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ERRATAS

- Foi publicado errado o local de realização do artigo Delineamento epidemiológico dos casos de melanoma cutâneo atendidos em um hospital terciário de Campinas, São Paulo, Brasil (v. 6, n. 3, p.262-6.). O local de realização do trabalho correto é Pontifícia Universidade Católica de Campinas(PUC-Campinas) - Campinas (SP), Brasil.

- Houve um equívoco na publicação do local de realização do artigo Tratamento cirúrgico do tumor glômico subungueal orientado pela ultrassonografia doppler (v.6, n. 3, p. 278-80.). O local correto é Instituto de Dermatologia Prof. Rubem David Azulay da Santa Casa da Misericórdia do Rio de Janeiro (IDPRDA/SCMRJ) – Rio de Janeiro (RJ), Brasil.

- Faltou publicar um quadro no artigo Ácido chiquímico para esfoliação cutânea, v. 6, n. 3, p. 242. O quadro faltante segue abaixo:

QUADRO 1: Ficha de avaliação sensorial

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Espalhabilidade	☐ ☐ ☐ ☐
Hidratação	☐ ☐ ☐ ☐
Suavidade da pele	☐ ☐ ☐ ☐
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INSTRUÇÕES AOS AUTORES

A Surgical & Cosmetic Dermatology, editada em 2009, constitui publicação médica destinada a difundir conhecimento e experiência nas áreas de Cirurgia Dermatologica, Cosmiatria e Procedimentos Dermatológicos Diagnósticos e Terapêuticos utilizando novas Tecnologias. É uma publicação trimestral da Sociedade Brasileira de Dermatologia que conta com o apoio científico da Sociedade Brasileira de Cirurgia Dermatológica e do Colégio Íbero Latino de Dermatologia, que baseia sua política ética e editorial nas regras emitidas pelo The International Committee of Medical Journal Editors (www.icmje.org). Os manuscritos devem estar de acordo com os padrões editoriais para artigos submetidos a periódicos biomédicos estabelecidos na Convenção de Vancouver (Requisitos Uniformes para Manuscritos Submetidos a Revistas Biomédicas), regras para relatos de ensaios clínicos e revisões sistemáticas (metanálises).

Serão produzidos exemplares impressos da versão em língua portuguesa, com resumos e títulos em inglês. A versão da língua inglesa estará disponível no website da SBD.

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As pesquisas em seres humanos devem ter a prévia aprovação de um Comitê de Ética em Pesquisa e obedecer aos padrões éticos da Declaração de Helsinki de 1975, revista em 2000.

ORIENTAÇÕES PARA O PREPARO DOS ARTIGOS

A preparação correta do manuscrito torna os processos de revisão e publicação mais eficientes. Assim, recomendamos alguns cuidados que podem facilitar significativamente a preparação dos manuscritos.

1- Os artigos devem ser originais e redigidos no idioma de origem do autor (português, espanhol ou inglês): a equipe editorial providenciará as versões necessárias.

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4- Os autores devem informar o nome com suas abreviaturas, a titulação máxima, as instituições aos quais estão vinculados e local de realização do trabalho. Um deles deve ser designado como autor correspondente, com endereço completo, números de telefone comercial e fax e endereço de e-mail.

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9- Devem ser evitadas informações introdutórias extensas e repetitivas, dando-se preferência às mais recentes, ainda não publicadas. Evite textos com repetição da mesma informação no resumo, introdução e discussão.

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12- Após a sequência de itens para cada tipo de trabalho podem se acrescentados agradecimentos, antes das referências bibliográficas.

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13B. Capítulo de livro:

Reppert SM. Circadian rhythms: basic aspects and pediatric implications. In: Styne DM, Brook CGD, editors. Current concepts in pediatric endocrinology. New York: Elsevier; 1987. p .91-125.

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É o relato de uma pesquisa investigativa original clínico-cosmiátrica ou relacionada a procedimentos na área de Dermatologia. Exemplos: estudos experimentais, estudos clínicos, comparações e descrições de técnicas ou de métodos de avaliação, estudos de áreas afins (ex: estudos farmacêuticos em cosmiatria).

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O texto deverá conter até 4000 palavras, 10 ilustrações e 35 referências e seguir o formato IMRDC (Introdução e objetivo, Métodos, Resultados, Discussão, Conclusão)

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.

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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.

b- Local: indicar onde o estudo foi realizado (instituição privada ou pública), citar que a pesquisa foi aprovada pelo Comitê de Ética em Pesquisa de sua instituição, os procedimentos de seleção, os critérios de inclusão e exclusão, e o número inicial de pacientes.

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"). Esses 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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Artigos originais, breves, abordando resultados preliminares de novos achados de interesse para a Cirurgia Dermatológica, Cosmiatria ou Oncologia cutânea entre outros. Texto com formatação semelhante ao artigo original, resumo estruturado de até 200 palavras. Limite: texto até 2000 palavras, 8 ilustrações e 15 referências.

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Poderão ser abordados temas cirúrgicos ou de cosmiatria, procedimentos, algoritmos , compilações, estatísticas. Estes trabalhos têm formato livre, porem devem conter resumo não estruturado de até 100 palavras e conclusões ou considerações finais. Limite: texto até 6000 palavras, 10 ilustrações e 60 referências. Os artigos de revisão sistemática ou metanálises devem seguir orientações pertinentes (http://cochrane.bireme.br)

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Os autores são solicitados a definir objetivos educativos para o artigo que transmitam o que o participante deve ter absorvido após completar a atividade de EMC (ex: identificar uma condição, conhecer seus tratamentos, selecionar a melhor técnica). O entendimento destes objetivos devem ser mensurados por meio de 10 perguntas com respostas em 5 alternativas, cujo gabarito deve também ser enviado.

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Imagens de dermatoscopia, microscopia confocal, ultrassom e outros métodos, aplicadas à cirurgia dermatológica e cosmiatria, acompanhadas de curta descrição. Resumo não estruturado de até 100 palavras,texto até 1200 palavras, 8 ilustrações e 10 referências.

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Descrição de casos ou serie de casos de particular interesse nas áreas de Cirurgia Dermatológica, Oncologia Cutânea, Cosmiatria, Tratamento de dermatoses inestéticas, Complicações, etc.

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Editorial

Dear Readers,

The Brazilian Society of Dermatology's journal, *Surgical & Cosmetic Dermatology*, enters its 7th year of publication honored with contributions from some of Brazil's most highly esteemed figures in the field of Dermatology.

In the New Techniques section of 2014's closing issue, the publication features articles describing two very interesting procedures that provide evidence of the comprehensive creativity and experience of Professor Neide Calil Gaspar and Professor Ival Peres Rosa. It is with great honor that our journal disseminates these techniques, which were developed and performed for many years by these respected experts in the field.

In addition, several other excellent articles – resulting from the diligence and hard work being carried out in Dermatologic Surgery and Cosmetic Dermatology clinics throughout Brazil—can be found in the current issue.

The Board of Editors most sincerely appreciates the contributions of these true masters, who graciously and generously reward us with their wisdom.

We wish all readers an excellent and productive 2015!

Dr. Bogdana Victoria Kadunc
Scientific Editor of *Surgical & Cosmetic Dermatology*

Continuing Medical Education

Field cancerization: a review article

Campo cancerizável: artigo de revisão

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ABSTRACT

Solar or actinic keratosis is a frequent pre-malignant lesion that often occurs in areas exposed to sunlight, and has a 6-10% relative risk of developing into squamous cell carcinoma. Patients with actinic keratosis have multiple and confluent subclinical lesions, leading to the characterization of the condition as being of the field cancerization type. They are multifocal areas with genetic mutations that may become the site of new primary tumors and local recurrence. In recent years, there has been increasing interest in the development of non-invasive diagnostic tests and treatment for these subclinical lesions, with an aim at preventing squamous cell carcinoma.

Keywords: keratosis, actinic; carcinoma, squamous cell; phototherapy.

RESUMO

A queratose solar ou actínica é lesão pré-maligna frequente que ocorre em áreas expostas à luz solar com risco relativo de seis a 10% de desenvolver carcinoma espinocelular. Pacientes com queratoses actínicas apresentam lesões subclínicas múltiplas e confluentes que caracterizam o conceito de campo de cancerização. São áreas multifocais com mutações genéticas que poderão constituir a sede de novos tumores primários e de recorrência local. Nos últimos anos, tem aumentado o interesse para desenvolver exames de diagnóstico não invasivos e tratamento dessas lesões subclínicas para prevenção do carcinoma espinocelular.

Palavras-chave: *ceratose actínica; carcinoma de células escamosas; fototerapia.*

INTRODUCTION

Solar or actinic keratosis (AK) is a common premalignant lesion that affects areas exposed to sunlight.[1,2] It occurs mainly in adults and the elderly due to chronic exposure to ultraviolet radiation.[3] In Australia it affects approximately 40-50% of individuals over the age of 40, due to the large proportion of individuals in the population with skin phototypes I and II. In the northern hemisphere, the prevalence range is 11-25% in the 40 years and older population.[4] It is estimated that the relative risk of an individual bearer of AK developing squamous cell carcinoma (SCC) is 6-10%.[4] The risk of AK progressing to an invasive SCC is calculated at 0.025%-20% per year (calculation based on population rather than on a single individual).[1,4] The groups at highest for development of SCC are: fair-skinned individuals with excessive exposure to sunlight (occupational or recreational), immunosuppressed patients, and the elderly.[4]

In some patients it is possible to observe multiple AK lesions and, in these cases, the concept of field cancerization can be used. Field cancerization is a region containing subclinical and multifocal precancerous abnormalities with genetic mutations that may become sites of new primary tumors and local recurrence.[5,6] Field cancerization has been the subject of some studies. It can be found in most clinically healthy skin areas around AK lesions and presents characteristic AK alterations in the histology.[7] In recent years there has been increasing interest in the development of noninvasive diagnostic tests to confirm not only clinically suspected AK lesions, but also to detect and define subclinical lesions.[5,6] Field cancerization should be treated, and new therapeutic strategies have been developed for this purpose.

