT

A 78-year-old man reported the onset of an asymptomatic, slow-growing lesion in the right upper eyelid ten years before. The patient was a smoker (three packs per day for 63 years), hypertensive (under use of 10mg enalapril 12/12 hours) and had had a CVA 9 years before. Also, he had been recently diagnosed with chronic obstructive pulmonary disease, due to the high smoking load, however was not using specific medications.

At the dermatological examination, the patient had a 1.6 cm x 1cm perlaceous nodule with a depressed center and inaccurate limits, located in the canthus of the right eye affecting both the upper and lower eyelids (Figure 1). Under dermoscopy, the lesion presented arboriform telangiectasias on the surface. The patient's nails and beard had a yellowish tone.

The patient underwent Mohs micrographic surgery, with two phases for complete removal of the tumor. The final surgical size was 2.3cm x 1.8cm, and the surgical wound affected the inner canthus of the right eye, upper and lower eyelid as well as the right (proximal) nasal lateral (Figure 2). A solid and adenoid basal cell carcinoma was evidenced.

Due to the involvement of three aesthetic units in an area of free edge and little local availability of tissue that could be mobilized without interfering with the ocular opening, the authors made a decision for closing the surgical wound using a full-thickness skin graft. The chosen donor area was the contralateral upper eyelid, due to the presence of redundant tissue with similar characteristics to that of the recipient area. A thin graft containing epidermis and dermis was sutured to the wound's edges with 6-0 nylon thread. Aimed at increasing the adhesion to the bed, a Brown's dressing was applied on the graft.

On the 7th postoperative day, the Brown's dressing and stitches were removed. The graft was violet in color, with areas of loss of the epidermis and covered by fibrinoid tissue. Only local cleansing was carried out in order to keep the site wet (Figure 3).

By day 14, the entire thickness of the graft was black and hardened (full-thickness necrosis). Debridement was performed with a blade, and the occlusive dressing was kept in place to ensure wetness of the wound bed (Figure 4-A). On day 21, the patient had an ulcer secondary to the loss of the graft due to necrosis (Figure 4-B).

In the 4th postoperative week, the second intention healing process ensured the complete closure of the surgical defect (Figure 5).

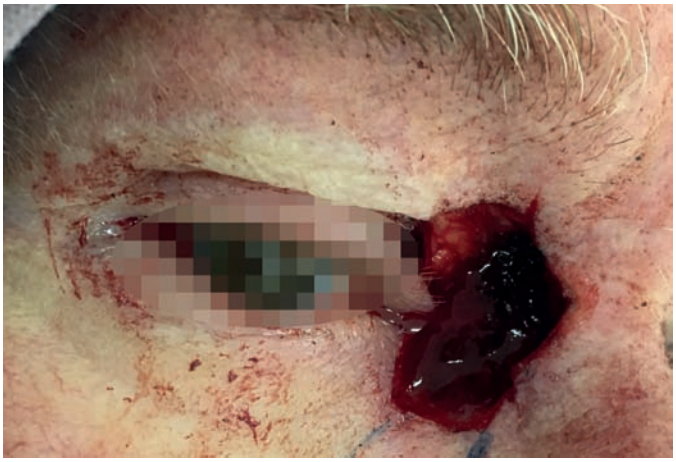

Figure 2: Operative wound after Mohs micrographic surgery, with Involvement of the right inner canthus, upper and lower eyelids, as well as right (proximal)

DISCUSSION

The most frequently used graft donor areas for the reconstruction of facial surgical defects are the retroauricular, preauricular and upper palpebral regions. The palpebral region offers reduced thickness of the epidermis and dermis, which facilitates adherence to the surgical bed and nutrition. [2] With the aging process, there is accumulation of skin in this region, and its use as a graft donor area in fact generates a cosmetic gain to the patient.[2]