Clinical picture

The clinical appearance of AK is that of a maculopapular lesion covered with dry, hard scales with a rough surface and variable in color (from yellow to dark brown), measuring from 0.5 to 1.0 cm. It can also converge and form plaques. Typically, AK lesions are located in areas exposed to sunlight such as the face, ears, neck, in the "V" of the neckline area, forearms, back of hands, legs, and in the scalp of bald individuals. The appearance of an erythematous halo or infiltration of the lesion, the presence of lesions more than 1 cm in diameter, fast growth, bleeding, erythema and ulceration may indicate progression to SCC.[3,4] In 2007 there was a proposal for the clinical classification of AKs into three subtypes: Grade 1 - lesions are slightly palpable, but not very visible; Grade 2 - lesions are in the shape of erythematous scaly plaques, easily palpable and visible; Grade 3 - hyperkeratotic lesions. There is controversy in the literature regarding how to differentiate a Grade 3 AK and an initial CEC.[8]

Patients with significant photodamage and AKs often have subclinical lesions that may be multiple, confluent, and become more apparent with time, a picture that is aligned with the field cancerization concept.[3] The number of sub-clinical lesions in a field cancerization area can be ten times higher than the number of clinically visible AKs. The high recurrence after treatment of AKs is due to the absence of treatment of these lesions. The diagnosis and treatment of AKs and subclinical lesions is key to preventing SCC.[4]

Actinic keratosis is currently considered an incipient *in situ* SCC that develops in a process involving several stages, where UV radiation leads to the formation of an AK field cancerization, culminating in the onset of SCC.[9] The SCC and the AK are often contiguous lesions. In a study evaluating more than 1,000 SCCs located in areas exposed to sunlight, almost 100% of the lesions showed histological alterations consistent with AKs in the periphery of the lesions.[4]

Diagnosis

A) Histopathological examination

The diagnosis of AK is based on the clinical picture, however the most frequently used test for its determination is a histology test. During the biopsy collection it is necessary that the dermis be included in order to exclude invasive SCC.[4]

The initial histologic picture for AK is characterized by the presence of atypical keratinocytes in the basal layer of the epidermis. In its progression it affects other layers of the epidermis. The maturation of the keratinocytes in the epidermis is poor, resulting in hyperkeratosis and parakeratosis. The epithelial tissue around the glands is spared, keeping their normal appearance and keratinization, with an orthokeratotic stratum corneum in the region over these annexes. Actinic keratosis often presents with a dermal solar elastosis and often has lymphocyte infiltration. Therefore, the AK has the following histologic characteristics: parakeratosis, cellular and nuclear pleomorphism, disorder in the epidermal architecture, dyskeratosis and cellular atypia in part of the epidermis, without involvement of the epithelial tissue of the cutaneous appendages. The histological picture of field cancerization's subclinical lesions is similar to that of the AK.[3,7,10-12]

Nevertheless, while histology remains the gold standard regarding AK and non-melanoma skin cancer, biopsies are not always a good approach for the diagnosis and treatment of these lesions. Therefore, noninvasive diagnostic tests represent a good alternative for more accurate diagnosis and monitoring of these lesions. Due to the fact that AK has a potential for progression into carcinoma *in situ* and invasive SCC, it should also be diagnosed and treated as swiftly as possible. The new noninvasive technologies that have helped in the diagnosis of these skin lesions are dermoscopic examination and, more recently, the *in vivo* confocal microscopy examination. Thus, these tests are important not only to detect clinically suspicious lesions of AKs or SCC, but also to detect and define subclinical lesions of field cancerization.

B) Dermoscopy

This technique consists of the use of an optical device that allows 10 to 70 times the image magnification. The basic physical principle of dermoscopy is the improvement of the light's refractive index when it passes through the stratum corneum. It makes it possible to view structures in the epidermis, dermal-epidermal junction, papillary dermis, and even reticular dermis. The dermoscopic evaluation is based on the identification of colors and structures having a well-established correlation with the histologic characteristics of the cutaneous lesions, allowing the noninvasive diagnosis of many skin lesions.[13]

There are few studies describing the dermoscopic standards of AK. According to Zalaudek et al. the most frequently described characteristic in the initial AK lesion is the red pigmentary pseudo network pattern ("strawberry vascular pattern").[14] As the lesion progresses into an intraepidermal carcinoma (IEC) a pattern called red starburst develops, in addition to the appearance of yellow-opaque diffuse scales. As the lesion gradually turns into an SCC, there is an increase in neovascularization, and dotted or glomerular grouped vessels develop, with the appearance of linear and irregular vessels later on. In addition, the scales become thicker, and ulcerations are often described.[15] Dermoscopy is also useful for the differential diagnosis between pigmented AK, lentigo maligna, and pigmented basal cell carcinoma.[7]

C) *In vivo* confocal microscopy (RCM)

In vivo confocal microscopy emerged as a potential resource to study epidermal cutaneous alterations. This is because it allows viewing the superficial skin layers *in vivo* and noninvasively, from images prepared by different reflexing rates of light from skin structures, with microscopic resolution similar to that of conventional histology.[12,16] In this manner, confocal microscopy (CM) can also be used for AK diagnosis with a sensitivity and specificity of 98%.[7] It can currently be considered a noninvasive method for the diagnosis of AK and field cancerization.[7] The findings of AK lesions under MC include irregular hyperkeratosis with parakeratosis, an architectural disarrangement and an increased nuclei of epidermal cells with pleomorphism. The architectural disarrangement pattern does not involve the thickness of the entire epidermis in cases of AK. The AK images may also have thick refractional bands in the dermis, corresponding to the solar elastosis.[3,11,17]

In addition to RCM, the identification of subclinical lesions can be carried out by evaluating the fluorescence under ultraviolet lamp after the application of 5-aminolevulinic acid and the erythema after topical treatment with imiquimod or 5-fluorouracil (5-FU).[3,18]

Field cancerization – the role of gene p53

In 1953, Slaughter et al. defined the expression *field cancerization* for the first time in a histology study on carcinomas in the oral cavity and their local recurrences. The authors described the appearance of carcinomas in multifocal areas, coalescing from premalignant lesions.[5] Field cancerization can be defined molecularly as the presence of mutated cells that can progress to cancerous cells. Molecular analysis of the tissue adjacent to the tumor (even when considered clinically "normal"), as well as of the post-excisional resection margins of tumors, have been carried out in order to allow for a better understanding of this phenomenon.[5,8]

The gene p53 is correlated to tumor suppression. Mutation of this gene occurs in 50% of all tumors and in most skin cancers.[19] Studies performed with molecular technologies showed mutations in the gene p53 in histologically normal tissues.[5]

The analysis of p53 gene mutations have established a clear link between exposure to UV rays, changes in DNA, and skin carcinogenesis. UVB radiation causes very specific changes in the DNA, producing cyclobutane and pyrimidone type pyrimidine dimers.[19] Flaws in DNA repair and replication induce mutations in the genome. The accumulation of these mutations in genes due to chronic exposure to sunlight results in the development of skin cancer.[19]

The mutation frequency of the p53 gene varies in different studies. Ziegler et al. showed a 66% rate of mutations in this gene in AK and 40% in Bowen's disease. Mutation studies in basal cell carcinoma (BCC) and SCC showed a mutation presence of 66% in BCC, 38% in non-aggressive BCC, 35% in aggressive SCC, 50% in non-aggressive SCC, and 10% in skin exposed to sunlight. UVA radiation leads to mutation in the SCC's basal layer, and UVB radiation in the suprabasal layer.[19]

Mutations in p53 arise in skin with apparently normal sun exposure levels. Recent studies in mice have shown that UV, in addition to inducing mutation, induces apoptosis of normal cells, creating an environment that is conducive to cell repopulation. This is the ideal environment for repopulation by clonal expansion of mutated cells.[19]

The results of these studies support the carcinogenesis model in which there is development of a contiguous field genetically altered with clonal alterations and development of multiple neoplasic lesions. The genetically modified stem cell forms a clonal unit of daughter cells, leading to an expanded field. Ultimately, a proliferating field gradually invades the normal epithelium. The clonal deviation can lead to the development of skin cancer in a contiguous field of pre-malignant cells.[9]

This concept has important clinical consequences for it explains the existence of several areas of pre-malignant disease, multiple sites of synchronous primary tumors and the presence of distant tumors. A genetically altered field increases the probability of development of the tumor's local recurrence and/or the appearance of a second tumor in the field. This finding has been described in esophageal, oropharynx, stomach, lung, colon, anus, bladder, cervix, and skin tumors.[9]

Thus, environmental carcinogenic influences, such as the role that tobacco and alcohol play in oropharyngeal tumors, explain the actinic damage caused to skin by ultraviolet radiation (UV), which leads to simultaneous alterations in a large proportion of epithelial cells. This also contributes to the development of premalignant lesions in areas exposed to sunlight.[9]

This model explains carcinoma recurrence after surgery and new cancers in the operated area. This concept and its clinical consequences are important for prevention, diagnosis, and treatment strategies in cases of non-melanoma skin cancer.[9]

The molecular biology analysis performed in locations adjacent to the tumor in the study of surgical margins without histological alterations shows changes in the microsatellite, chromosome instability and alterations of the p53 gene, all demonstrated by DNA amplification, immunohistochemistry, and *in situ* hybridization techniques.[5]

The recognition of field cancerization as an area of genetic alteration of cells with risk for SCC development leads to a new paradigm in the definition of the term used for local recurrence and in the importance of treating this field. The definition of local recurrence should be reconsidered, as this lesion may originate from remaining tumor cells, such as the cells present in field cancerization.[5]

Thus, high levels of p53 (evidenced by immunohistochemistry) due to mutations and increased gene expression can be considered biological markers of actinic damage and of field cancerization. Aligned with this concept, clinically normal areas present early alterations linked to clonal expansion of genetically modified neoplastic cells.