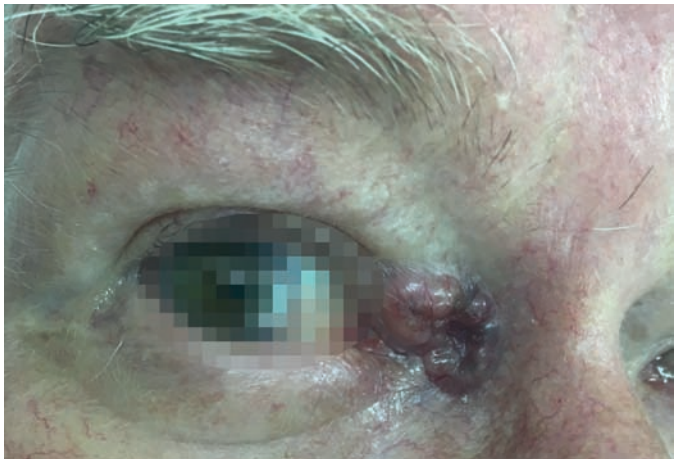

Figure 1: Perlaceous nodule with arboriform telangiectasias, located in the right canthus, affecting both eyelids

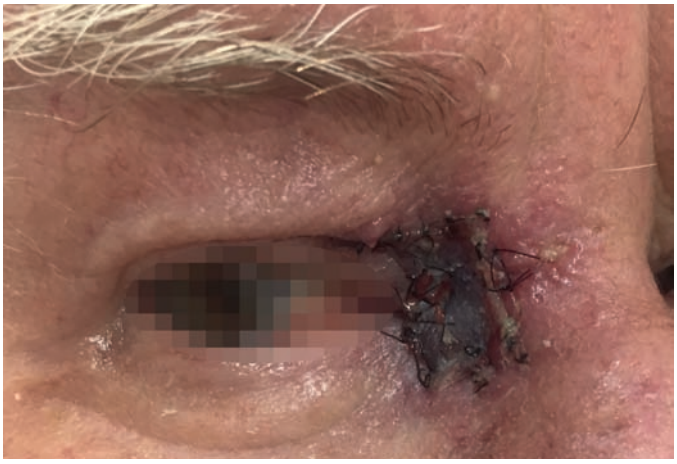

Figure 3: Seventh postoperative day - violaceous graft with areas of epidermal loss

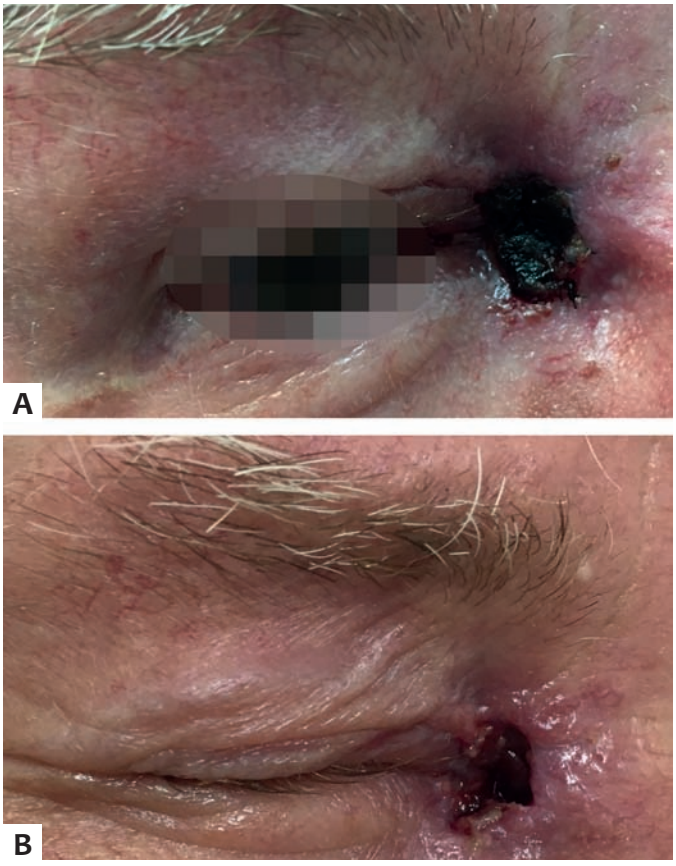

Figure 4 - A - Full-thickness necrosis of the graft on the 14th postoperative day **B -** Ulcer secondary to graft loss (21st postoperative day)

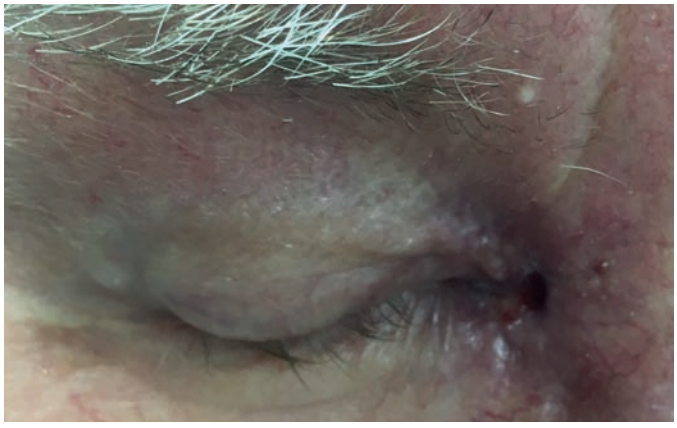

Figure 5: Complete healing by second intention on the 28th postoperative day

Graft integration involves adherence to the bed, adequate perfusion, and donor skin viability. In the first 24 hours, its nutrition and fixation occurs by transudation from the bed, with the formation of a fibrin mesh. The second phase, termed inosculatory, sees the anastomosis of small capillaries communicating the graft's surface to the recipient bed. From the 5th to the 7th postoperative day there is true blood flow, resulting from the emergence and proliferation of new vessels.[3]

Of the total skin grafts, 20% have some degree of necrosis. Most of the time, there are alterations only in the granulosum, lucidum and corneum layers (partial necrosis). When the basal and spinosum layers are affected, there is total necrosis of the graft.[4]

Roughly 12% of the patients who undergo Mohs micrographic surgery have postoperative complications, with graft loss accounting for one-third of the total.[5] Factors that may trigger necrosis include hematoma or seroma formation, infection, poorly vascularized bed, poor adhesion of the graft to the bed, excessively thick graft and with subcutaneous cellular tissue. Infection rates, even when adjusted for the type of the surgery, size of the incision and tissular trauma, increase according to a linear ratio *vis à vis* longer surgical times.[6,7] Cutaneous surgeries involving grafting are generally procedures of longer duration and complexity, which might result in a risk of postoperative infection . Total thickness skin grafts are more resistant to infection than those of partial thickness, and loss of the graft resulting from infection is more common in grafts implanted in the lower extremities or in those performed in multiple sites in the same surgical time.[8]

Characteristics of patients, such as obesity, malnutrition, anemia, immunosuppression, use of medicaments and comorbidities also greatly alter the healing process.[9,10]

Pérez-Guisado et al. found that 18% of smokers had graft necrosis.[11] This risk is linked to the number of cigarette packets consumed per day: patients who experience necrosis smoke significantly more than those who are also smokers however do not experience necrosis after undergoing a grafting procedure.[12] Smoking induces a decrease in the number of macrophages and neutrophils, and an increase in platelet aggregation, which stimulates the formation of microcoagulants.[13] Nicotine causes vasoconstriction, which lasts up to 10 minutes after smoking cessation, facilitating the occurrence of acute microvascular occlusion and tissue necrosis.[12]

Cigarette smoke contains carbon monoxide and hydrogen cyanide. The former has 220 times more affinity for hemoglobin than oxygen, reducing the ability of oxygen conveyance to the tissues. On its turn, hydrogen cyanide is able to inhibit cellular respiration, resulting in lactic acidosis and cytotoxic hypoxia.[12] Cavichio et al. have identified ten studies that show that cessation of smoking for a minimum period of four weeks is beneficial in reducing healing complications in surgical wounds.[14]

In periocular graft surgeries, 15% of patients experience complications. Of this total, graft loss corresponds to 10%.[15] In the present clinical case, the donor area (contralateral upper eyelid), as well as the execution of the surgical technique, were adequate. There was no postoperative infection, graft displacement or even hematoma formation. Reconstructive failure was attributed to poor bed perfusion induced by long-term smoking, which was also responsible for the yellowing of the nails and beard hairs, as well as for the development of chronic obstructive pulmonary disease.

CONCLUSION

Smoking is a complication factor for the healing process, as it interferes with the process of plasma soaking and graft neovascularization. The inflammatory stimulus, the oxidative stress and the endothelial dysfunction caused by the cigarette are promoters of necrosis of the grafted tissue.