Treatment

A) Objectives of the treatment

The treatment of AK aims to prevent the risk of progres-

sion into SCC. There are several options to consider. In addition to selecting a technique, other factors to take into account are the number, location, and extent of the AK, as well as the patient's age, comorbidities, immunosuppression (transplants), previous history of skin cancer, continuous exposure to sunlight (rural workers, athletes), and cost and conditions for performing the treatment.[3,20]

In addition to treatment, patients should also be advised to avoid exposure to the sun by using sunscreens and wearing adequate clothing, staying in the shade as much as possible and avoiding artificial sources of UV radiation, such as tanning beds.[3]

There are randomized studies showing that low-fat diets decrease the incidence of AK. The use of fish oil and the practice of drinking red wine – due to the presence of resveratrol – can also act as chemopreventive agents in the development of AKs.[3] The use of nonsteroidal anti-inflammatory drugs has in some studies also shown chemopreventive action in the development of AK and SCC.[3]

The use of retinoids in chemoprevention of SCC is indicated in renal transplant patients (20 mg/day acitretin). The drug has an immunomodulatory effect, increasing the number of Langerhans cells after 12 months, both in covered areas and in those exposed to sunlight.[21]

The treatment of field cancerization is performed in multiple areas of AK, visible or palpable, or throughout the area injured by exposure to UV. The treatment of the field is also indicated for new and recurrent lesions, and those that have been treated up to one year before.[3]

The treatment of the field can be accomplished through the self-administered application of topical substances by the patient, photodynamic therapy performed at the clinic, and resurfacing techniques with ablative and non-ablative lasers, dermabrasion, and medium and deep chemical peels.[3]

The various treatment modalities show different advantages and disadvantages in terms of efficacy and tolerability, duration of treatment, discomfort, recovery, patient adhesion and outcome. There is no formal guideline for the treatment of field cancerization. It is recommended that AKs be treated in order to prevent progression into CEC[3] and that field cancerization be treated so as to avoid recurrence and new lesions. In 2007, the British Academy of Dermatology recommended the use of photodynamic therapy for the treatment of multiple and confluent AKs.[2]

B) Conventional AK therapy

There are several treatment modalities for treating AKs, including ablative procedures such as curettage, surgery, laser, and cryotherapy – usually aimed at treating individual lesions – and topical treatments, such as photodynamic therapy, imiquimod, 5-fluorouracil (5-FU) and diclofenac – used to treat individual lesions and field cancerization. Field cancerization areas are also important due to the fact that they are related to morbidity and mortality in patients who underwent organ transplantation, being also relevant in preventing progression into SCC. The treatment of individual lesions does not prevent this progression.[3,22]

B) 1. Destructive methods

I. Cryotherapy

Cryotherapy is the most common treatment for AK. The complete response rate is 67.2%, with 39.0% of responses with freezing times shorter than 5 seconds, 69.0% of responses with freezing times longer than 5 seconds and 83.0% with freezing times in excess of 20 seconds. It is usually well tolerated but can cause discomfort in the application and secondary dischromia.[1]

II. Surgery, curettage, and electrocoagulation

This is the method of choice when aiming at collecting material for pathological examination. It has the disadvantage of needing local anesthesia and can result in scar formation. It can be used in combination with photodynamic therapy. These two destructive methods treat only localized AKs.[1] Surgical excision is not indicated routinely and is used when there is suspicion of invasive SCC.[22]

III. Resurfacing procedures

Procedures such as CO_2 and erbium:YAG lasers can be used to treat AK with a 90.0% response level, in periods of up to 42 months (evidence level C, III). Possible side effects are hyper/hypopigmentation, scarring, and infection and acne, in addition to prolonged healing time. Dermabrasion and microdermabrasion can also be used with the same potential side effects (evidence level C, III). Chemical peels cause necrosis in different layers of the epidermis, depending on the application's concentration, agent, and duration. The most common agent is trichloroacetic acid, which at 35% provides medium peeling and at 50% provides deep peeling. Other agents, such as phenol, can also be used to treat AK. The effectiveness of the chemical peels may reach 75%, with a 35% recurrence level (evidence level C, III).[23]

B) 2. Topical therapy

The most frequently used drugs in topical therapy are 5-FU, 5% and 3.75% imiquimod cream and 3% diclofenac sodium gel. The response to the treatment with such drugs reaches 50% of complete responses and 70% of partial responses. A patient's adherence is often compromised due to the degree of irritation caused, leading to early dropout. Short-term therapies may enhance adherence to the treatment. The latest drug in the treatment of AK is ingenol mebutate, which has the advantage of being used for only two or three days, depending on location, increasing treatment adherence.[1,3]

I. 5-fluorouracil (5-FU)

This therapy has been used for about 40 years.[24] The 5-FU is a topical chemotherapeutic drug used in AKs of the head and neck, and is considered the gold standard in regards to other topical treatments.[3] It is an antimetabolic drug because it inhibits the synthesis of DNA. Its commercial applications are 0.5%, 1.0%, 2.0%, and 5.0%, in different vehicles.[23] The British Association of Dermatology's 2007 guidance recommends using 5-FU twice a day for up to six weeks with efficacy of up to 12 months (evidence level A, I).[2] The response is noticeable 1 to 2

months after the end of the treatment. Studies show that the response for localized disease occurs in 50% of cases, with recurrence in 55% of cases.[23,25,26] Side effects take the form of irritation at the application site, such as dry, erythematous and ulcerated skin, with pain and edema. Adverse events can lead to the discontinuation of treatment.[3] Less aggressive treatment regimens exist, such as pulse therapy (evidence level B, III, 3b).[27]

There are studies on the association of 0.5% 5-FU to 10% salicylic acid in a gel vehicle applied once or twice a day for the treatment of AK, with an aim of strengthening the keratolytic effect.[28]

When comparing cryotherapy with topical use of 5-FU and imiquimod for the treatment of AK, it was possible to observe that 68% of patients treated with cryosurgery, 96% of patients treated with 5-FU, and 85% of patients treated with imiquimod showed clinical improvement. Histologic response was 32% to cryosurgery, 67% to 5-FU, and 73% to the treatment with imiquimod. The 12-month follow-up of these patients' field cancerization treatment observed a 4% response to cryotherapy, 33% to 5-FU and 73% to the treatment with imiquimod. The patients in the imiquimod group were considered to have had the best aesthetic outcomes ($p = 0.0001$).[23]

II. Imiquimod

Imiquimod is a topical immunomodulating drug, agonist of the toll-like receptor, which stimulates local immunity.[29] The drug stimulates the expression of genes of adaptive cellular immunity by activating macrophages, dendritic cells, cytotoxic T-cells and natural killer cells. As a consequence, it leads to the destruction of the lesion by immune-mediated apoptosis.[29] More recently, it has been found that imiquimod also has a direct antineoplastic action on the mitochondria.[1] It is commercially available in 3.75% and 5.0% concentrations.[2]

The British Association of Dermatology's 2007 guidance recommends using imiquimod for up to 16 weeks (evidence level B, I). The remission rate is 84% while the rate of recurrence is 10% in one year and 20% in two years (evidence level B, II). This topical therapy can treat subclinical lesions (field cancerization) and hardly generates scars.[2,27] The US FDA has approved the use of this drug once a day, twice a week for 16 weeks in the topical treatment of non-hypertrophic keratoses.[1] It is, however, a long treatment and may decrease a patient's adherence. It presents cutaneous reactions such as erythema, pruritus, burning sensation, pain, erosions and ulcerations, which can impact a patient's adherence and final outcome. In many cases there is a need to reduce the frequency of applications in order to prevent the interruption of the treatment.[30]

In a comparative study of AK treatment with imiquimod, 5-FU and cryosurgery, the initial effectiveness was 85%, 96%, and 68%, respectively. The recurrence after one year of treatment was 73%, 33%, and 4%, respectively – therefore the results were superior to the imiquimod's.[23]

III. Diclofenac

Diclofenac is a non-steroidal anti-inflammatory that blocks cyclooxygenase-2 (COX-2). Actinic keratosis and non-melanoma skin cancers have increased activity of COX-2. [1] It had a 50% efficacy in a study at 3% concentration in 96 patients with 5 or more AKs in an application area of 5cm2 for 90 days.[1] Another paper describes a 70% efficacy after 60 days of use.[1] The treatment is well tolerated with a low rate of side effects (erythema, pruritus, paresthesia, exanthema, dry skin, and contact dermatitis). The treatment is long and there are no signs of improvement within 30 days of its completion.[3]

IV. Tretinoin

The use of tretinoin has demonstrated good response in 55% of patients using a concentration of 0.3% and in 35% of patients at a concentration of 0.1% twice a day for 16 weeks. According to Misiewicz et al., the use of topical tretinoin can be beneficial in patients with AK.[31]

V. Ingenol

The latest drug in the treatment of AK is 0.05% ingenol mebutate applied once a day for two consecutive days (except for on facial skin), with a complete response in 71% of patients.[3] The 0.015% ingenol mebutate applied on facial skin once a day for three consecutive days showed a complete response in 50% of patients, with partial responses in 85% of patients.[3]

The ingenol mebutate is a diterpene ester derived from Euphorphia peplus. Its mechanism of action is not fully understood, but *in vivo* and *in vitro* models showed a dual mechanism of action: the induction of local cellular death by disrupting the mitochondria of the plasma membrane and tumor cells, and the production of pro-inflammatory cytokines and mass infiltration of neutrophils and other inflammatory cells which give rise to the immune response.[3]

VI. Resiquimod

Resiquimod is a non-specific immunity modulating imidazoquinoline amine. It has a higher potency in inducing cytokine expression than that of imiquimod.[3] In a European phase 2 study of the drug, the rate of complete cure after one therapy course was 40%, with the gel at 0.01%. That rate was 74.2% at a 0.03% concentration; 56.3% at a 0.06% concentration and 70.6% at a 0.1% concentration.[3] The discontinuation rate due to local and systemic cutaneous reactions after the first course of treatment with each resiquimod gel concentration was 0%, 13%, 31%, and 38%, respectively. The authors concluded that the efficacy in the treatment of AK was similar among the tested concentrations, however the gel at 0.01% and 0.03% was better tolerated than it was at higher concentrations.[3]

C) Photodynamic therapy

Photodynamic therapy (PDT) is effective in the treatment of AK.[2] The PDT concept is based on the induction of the proliferative cells' cytotoxicity by using a light source.[32] The treatment begins with the application of 5-aminolevulinic acid (ALA) or methyl aminolevulinic acid (MAL), which are photosynthetizing agents.

These topical substances are converted into protopor-

phyrin IX, which generates reactive oxygen in dysplastic keratinocytes under exposure to light with adequate wavelength (blue light, 14 - 18 hours after ALA application, and red light, 3 hours after the application of MAL).[2] The production of reactive types of oxygen destroys dysplastic keratinocytes that constitute the AKs. The treatment can cause pain of varying degrees. Photodynamic therapy is mainly used for non-hyperkeratotic lesions of the face and scalp, and can be particularly useful in cases of multiple or confluent AK lesions (field cancerization area), or those showing a poor response to therapy. Photodynamic therapy is generally well tolerated, however there are cases with more susceptibility to pain. Several factors, such as location, extent and type of lesion, fluence, light source, number of sessions and skin phototype, were described.[2,33] It produces excellent aesthetic results, with regression of more than 90% of the lesions.[2]

The British Photodermatology Group published a guidance for the use of photodynamic therapy in 2002, with instructions to remove keratin crusts by means of light curettage prior to the application of the drug, which must be occluded for three hours before irradiation. According to the Group, the treatment can cause pain, nevertheless it is safe.[34] In general, the treatment is well tolerated and yields good results with response in more than 90% of lesions.[3] There are studies showing response rates of 69-91% when used to treat facial and scalp AKs with two treatment cycles.[1,23,35]

The clinical and histological improvement in the field cancerization after several MAL-PDT sessions is proven. There is a reduction in the severity and extent of the keratinocyte atypia, associated with a decreased expression of the p53 gene.[36]

Recent studies have shown that photodynamic therapy can be performed outdoors and works with protoporphyrin IX activation by daylight, allowing for the treatment of AK lesions at home. Wiegell et al. have compared the effects of MAL-PDT application illuminated by red LED after a three-hour incubation period with the MAL-PDT illuminated by daylight for 2.5 hours after a thirty-minute incubation period for the treatment of the face and scalp AK. Continuous activation of protoporphyrin IX with PDT light has proven as effective as conventional MAL-PDT and was associated with post-treatment erythema and crusting, however with less pain. The authors concluded that PDT with daylight could provide faster treatment, more convenience and greater cost effectiveness.[37]

D) Combined treatment of injury and treatment field

In patients with many AKs, the combined treatment of the lesion and field would be effective in reducing lesions in multiple foci and subclinical lesions in areas exposed to sunlight.[3] Potential benefits include the total whitening of the lesions with minimal skin reaction and better cosmetic results.[23] There are studies that show that in AKs, the combination of cryotherapy and imiquimod in subclinical lesions was superior to the use of cryotherapy combined with a placebo in a three-month period (imiquimod group's response = 58% versus placebo group's response = 34%).[23] The use of 5-FU after cryotherapy for treatment of residual facial AK proved superior to the use of cryotherapy combined with placebo cream for six months (5-FU group's response = 67%, placebo group's response = 45%).[23]

In a pharmacological study, Gold examined the use of imiquimod, diclofenac, 5-FU or PDT combined with cryotherapy for the treatment of AK. The treatment with imiquimod was the most expensive, followed by 5-FU and diclofenac. PDT was the most cost effective treatment.[23]

E) Other modalities

There are studies featuring several other drugs, however they are small and little discussed in the related literature. Polyphenols (green tea) have been shown to inhibit the growth of cancer cell lineages and suppress the phosphorylation of the receptor's growth factor.[23] Betulinic acid is a natural pentacyclic triterpenoid that has potential antitumor properties as a result of its inhibition of topoisomerase.[23]

Piroxicam is a nonsteroidal anti-inflammatory drug that blocks cyclooxygenase-1 and cyclooxygenase-2. A 2010 Italian study evaluated the efficacy and safety of 1% piroxicam gel applied twice daily for 12 weeks for the treatment of 31 AK lesions, with the complete regression of 50% of the lesions. Adverse effects included erythema, mild pruritus, dry skin, and more rarely, cutaneous eruption.[23]

6. Prevention and chemoprevention

Prevention of SCC development is an important part of the management and treatment of AK.[38] The first step is to educate the patient about the risks of UV radiation and measures of solar protection that present evidence level AI according to the European Guidance 2011. Several studies show that the use of sunscreen is effective in the prevention and reduction of AKs. Controlled studies show that regular application of sunscreen resulted in a positive impact in patients who underwent organ transplantation.[39-42]

In dermatology, the term *chemoprevention* refers to the use of topical or systemic drugs that have the ability to inhibit or reverse a progression into skin cancer. These drugs include retinoids, T4 endonuclease V, polyphenolic antioxidants (such as the epigallocatechin gallate, found in green tea and grape seed extract), silymarin, isoflavone, genistein, nonsteroidal anti-inflammatories, curcumin, lycopene, vitamin E, beta carotene, selenium among others.[43]

CONCLUSION

The proper diagnosis and treatment of AK are crucial to the prevention of invasive SCC. The targeted field therapy is mainly used for multiple visible or palpable lesions in contiguous areas of skin, for subclinical lesions, and for all sun-damaged skin in areas at risk for subclinical lesions. The treatment of field cancerization is important for preventing recurrence and the emergence of new neoplastic and pre-neoplastic lesions. Currently available topical agents require prolonged treatment courses, often causing skin irritation, and are associated with the early interruption of the treatment, impairing results.[3] As a con-

sequence, new drugs are being studied.

The combination of the targeted treatment of the lesion and the treatment of field cancerization offers greater efficiency.[23] Further studies are necessary to determine the best combination therapies and their standardization.

With the field therapy's reduced duration of treatment and decreased severity of adverse events – consequently leading to better adherence to treatment – comes an increase the patient's satisfaction, a decrease in the risk of recurrence, and a reduction in costs.[23]

REFERENCES

1. Berman B, Villa AM, Ramirez CC. Mechanisms of action of new treatment modalities for actinic keratosis. J Drugs Dermatol. 2006;5:167-73.
2. Berker D, McGregor JM, Hughes BR. Guidelines for the management of actinic keratoses Br J Dermatol. 2007;156(2):222-30.
3. Berman B, Cohen DE, Amini S. What is the role of field-directed therapy in the treatment of actinic keratosis? Part 1: overview and investigational topical agents. Cutis. 2012;89(5):241-50.
4. Quaedvlieg PJF, Tirsi E, Thissen MRTM, Krekels GA. Actinic keratosis: how to differentiate the good from the bad ones? Eur J Dermatol. 2006;16(4):335-9.
5. Braakhuis BJ, Tabor MP, Kummer JA, Leemans CR, Brakenhoff RH. A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. Cancer Res. 2003;63(8):1727-30.
6. Torezan LA, Festa-Neto C. Cutaneous field cancerization: clinical, histopathological and therapeutic aspects. An Bras Dermatol. 2013;88(5):775-86.
7. Ulrich M, Maltusch A, Rowert-Huber J, Gonzalez S, Sterry W, Stockfleth E, et al. Actinic keratoses: non-invasive diagnosis for field cancerization. Br J Dermatol. 2007;156(Suppl):13-7.
8. Röwert-Huber J, Patel MJ, Forschner T, Ulrich C, Eberle J, Kerl H, et al. Actinic keratosis is an early in situ squamous cell carcinoma: a proposal for reclassification. Br J Dermatol. 2007;156:8-12.
9. Kaufmann R. The Concept of Field cancerization. e-Supplement Abstracts of the 6th Congress of the European Association of Dermatologic Oncology. 2010;20;p. e13.
10. Ulrich M, Forschner T, Rowert-Huber J, Gonzalez S, Stockfleth E, Sterry W, et al. Differentiation between actinic keratoses and disseminated superficial actinic porokeratoses with reflectance confocal microscopy. Br J Dermatol. 2007;156(Suppl):47-52.
11. Ulrich M, Maltusch A, Rius-Diaz F, Rowert-Huber J, Gonzalez S, Sterry W, et al. Clinical applicability of in vivo reflectance confocal microscopy for the diagnosis of actinic keratoses. Dermatol Surg. 2008;34(5):610-9.
12. Rishpon A, Kim N, Scope A, Porges L, Oliviero MC, Braun RP, et al. Reflectance confocal microscopy criteria for squamous cell carcinomas and actinic keratoses. Arch Dermatol. 2009;145(7):766-72.
13. Rezze GG, Paschoal FM, Hirata SH. Atlas de Dermatoscopia Aplicada. 2 ed. São Paulo: Lemar; 2014.
14. Zalaudek I, Giacomel J, Argenziano G, Hofmann-Wellenhof R, Micantonio T, Di Stefani A, et al. Dermatoscopy of facial non-pigmented actinic keratosis. Br J Dermatol. 2006;155:951-6.
15. Zalaudek I, Giacomel J, Schmid K, Bondino S, Rosendahl C, Cavicchini S, et al. Dermatoscopy of facial actinic keratosis, intraepidermal carcinoma, and invasive squamous cell carcinoma: A progression model. J Am Acad Dermatol. 2012;66:589-97.
16. Ulrich M, Stockfleth E, Roewert-Huber J, Astner S. Noninvasive diagnostic tools for nonmelanoma skin cancer. Br J Dermatol. 2007;157(Suppl):56-8.
17. Wurm EMT, Curchin CES, Lambie D, Longo C, Pellacani G, Soyer HP. Confocal features of equivocal facial lesions on severely sun-damaged skin: Four case studies with dermatoscopic confocal and histopathologic correlation. J Am Acad Dermatol. 2012;66(3):463-73.
18. Sanmartin O, Guillen C. Images in clinical medicine. fluorescence diagnosis of subclinical actinic keratoses. N Engl J Med. 2008;358(19):e21.
19. Benjamin CL, Ananthaswamy HN. p53 and the Pathogenisis of Skin Cancer. Toxicol Appl Pharmacol. 2007;224(3):241-8.
20. Stockfleth E, Ferrandiz C, Grob JJ, Leigh I, Pehamberger H, Kerl H, et al. Development of a treatment algorithm for actinic keratoses: a European consensus Eur J Dermatol. 2008;18:651-9.