The surgeon should be aware of the increased risk of complications in patients with smoking habits and needs to advise him or her to cease smoking for at least four weeks before the procedure. ●

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DECLARATION OF PARTICIPATION:

Ana Cláudia Cavalcante Espósito | ORCID 0000-0001-9283-2354
Literature reports analysis, literature compilation, preparation of the initial manuscript

Angela Sanderson | ORCID 0000-0002-3293-4508
Literature data compilation, image editing, review of the initial version of the manuscript, organization of references

Jorge Ocampo-Garza | ORCID 0000-0002-1307-3407
Literature data compilation, image editing, review of the initial version of the manuscript, organization of references

Gustavo Alonso | ORCID 0000-0003-0484-6399
Final review of the manuscript, preparation of the final version

Carlos D'Apparecida S. Machado Filho | ORCID 0000-0003-4362-1563
Final review of the manuscript, preparation of the final version

Luiz Roberto Terzian | ORCID 0000-0002-9342-7227
Final revision of the manuscript, preparation of the submission version

Case Reports

Autors:
Isabella Lemos Baltazar[1]
Talita Pollo[1]
Flávia Regina Ferreira[1]
Elisangela Manfredini Andraus de Lima[1]
Fernanda da Rocha Gonçalves[2]
Samuel Henrique Mandelbaum[1]

[1] Department of Dermatology, Hospital Universitário de Taubaté, Universidade de Taubaté, Taubaté (SP), Brazil.
[2] Hospital do Servidor Público Estadual, São Paulo (SP), Brazil.

Correspondence:
Flávia Regina Ferreira
Avenida Granadeiro Guimarães, 270 - Centro - 12020-130, Taubaté (SP), Brasil.
Email: dermagica@uol.com.br

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This study was performed at the Hospital Universitário de Taubaté, Universidade de Taubaté, Taubaté (SP), Brazil.

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Basal cell carcinoma, papillary syringocystadenoma, apocrine adenoma and trichilemmoma on nevus sebaceous of Jadassohn

Carcinoma basocelular, siringocistoadenoma papilífero, adenoma apócrino e triquilemoma sobre nevo sebáceo de Jadassohn

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.20181021107

ABSTRACT

Described by Jadassohn and also known as organoid nevus, nevus sebaceous is considered a hamartoma that exhibits follicular, sebaceous, eccrine and apocrine malformations of varying degrees. Between 10% and 30% of patients with sebaceous nevi of Jadassohn are at risk of developing cutaneous or adnexal neoplasia during adulthood. The authors describe the case of a patient with nevus sebaceous of Jadassohn associated with multiple tumors (benign and malignant) of different strains, highlighting the importance of the dermatologist physician's knowing this entity and how to perform an examination of the scalp.

Keywords: Carcinoma, Basal Cell; Hamartoma; Neoplasms; Nevus sebaceous of Jadassohn

RESUMO

Descrito por Jadassohn e também conhecido como nevo organoide, o nevo sebáceo é considerado hamartoma que exibe má-formação folicular, sebácea, écrina e apócrina de graus variados. Durante a idade adulta, de dez a 30% dos pacientes com nevo sebáceo de Jadassohn têm risco de desenvolver neoplasia cutânea ou anexial. Relatamos caso de paciente com nevo sebáceo de Jadassohn associado a múltiplas neoplasias (benignas e malignas) de diferentes linhagens e ressaltamos a importância do conhecimento dessa entidade e do exame do couro cabeludo por parte do dermatologista.

Palavras-Chave: *Carcinoma basocelular; Hamartoma; Nevo sebáceo de Jadassohn; Neoplasias*

INTRODUCTION

Originally described by Jadassohn in 1895, it was only in 1932 that it was termed "sebaceous nevus", which was introduced by Robinson.[1,2] This condition is a relatively prevalent congenital hamartoma that classically develops through phases of growth and maturation, exhibiting follicular, sebaceous, eccrine and apocrine malformations of varying degrees.[3,4] Several HRAS and KRAS activating mutations have been reported in sebaceous nevi, allowing some authors to see them as a result of a proliferative state of total skin somatic mosaic.[4]

During adulthood, 10% to 30% of patients with nevus sebaceous of Jadassohn (NSJ) are at risk of developing cutaneous or adnexal neoplasia.[3,4]

The authors of the present case report a case of patient bearing NSJ associated to multiple neoplasms (benign and ma-

lignant) of different lineages, emphasizing the importance of knowing this condition and of undergoing examination of the scalp by a dermatologist.