21. Carneiro V, Sotto MN, Azevedo LS, Ianhez LE, Rivitti EA. Acitretin and skin cancer in kidney transplanted patients. Clinical and histological evaluation and immunohistochemical analysis of lymphocytes, natural killer cells and Langerhans' cells in sun exposed and sun protected skin. Clin Transpl. 2005;19(1):115.
22. Stockfleth E, Terhorst D, Braathen L, Cribier B, Cerio R, Ferrandiz C, et al. [Internet]. Guideline on Actinic Keratoses. Available from: http://www.euroderm.org/images/stories/guidelines/guideline_Management_Actinic_Keratoses-update2011.pdf
23. Berman B, Cohen DE, Amini S.What is the role of field-directed therapy in the treatment of actinic keratosis? Part 2: commonly used field-directed and lesion-directed therapies. Cutis. 2012;89(6):249-301.
24. Eaglstein WH, Weinstein GD, Frost P. Fluorouracil: mechanism of action in human skin and actinic keratoses. Arch Dermatol. 1970;101(2):132-9.
25. Lawrence N, Cox SE, Cockerell CJ, Freeman RG, Cruz PD Jr. A comparison of the efficacy and safety of Jessner's solution and 35% trichloroacetic acid vs 5% fluorouracil in the treatment of widespread facial actinic keratoses. Arch Dermatol. 1995;131(2):176.
26. Levy, S, Furst, K, Chern, W. A pharmacokinetic evaluation of 0.5% and 5% fluorouracil topical cream in patients with actinic keratosis. Clin Ther. 2001;23(6):908.
27. Stockfleth E, Kerl H. Guideline subcomittee of the European Dermatology Forum. Guidelines for the management of actinic keratoses. Eur J Dermatol. 2006;16(6):599-606.
28. Study on the efficacy of LAS41005 in the treatment of actinic keratosis [Internet]. [published 2009 Sept 29. updated 2012 Mar 29]. Available from: http://clinicaltrials.gov/ct2/show/NCT00987246?term=las+41005&rank=1.
29. Torres A, Storey L, Anders M, Miller RL, Bulbulian BJ, Jin J, et al. Immune-mediated changes in actinic keratosis following topical treatment with imiquimod 5% cream. J Transl Med. 2007;5:7.
30. Stockfleth E, Sterry W, Carey-Yard M, Bichel J. Multicentre, open-label study using imiquimod 5% cream in one or two 4-week courses of treatment for multiple actinic keratoses on the head. Br J Dermatol. 2007;157(Suppl 2):41-46.
31. Misiewicz J, Sendagorta E, Golebiowska A, et al. Topical treatment of multiple actinic keratoses of the face with arotinoid methyl sulf- one cream vs. tretinoin cream: a double blind comparative study. J Am Acad Dermatol. 1991;24:448-51.
32. Torezan L, Niwa AB, Neto CF. Photodynamic therapy in dermatology: basic principles. An Bras Dermatol. 2009;84(5):445-59.
33. Chaves YN, Torezan LA, Niwa AB, Sanches Junior JA, Festa Neto C. Pain in photodynamic therapy: mechanism of action and management strategies. An Bras Dermatol. 2012;87(4):521-6; quiz 527-9.
34. Morton CA, Brown SB, Collins S, Ibbotson S, Jenkinson H, Kurwa H, et al. Guidelines for topical photo- dynamic therapy: report of a workshop of the British Photoderma- tology Group. Br J Dermatol. 2002;146(4):552-67.
35. Pariser DM, Lowe NJ, Stewart DM et al. Photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: results of a prospective randomized multicenter trial. J Am Acad Dermatol. 2003;48(2):227-32.
36. Szeimies RM1, Torezan L, Niwa A, Valente N, Unger P, Kohl E, et al. Clinical, histopathological and immunohistochemical assessment of human skin field cancerization before and after photodynamic therapy. Br J Dermatol. 2012;167(1):150-9.
37. Wiegell SR, Haederdsal M, Philipsen PA, Eriksen P, Enk CD, Wulf HC. Continuous activation of PpIX by daylight is as effective as and less painful than conventional photodynamic therapy for actinic keratoses; a randomized, controlled, single-blinded study. Br J Dermatol. 2008;158(4):740-6.
38. Armstrong BK, Kricker A. The epidemiology of UV induced skin cancer. J Photochem Photobiol B. 2001;63(1-3):8-18.
39. Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. N Engl J Med. 1993;329(16):1147-51.
40. Darlington S, Williams G, Neale R, Frost C, Green A. A randomized controlled trial to assess sunscreen application and beta carotene supplementation in the prevention of solar keratoses. Arch Dermatol. 2003;139(4):451-5.
41. Green A, Williams G, Neale R, Hart V, Leslie D, Parsons P, et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. Lancet. 1999;354(9180):723-9.
42. Naylor MF, Boyd A, Smith DW, Cameron GS, Hubbard D, Neldner KH. High sun protection factor sunscreens in the suppression of actinic neoplasma. Arch Dermatol. 1995;131(2):170-5.
43. Wright TI, Spencer M, Flowers FP. Chemoprevention of nonmelanoma skin cancer. J Am Acad Dermatol. 2006;54(6):933-46.

Questions for continuing medical education - CME

1. The relative risk of an individual AK bearer developing SCC is:
a) 6-10%
b) 0.025-20%
c) 11-25%
d) 80%
e) more than 20%

2. Field cancerization is a concept:
a) on which there are few studies
b) that refers to the region with subclinical pre-neoplastic, however focal abnormalities
c) that refers to the region with multifocal pre-neoplastic abnormalities with genetic mutations
d) that explains the recurrence of tumors
e) c and d are correct

3. The high recurrence of AK after treatment is due to:
a) inadequate treatment of the AK with cryotherapy
b) repeating treatments of the AKs with 5-FU
c) lack of adequate treatment of subclinical lesions
d) therapies that use 5-FU
e) b and c are correct

4. Regarding AK:
a) the use of dermoscopy and confocal microscopy negates the need for pathological examination of SCC diagnosis
b) the gold standard for diagnosis is pathology
c) confocal microscopy negates the need to perform a pathological examination when there is suspicion of SCC
d) dermoscopy negates the need to perform a pathological examination for the diagnosis of SCC
d) the gold standard for diagnosis is dermoscopy

5. Regarding the dermoscopic examination, it is possible to say:
a) the "red starburst" pattern is pathognomonic of AK
b) glomerular structures are characteristic of AKs
c) pigmented AK is easily diagnosed by dermoscopy and confocal microscopy
d) the most frequently described characteristic of an AK's initial lesion is the red pigmentary pseudo-network pattern
e) none of the above

6. Choose the correct alternative:
a) Field cancerization can be observed by in vivo confocal microscopy
b) Field cancerization can be observed through evaluation of fluorescence under the UV lamp after the application of 5-aminolevulinic acid
c) Perilesional erythema after topical treatment with imiquimod and 5-FU demonstrates the presence of field cancerization
d) all of the above are correct
e) all of the above are incorrect

7. Choose the correct alternative:
a) it is possible to find p53 gene mutations in histologically normal tissues
b) the damage caused by UV in the p53 gene occurs only in tumors
c) the accumulation of mutations can be corrected with the inactivation of p53
d) phototype V individuals never have mutations in the p53 gene
e) the inactivation of p53 with photodynamic therapy induces clonal repopulation

8. Choose the correct alternative:
a) The treatment of AK is aimed at preventing the progression of AK into SCC
b) Few therapeutic modalities are effective in treating AK
c) According to the British Academy of Dermatology's guidance, PDT should be used to treat invasive SCC in field cancerization areas
d) a and c are correct
e) all of the above are incorrect

9. Regarding the treatment of AK:
a) the method of choice is cryotherapy
b) when there is a suspicion of SCC, histopathology should be performed
c) medium and deep peels are not effective in the treatment of field cancerization
d) chemical peels should not be carried out in cases where AK is suspected.
e) the best therapeutic result occurs when the field cancerization and AK are treated with liquid nitrogen

10. Choose the correct alternative:
a) regarding PDT, it is possible to state that it is best indicated for the treatment of AK associated SCC
b) the blocking of toll-like receptors stimulates local immunity
c) imiquimod's mechanism of action takes place through toll-like receptors
d) PDT effectiveness is not associated with the expression of p53
e) outdoor PDT is totally contraindicated in tropical countries

Key
Hidradenitis Suppurativa: Update and review of therapeutic modalities. 2014;6(3):206-12.

1 b, 2e, 3c, 4a, 5d, 6e, 7e, 8c, 9b, 10a

Answers must be submitted online using the website www.surgicalcosmetic.org.br.
The deadline for submitting answers will be provided by e-mail with a direct access link for the journal.

Artigo 2

Original Articles

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Conflict of interest: None

Clinical study to assess abdominal circumferential reduction after treatment with low-frequency diode laser

Estudo clínico para avaliar a redução da circunferência abdominal após tratamento com laser diodo de baixa frequência

ABSTRACT

Introduction: Obesity is a major health problem worldwide due to its high morbidity and mortality.

Objective: To evaluate the reduction of abdominal fat in volunteers who underwent low-frequency diode laser therapy.

Methods: A total of 60 volunteers (18 to 50 years of age, with a BMI of between 18.5 kg/m2 and 30 kg/m2, and who had abdominal fat), underwent a treatment performed twice a week for 31 days and were then evaluated. The abdominal circumference was evaluated in three locations, with photographic and ultrasound images taken of the studied area.

Results: There was a reduction in the abdominal circumference measurements in the evaluated sites, with dermal compression and a significant reduction of hypodermis verified through ultrasound.

Conclusion: The low-frequency diode laser therapy showed significant results in the reduction of localized fat and abdominal circumference measurements.

Keywords: laser; abdominal fat; lypolisis.

RESUMO

Introdução: *A obesidade é um dos principais problemas de saúde no mundo, devido a sua elevada morbimortalidade.*

Objetivo: *Avaliar a redução da gordura abdominal em voluntários submetidos à terapia com laser diodo de baixa frequência.*

Métodos: *Foram avaliados 60 voluntários, entre 18-50 anos de idade, com IMC entre 18,5kg/m2 e 30kg/m2 e com gordura abdominal, com tratamento realizado duas vezes por semana, durante 31 dias. Avaliou-se a circunferência abdominal em três áreas, com tomadas de imagens fotográficas e ultrassom da área avaliada.*

Resultados: *Houve redução nas medidas da circunferência abdominal nas áreas avaliadas, com significativas compactação ultrassonográfica dérmica e redução ultrassonográfica da hipoderme.*

Conclusão: *A terapia com laser diodo de baixa frequência apresentou resultados significativos na redução de gordura localizada e medidas de circunferência abdominal.*

Palavras-chave: *laser; gordura abdominal; lipólise.*

INTRODUCTION

Obesity is a major health problem worldwide due to its high prevalence and morbidity. It is diagnosed using the body mass index (BMI), an anthropometric indicator.[1]

The layout of fat in the central region, determined by waist circumference characterizes visceral obesity and is associated with metabolic disorders[2-4] such as hypertension, dyslipidemia, fibrinolysis, metabolic syndrome, chronic inflammatory process, atherosclerosis development acceleration, and may also result in cardiovascular or cerebrovascular events.[1,5]

Laser therapy is a non-invasive procedure that can be used to reduce localized fat. It uses a wavelength specific to adipose cells while preserving adjacent structures such as nerves, blood vessels, and skin.[6]

In the present study, the authors used a low-frequency diode laser device (685nm, 40mW, 1.3watts, 120Joules / cm^2 / 10 minutes) consisting of four plates with nine emission sources, which remained in contact with the skin during the session. Furthermore, the equipment has two lymphatic stimulation probes with a laser-emitting source at each, which are placed in the lymphatic drainage region of the treated area.

The present study is aimed at evaluating the reduction of abdominal fat in volunteers undergoing procedures with a low-frequency diode laser available on the Brazilian market.

METHODS

A total of 60 healthy female volunteers aged between 18 and 50 years, skin phototypes I to III (Fitzpatrick classification), with 18.5 > BMI < 30.0 kg/m^2, who had fat deposits in the abdomen were selected for evaluation. They were followed up for 31 days, after the study had received approval from the Institution's Research Ethics Committee.