CASE REPORT

A 65-year-old female patient complained of pruritus on the scalp for a month. On examination, it was possible to observe in the occipital region: a slightly erythematous verrucous plaque measuring around 2.5 cm on its longest axis (Figures 1 and 2). According to the patient, she bore an asymptomatic lesion on the scalp since birth, and that had been pruritic for a month. The authors decided to carry out an incisional biopsy of the lesion, which was sent to histological examination, evidencing a nodular basal cell carcinoma (Figure 3). The complete excision of the lesion was performed with safety margins. The histology revealed a sebaceous nevus associated with syringocystadenoma papilliferum, apocrine tubular adenoma, trichilemmoma (Figures 4 to 7), and scarring dermal fibrosis.

DISCUSSION

The NSJ, also known as organoid nevus, emerges more frequently in the scalp, however it can arise in the face and, less commonly, in the limbs.[3,5] It occurs in approximately 0.3% of individuals, with no gender preference. The lesion is usually present at birth and has the appearance of a well-defined plaque composed of multiple confluent yellow-orangish or yellow-brownish papules, predominantly in the scalp, where it progresses with alopecia at the site of the lesion.[3] It has a bimodal distribution: during puberty its surface becomes thickened and verrucous due to hormonal stimuli to the eccrine and apocrine components, while in adulthood the lesion may become nodular with the occurrence of ulcerations and crusts. The possibility of

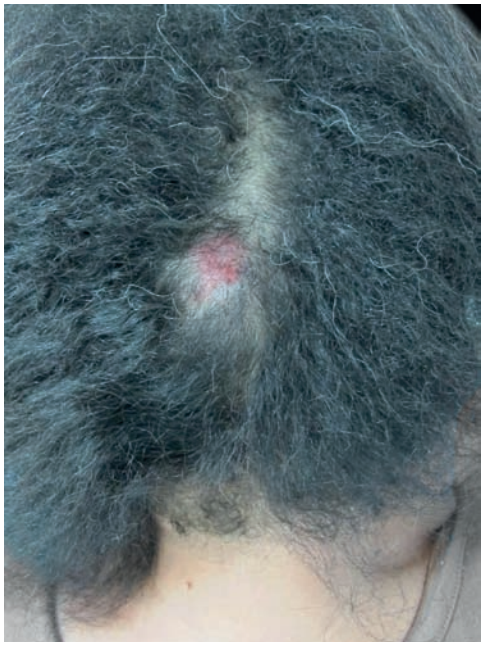

Figure 1: Occipital region: slightly erythematous verrucous plaque

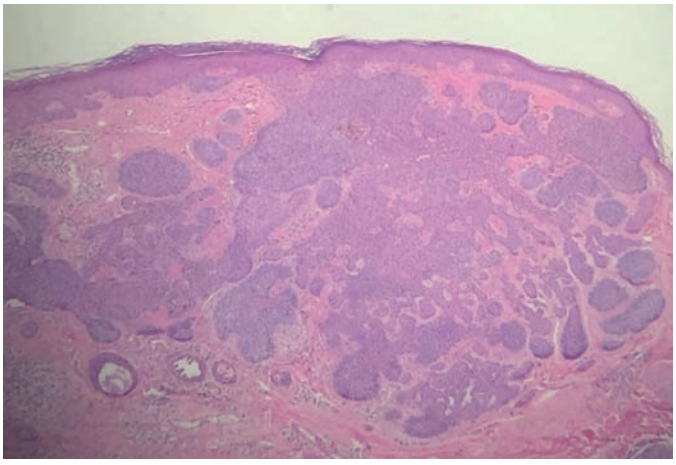

Figure 3: Basaloid epithelial proliferation forming blocks with peripheral palisade, compatible with basal cell carcinoma (Hematoxylin & eosin x40)