The visits occurred on the days 0 (D0), 3 (D3), 7 (D7), 10 (D10), 14 (D14), 17 (D17), 21 (D21), 24 (D24), 28 (D28), and 31 (D31). The following assessments were performed at each visit: evaluation of waist circumference (both before and after the laser application) in three predefined areas: upper (4.0 cm above the navel), median (on the navel) and lower (4.00 cm below the navel); measurement of the height of the navel from the floor (the patients were barefoot); application of a questionnaire to assess degree of pain (0-10 scale). In addition to these procedures, a satisfaction questionnaire (0-10 scale) was applied, the weight was measured, and the BMI was calculated at D0, D14, and D31 visits.

In each of these 10 visits, the volunteers underwent an application of a low-frequency diode laser (i-Lipo, Chromogenex Comércio, Importação, Exportação de Produtos Médicos Ltda. ANVISA Class II. 80332760006; 685nm, 40mW, 1.3watts, 120Joules/cm^2/10 minutes) for 20 minutes. The plates were placed on the skin in the region to be treated; two emission probes with the same wavelength were placed on the point of lymphatic drainage in the area.

As directed by the manufacturer the volunteers were asked to perform 30 minutes of aerobic activities during the subsequent 60 minutes. The clinical efficacy assessment was carried out by analysis of photographs and ultrasound examinations aimed at comparing the thicknesses of the dermis.

The descriptive statistics and the evaluation questionnaires allowed to draw conclusions about the participants' demographic profile. In order to analyze the changes between assessments, the ANOVA for repeated measurements, followed by the contrast profile test were used to compare the results of the physical measurements (waist circumference, weight, BMI, ultrasound data). Data were processed into ranks due to the lack of normal distribution. The significance level was set at 5.0%. The SAS (version 9.3) software was used to perform the analyses.

RESULTS

Fifty volunteers (from a total of 60) completed the study. Of these, 11 (22.0%) had skin phototype II, and 39 (78.00%) had phototype III, with a mean age of 39 years (range = 18 to 51 years).

The results of the evaluation of satisfaction with the laser application, immediately after each session was finished, were positive throughout the study period (D0 = 8.50; D14 = 8.62; D31 = 9.26), without statistically significant variation in the results in the comparison between visits (p = 0.4771; Table 1). Regarding the pain scale, 50 participants reported Grade 1 in all visits – except for one who reported Grade 2 pain on D0, progressing to Grade 1 in the other assessments (Table 2).

The variables *weight* (p = 0.9427; Table 3) and *BMI* (p = 0.9016; Table 4) did not present statistically significant reduction in the comparison between the visits and the baseline. Regarding the measurement of the navel's height, there was a statistically significant reduction in the comparative results between the visits and the baseline (D0 = 94.50 cm; D31 = 93.49cm; D0 vs. D31: 1.07% reduction; p <0.0001) (Graph 1).

As depicted in Figure 2, the diode laser therapy decreased by 4% (p <0.0001; Graph 2A); 3.3% (p = 0.0026; Graph 2B) and 3.7% (p <0.0001; Graph 2C), respectively in the upper, median, and lower waist circumferences when measured before the laser session. Nevertheless, an interesting fact is that when evaluating these measurements after the completion of the session, it was observed that for the upper, median, and lower circumferential

Table 1: Degree of volunteer satisfaction with the treatment, seen at D0, D14, and D31, assessed shortly after the laser application

Visit	Mean	Median	SD	Min.	Max	P-value
D0	8.50	10	2.52	1	10	0.5586
D14	8.62	10	2.17	1	10	
D31	9.26	10	1.59	3.00	10	

Table 2: Pain assessment, asked at every visit immediately after the laser application

Visit	D0		D3		D7		D10		D14		D17		D21		D24		D24		D28		D31	
Grade	F	%	F	%	F	%	F	%	F	%	F	%	F	%	F	%	F	%	F	%	F	%
1	49	98	50	100	50	100	50	100	50	100	50	100	50	100	50	100	50	100	50	100	50	100

Table 3: Weight variation – D0 (baseline before the application), D14, and D31 after the laser application

Visit	Mean	Median	SD	Min.	Max	P-value
D0	65.13	66.75	7.50	49.50	85.60	0.9427
D14	65.71	66.30	7.92	46.80	89.50	
D31	65.63	66	7.85	46.50	88.90	

Table 4: BMI variation – D0 (baseline before the application), D14, and D31 after the laser application

Visit	Mean	Median	SD	Min.	Max	P-value
D0	26.03	26.14	2.17	21.15	30	0.9016
D14	25.86	25.89	2.37	20	31.60	
D31	25.85	25.95	2.32	19.86	32.01	

Table 5: Evaluation of the reduction in the baseline measurements from the ultrasonography (D0) as compared with those taken on D31, regarding the thickness of the dermis

Visit	Mean	Median	SD	Min.	Max	P-value
D0	0.16	0.15	0.04	0.03	0.27	0.0003
D31	0.13	0.13	0.03	0.08	0.22	

Table 6: Evaluation of the reduction of the ultrasonography's baseline measurements (D0) as compared with those taken on D31, regarding the dermis' thickness

Visit	Mean	Median	SD	Min.	Max	P-value
D0	1.32	1.09	0.62	0.49	3.44	0.0229
D31	1.05	1.01	0.45	0.36	2.56	

measurements, the reduction was 4.0% (Graph 2B), 3.47% (Graph 2D), and 4.0% (Graph 2F), respectively (all with p <0.0001). When carrying out the before and after analysis, the circumferential measurements were always lower after the application, suggesting that the technology had an immediate effect on the decrease of the measurements.

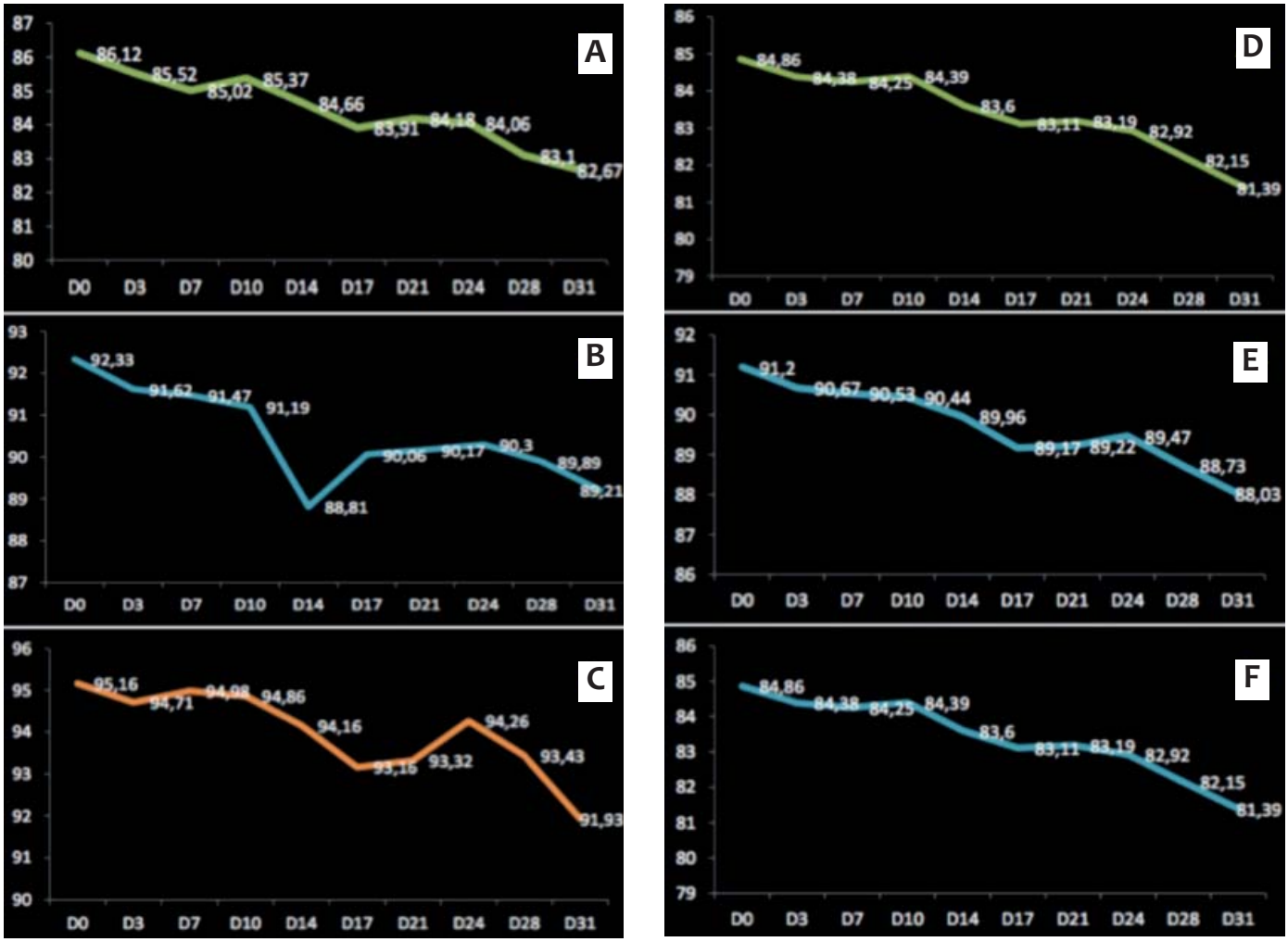
Graph 1: Evaluation of the height of the navel relative to the ground on D0, D3, D7, D10, D14, D17, D21, D24, D28, and D31

The analysis of the ultrasound data also showed a significant reduction from the baseline measurements (D1), and those taken on D31 of the dermis and hypodermis (18.75% and 20.45%, respectively; p <0.0003 for the dermis and p = 0.0229 for the hypodermis) (Tables 5 and 6, respectively; Figure 1). The reduction of abdominal thickness can also be visualized through the photographs taken on D0 and D31 (Figure 2).

DISCUSSIONS

Central or visceral obesity is closely related to potentially life-threatening cardiovascular complications.[1,5] Behavioral measures based on lifestyle changes, weight loss, physical activity, and cessation of harmful habits (smoking, alcohol use) are key for primary and secondary prophylaxis of these events.[7]

Jackson *et al.* published the benefits of using a diverse, low frequency diode laser device (532nm) to treat gynoid lipodystrophy in 34 volunteers (three 30-minute applications per week, in the region of the thighs and buttocks). A group with the same number of volunteers underwent a "placebo"



Graph 2: Evaluation of the waist circumference in the navel region, before and after the application of low frequency laser on D0, D3, D7, D10, D14, D17, D21, D24, D28, and D31. Above the navel's height (before A, after D), at the navel's height (before B, after E) and below the navel's height (before C, after F).

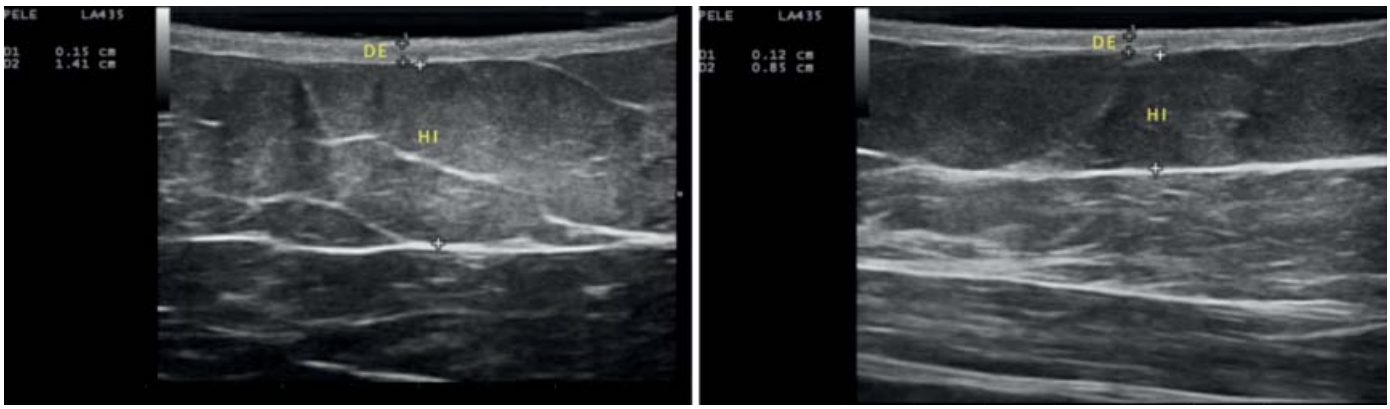


Figure 1: Evaluation of an ultrasound image obtained before (D0A) and after (D31B) the application of low-frequency laser (DE - dermis, HI - hypodermis).

treatment (without emission of energy).[8] For these authors, 19/34 (55.8%) of the volunteers had a statistical reduction of one level in the Nurnberger-Muller scale, as compared with 3/34 (8.8%) from the untreated group. The treated group also saw an improvement in their body circumference, weight, and body mass index. Six weeks after the end of the study, four volunteers from the treated group still had favorable results, a fact that was not observed in the untreated group.

Although there was no reduction in weight and body mass index in the volunteers of the present study, the low fre-

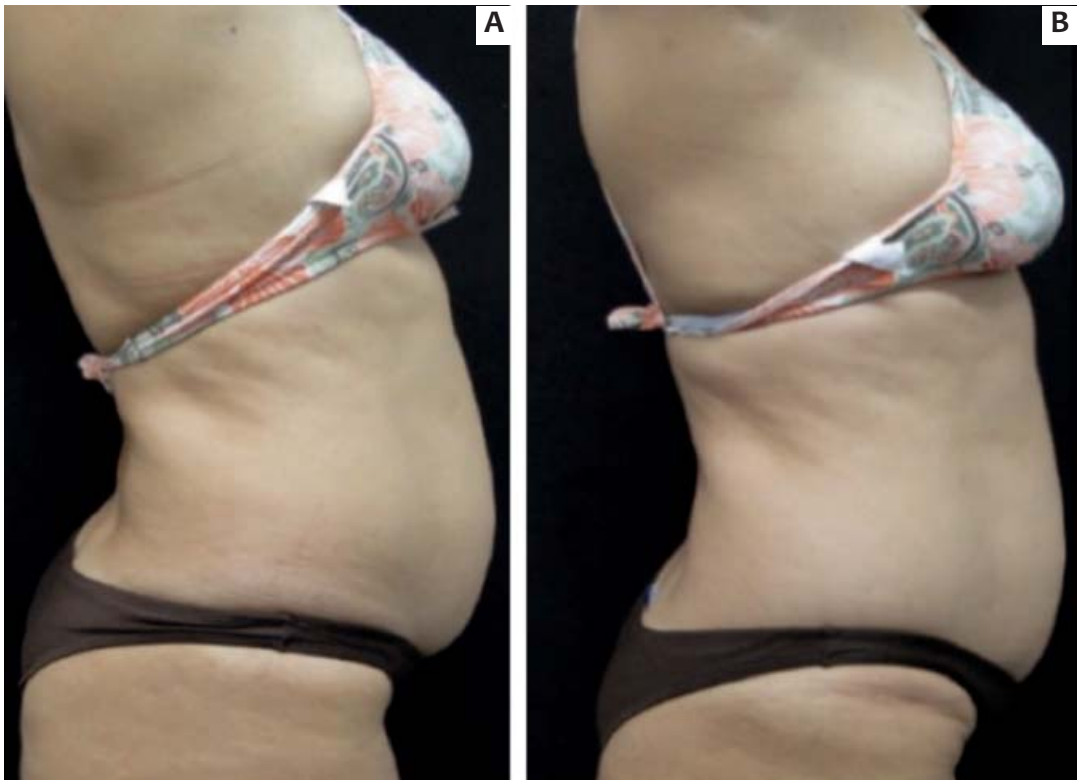


Figure 2: Evaluation of the photographic image of the abdominal region obtained before (D0A) and after (D31B) the low frequency laser application

quency diode laser therapy showed significant results for the reduction of localized fat, which were demonstrated through the reductions in the abdominal circumference measurements, the change in the height of the navel, and the ultrasound scale of the hypodermis. Also, there was dermal compression by the ultrasound. These results are unprecedented in the literature regarding the technological device studied.

CONCLUSIONS

The results obtained demonstrate the potential of the low potency diode laser to become an auxiliary technology in the reduction of abdominal fat. ●

REFERENCES

1. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation on obesity. Geneva: World Health Organization; 1998.
2. Organização Mundial da Saúde. Physical status: the use and interpretation of anthropometry. Geneva; WHO; 1995.
3. Cabrera MAS, Jacob Filho W. Obesidade em idosos: prevalência, distribuição e associação com hábitos e comorbidades. Arq Bras Endocrinol Metab. 2001; 45(5):494-501.
4. Martins IS, Marinho SP. O potencial diagnóstico dos indicadores da obesidade centralizada. Rev Saúde Pública. 2003; 37(6):760-7.
5. Janssen I, Heymsfield SB, Allison DB, Kotler DP, Ross R. Body mass index and waistcircumference independently contribute to the prediction of non-abdominal, abdominalsubcutaneous and visceral fat. Am J Clin Nutr. 2002; 75(4):683-8.
6. Neira R, Arroyave J, Ramirez H, Ortiz CL, Solarte E, Sequeda F, et al. Fat liquefaction: Effect of low level laser energy on adipose tissue. Plast Reconstr Surg. 2002; 110(3): 912-22.
7. World Health Organization / Food and Agriculture Organization. Diet, nutrition and the prevention of chronic diseases. Geneva: World Health Organization; 2003. (TechnicalReport Series, 916).
8. Jackson RF, Roche GC, Shanks SC. A Double-Blind, Placebo-Controlled Randomized Trial Evaluating the Ability of Low-Level Laser Therapy to Improve the Appearance of Cellulite. Lasers Surg Med. 2013;45(3):141-7.

Photodynamic therapy versus imiquimod in the treatment of multiple actinic keratoses of the face: a comparative randomized study

Terapia fotodinâmica e imiquimode no tratamento de ceratoses actínicas múltiplas da face: um estudo comparativo e randomizado

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ABSTRACT

Introduction: The importance of early diagnosis and treatment of actinic keratoses is well established. There are several effective therapeutic options for the treatment of this condition.
Objectives: To compare the efficacy and patient preference between 5% imiquimod cream and photodynamic therapy in the treatment of actinic keratoses.
Methods: Twelve patients with a total of 245 lesions were treated with MAL-PDT and 5% imiquimod cream. Randomization was performed in order to determine the hemiface (left or right) for each treatment. First, the patients underwent MAL-PDT. After one month, they started using imiquimod in the other hemiface twice a week for 16 weeks. After six months, the two treatments were analyzed for efficacy, tolerability, patient preference, and aesthetic results using the observations of a blinded investigator.
Results: Both treatments showed good therapeutic responses, with 72% of lesions treated with MAL-PDT and 76% of lesions treated with imiquimod having complete improvement. The average size of residual lesions was similar in the two treatments. Ten patients (83%) preferred the treatment with photodynamic therapy (p = 0.03).
Conclusions: Photodynamic therapy and imiquimod are effective in the treatment of actinic keratoses. The results of this study showed similar efficacy and good aesthetic results with the two treatments. Nevertheless, most patients preferred the photodynamic therapy.
Keywords: keratosis, actinic; treatment outcome; therapeutic.

RESUMO

Introdução: *A importância do diagnóstico e tratamento precoces das ceratoses actínicas (CA) está bem estabelecida. Existem várias opções terapêuticas eficazes no tratamento das CA.*
Objetivos*: Comparar a eficácia e preferência do paciente entre imiquimode creme 5% e terapia fotodinâmica para o tratamento de CA.*
Métodos: *12 pacientes com total de 245 lesões foram tratados com MAL-PDT e imiquimode creme 5%. Foi realizada randomização para determinar a hemiface (direita ou esquerda) para cada tratamento. Inicialmente os pacientes foram submetidos a MAL-PDT. Após um mês, iniciaram o uso de imiquimode no outro lado da face, duas vezes por semana durante 16 semanas. Após seis meses, os dois tratamentos foram analisados por um investigador cego quanto a eficácia, tolerabilidade, preferência do paciente e resultado estético.* ***Resultados:*** *Ambos os tratamentos apresentaram boa resposta terapêutica: 72% das lesões tratadas com MAL-PDT e 76% das tratadas com imiquimode tiveram melhora completa. O tamanho médio das lesões residuais foi similar com os dois tratamentos. 10 pacientes (83%) preferiram o tratamento com PDT (p: 0,03).*
Conclusões: *PDT e imiquimode são eficazes no tratamento das CA. Os resultados deste estudo mostraram eficácia similar e bons resultados estéticos com os dois tratamentos. Entretanto, a maioria dos pacientes preferiu a PDT.*
Palavras-chave: *ceratose actínica; resultado de tratamento; terapêutica.*

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INTRODUCTION

Actinic keratoses (AK) are dysplastic epidermal lesions induced mainly by chronic exposure to sunlight. Ultraviolet radiation can contribute to the keratinocytes' neoplastic transformation at the molecular level, as well as induce local and systemic immune response suppression, which normally regulates the destruction of malignant cells. Actinic keratoses lesions are considered to be part of a continuum of cellular damage, mutation, and histological processing, which can extend into the dermis as a squamous cell carcinoma, with metastatic potential.[1] Therefore, it is recommended that all AK lesions be treated in order to avoid a possible invasive lesion, metastasis and even eventually death.[1]