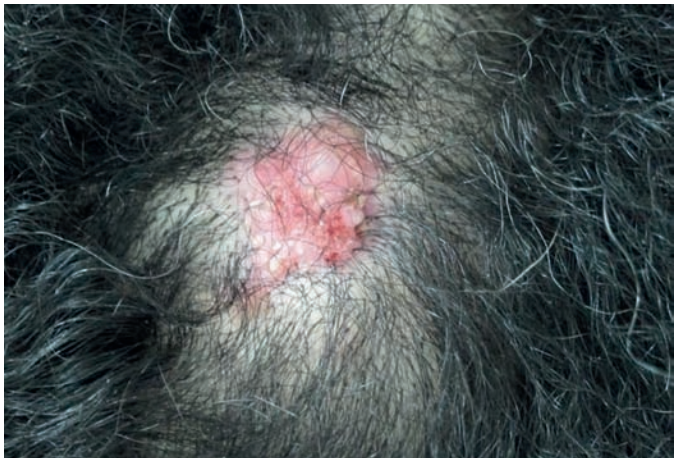

Figure 2: Occipital region: detail of the lesion

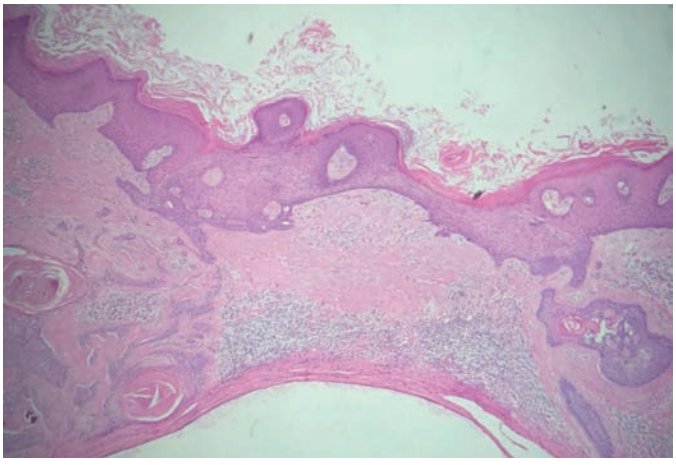

Figure 4: Cutaneous papillomatosis with hyperkeratosis and acanthosis, compatible with sebaceous nevus (Hematoxylin & eosin x100)

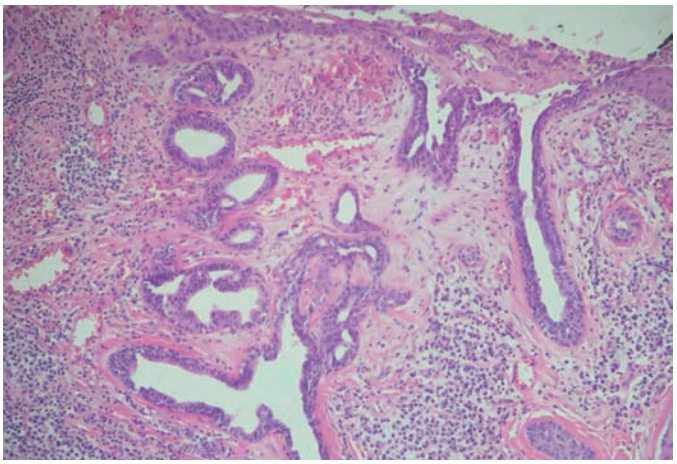

Figure 5: Glandular epithelial proliferation, compatible with syringocystadenoma papilliferum (Hematoxylin & eosin x100)

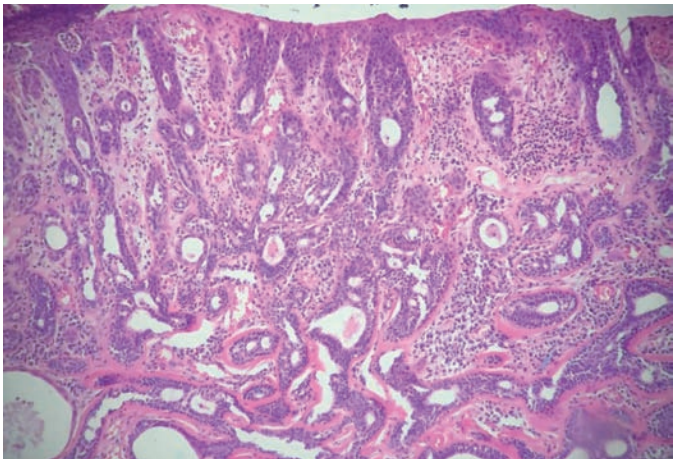

Figure 6: Glandular epithelial proliferation with characteristics typical of apocrine adenomatous lesion (Hematoxylin & eosin x40)

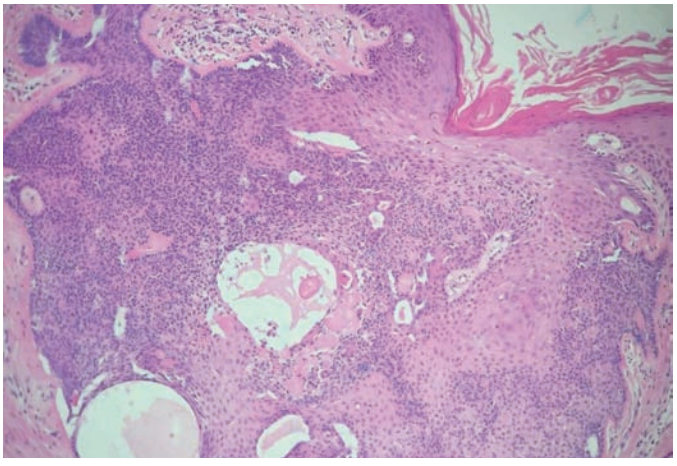

Figure 7: Basaloid epithelial proliferation connected to the epidermis, with presence of corneous cysts and clear cell's trichilemmoma-like components (Hematoxylin & eosin x100)

secondary neoplasms in this phase ranges from 10% to 30%, the main ones being basal cell carcinoma, papillary syringocystadenoma (both observed in the patient described in the present report), and trichoblastoma.[3]

Other tumors already described in association with NSJ include benign ones –trichilemmoma (also present in the described patient), trichoadenoma, nodular hidradenoma, apocrine hidrocystomas, syringoma, apocrine nevus, poroma, spiradenoma, keratoacanthoma, piloleiomyoma, osteoma, melanocytic nevus, seborrheic keratosis and keratoacanthoma; [4,6-8] and malignant ones – squamous cell carcinoma, sebaceous carcinoma, apocrine carcinoma, leiomyosarcoma, eccrine porocarcinoma, and melanoma.[6,9]

There is no consensus on the ideal approach. Some authors recommend early surgical excision (pre-pubertal) aimed at preventing malignant and aesthetically disfiguring transformations. Others, however, advocate a more conservative behavior. Future studies might identify molecular markers or genetic alterations that could indicate a greater risk of neoplastic transformation, thus avoiding unnecessary surgical interventions.[10]

The diversity of tumors of different lineages detected in a single lesion motivated the authors to prepare this report emphasizing the importance of the knowledge and development of this entity (NSJ), and calling attention to the relevance of the examination of the scalp during dermatological consultations. ●

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DECLARATION OF PARTICIPATION:

Isabella Lemos Baltazar | ORCID 0000-0002-9731-4414
Conceptual development, photographic records, literature review; preparation, write up and approval of the manuscript's final version

Talita Pollo | ORCID 0000-0003-4877-7970
Conceptual development, photographic records, literature review; preparation, write up and approval of the manuscript's final version

Flávia Regina Ferreira | ORCID 0000-0001- 5679-4282
Conceptual development, research project oversight, literature review; preparation, write up, critical review and approval of the manuscript's final version

Elisangela Manfredini Andraus de Lima | ORCID 0000-0002-2390-0410
Conceptual development and planning of the research project, therapeutic approach implementation, approval of the final version

Samuel Henrique Mandelbaum | ORCID 0000-0002-4631-4828
Conceptual development, literature review, approval of the manuscript's final version

Fernanda Rocha Gonçalves | ORCID 0000-0003-2933-2845
Conceptual participation in the diagnosis, photographic records, histological examination description, approval of the final version

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