There are many available options for the effective treatment of AK. Most have high cure rates – between 75% and 90%.[2] The most common treatments are curettage, and cryotherapy.[2-4] Topical 5-fluorouracil is the third most commonly used option.[2, 3]

Imiquimod is an immune response modifier for topical use that is approved for the treatment of AK, superficial basal cell carcinomas, external genital warts, Bowen's disease, lentigo maligna, molluscum contagiosum, verruca vulgaris, and stucco keratosis.[5] It regulates the production of cytokines such as interferon-alpha, tumor necrosis factor-alpha, various interleukins of the innate immune response, as well as promoting cellular immune response type 1 T-helper.[6, 7] In many studies, the complete and partial improvement of a AK was greater in the imiquimod group than in the placebo's, always with statistically significant differences. The total improvement rate of AKs treated with imiquimod ranged between 45% and 84% for the 16-week treatment scheme and 54% for the 8-week treatment scheme.[8, 9]

Photodynamic therapy (PDT) involves the use of a photosensitizing agent and the light of a precise wavelength to cause the death of specific cells, therefore allowing the treatment of AK lesions. Two topical photosensitizers can be used: 5-aminolevulinate (ALA) and methyl aminolevulinate (MAL) – ALA's methyl ester. MAL offers advantages over ALA since it has better skin penetration, due to the increased lipophilicity and high specificity for neoplastic cells.[10] PDT has been associated with lower morbidity and better cosmetic results when compared with cryotherapy, the most frequently used modality in the treatment of AK.[11]

The main objectives of the present study were to compare the clinical responses of PDT and imiquimod in the treatment of AK, and assess whether there is a patient preference for either of the treatments.

MATERIALS AND METHODS

Study population

The patients selected for the study were to be at least 20-years-old and have from 3 to 10 AK lesions in each hemiface or 6 to 10 AK lesions each.

They were recruited at the Dermatology Ambulatory of the Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, Brazil.

The exclusion criteria were: suspected facial skin cancer, other cutaneous lesions on the face that could affect the clinical evaluation, alcohol or drug dependence, and clinically unstable systemic diseases.

Patients could not be currently using interferon or similar medicaments, other immunomodulating drugs, immunosuppressant drugs, cytotoxic drugs, or any topical treatment for AK lesions in the 3 months prior to the beginning of the study.

The use of moisturizers, retinoids, alpha- or beta-hydroxyacids, and topical corticosteroids in the treated areas was not allowed.

Study design

With the patients having signed a free and informed term of consent approved by the Institution's Research Ethics Committee, the study commenced.

The AK lesions were clinically diagnosed, measured (greatest diameter, in centimeters), mapped, photographed, with each patient being tagged with a number. After inclusion in the study, each received a randomization code, having been drawn for each of the treatment modalities. The patients received PDT with MAL and 5% imiquimod cream on alternate sides of the face (the randomization was used to determine which side of the patient's face should receive each of the treatments). Initially, the randomized side of the face received PDT with MAL, with the topical treatment with imiquimod 5% cream being initiated one month later, on the opposite side.

The same experienced dermatologist who performed the baseline evaluation and the total lesion count at the beginning of the study carried out the final assessment of each patient after the treatment, with the remaining lesions being measured and photographed again.

Each lesion was prepared prior to PDT with light curettage in order to remove hyperkeratotic scales and crusts, usually without bleeding. Topical anesthesia was not necessary. A 1 mm thick layer of 160 mg/g MAL cream (Metvix®; Tafarnaubach Penn Pharmaceutical Services Ltd., Tafarnaubach Industrial Estate, Tredegar Gwent, UK) was applied on each lesion, covering 5 mm of the adjacent skin. Each lesion was then covered with an occlusive dressing and aluminum foil for 3 hours. Next, the dressing was removed and the clean cream with 0.9% saline solution was applied immediately before illumination with red light using the light emitting diode device (Aktilite® CL 128, PhotoCure Inc., Oslo, Norway), with the following parameters: approximate 634 wavelength = 3.0nm, fluence = 37J/cm^2, irradiance = 50mW/cm^2 at 50 mm distance from the skin's surface, with a maximum variation of ± 10% in the target area over eight minutes. The patient and the medical team used protective goggles during the illumination period.

One month after receiving PDT with MAL, the patients started treatment with imiquimod cream. The medication (Aldara crem®, 3M Health Care Limited - Loughborough - Leicestershire, England) was supplied to the patient in 32 sachets of 250.0 mg. Patients were instructed to apply 5% imiquimod cream in the AK lesions of the contralateral hemiface that had

undergone PDT, twice a week for 16 weeks. The patient should apply the cream in the evening and remove it the morning, subsequently applying a 30 SPF sunscreen (provided by the study) on the whole face. In order to increase adherence to the treatment, a poster with the topography of the lesions to be treated was provided. The patients were evaluated monthly.

The final evaluation was carried out by the same evaluator, who acted in a blinded capacity for the treatments performed on each side of the face. The lesions were examined, photographed, classified, and measured.

The patients were assessed for safety and tolerance in Weeks 1 and 4 after the PDT session , and in Weeks 4, 8, 12, and 16 during the treatment with imiquimod. Local and systemic adverse effects that might have occurred were looked for and recorded at each visit. The presence and severity of erythema, edema, vesicles, ulcers, and crusts were recorded on a scale from 1 to 4 (where 1 corresponded to the lack of reaction and 4 the presence of intense reaction). Safety was assessed at each visit by monitoring the occurrence of local and/or systemic side effects.

Patients with persistent AK lesions at the end of the study received alternative treatments (cryotherapy or chemical cauterization).

Statistical analysis

Based on previous studies,[12,13] the minimum sample of 11 patients was calculated to demonstrate the difference of one standard deviation in the individual responses and preferences, and the presence of side-effects when both methods were compared (with 90% power, considering $\alpha = 0.05$).

The analyses were performed on a *intention to treat* basis. The data were processed using the software SPSS, version 14. 0.

The Wilcoxon and McNemar tests were used to compare imiquimod and PDT with MAL regarding the partial or complete cure of the lesions and adverse effects. The Bimodal Exact test was used to evaluate the patients' therapeutic preferences.

RESULTS

Twelve patients with a total of 245 lesions were included in the *intention to treat* analysis. All were women with Fitzpatrick's skin phototypes I or II. The average age was 69 years (ranging from 47 to 80 years). Only one patient had not undergone treatment for AK before entering the study. Cryotherapy was the most frequently used therapeutic modality prior to the study. Only one patient discontinued the use of imiquimod due to discomfort at the application sites during the 2nd month of treatment. Eleven patients completed the study.

The average baseline number of AKs in the treated areas was 20 (± 8) lesions per patient. AKs in hemifaces treated with PDT and imiquimod had similar baseline characteristics (Table 1).

The two treatment methods showed good therapeutic response: 72% of lesions treated with PDT and 76% treated with imiquimod had complete improvement. The average sizes of residual lesions were similar after the two treatments (Table 2).

Regarding adverse effects, local cutaneous reactions (erythema, pruritus, pain, edema, vesicles, crusting) and systemic symptoms (headache, fever, malaise, weakness) were observed on the days following PDT and during the months of treatment with imiquimod; there was no statistically significant difference (Table 3). However, in the hemifaces treated with PDT, the local skin reactions were more intense in the 7 days after the sessions. With imiquimod, these signals tended to persist during the 16 weeks of treatment.

Serious or unexpected adverse reactions were not observed during the study. All patients showed some – mild in general – skin reaction (Figures 1 and 2).

During the PDT procedure, the pain was classified according to a pain scale (0 to 10). The mean value was 7, with a standard deviation of 5-8.

Table 1: Characteristics of the AK before the treatments

	PDT	Imiquimod	p
Number of AKs per patient (median, min-max)	10 (5 - 18)	11 (3 - 18)	0,81
Total AKs (n)	**120**	**125**	-
AK sizes in cm (median)	0.96 (0.46 - 2.05)	0.98 (0.33-2.06)	0.75

Table 2: Characteristics of the AK after the treatments

	PDT	Imiquimod	p
Number of AKs per patient (median, min-max)	2 (0 - 8)	2 (0 - 7)	0,72
Total AKs (n)	**34**	**30**	-
AK sizes in cm (median)	0.14 (0 to 0.48)	0.12 (0 to 0.65)	0.53

* Data are presented in number or median (min, max)

Table 3: Adverse effects during the treatment

Score (1-4)	PDT	Imiquimod	p
Erythema	3 (2-4)	3 (2-4)	0.51
Pruritus	2 (1-3)	2 (1-3)	0.79
Pain	1 (1-3)	2 (1-3)	0.75
Edema	1 (1-2)	1 (1-3)	0.40
Crusts	2 (1-3)	2 (2-3)	0.33

*Acute pain during PDT was evaluated separately

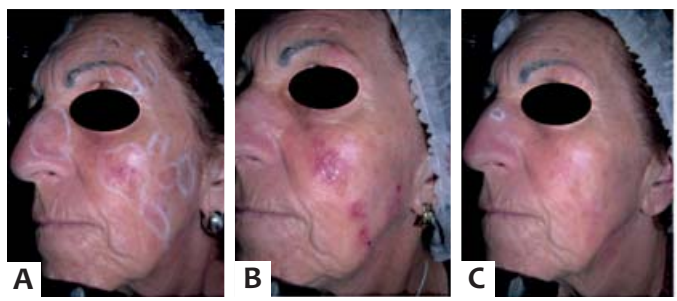

Figure 1: The left hand side of a patient's face before **(A)**, during **(B)** and 16 weeks after **(C)** the treatment with imiquimod

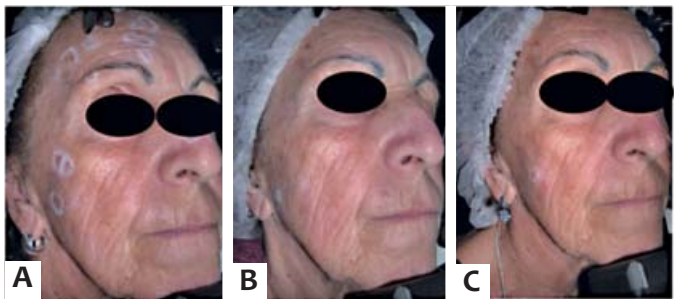

Figure 2: The right hand side of the same patient's face before **(A)**, 1 month after **(B)** and six months after **(C)** the treatment with PDT

Any irritation reported at the site of injection during the study was deemed to be related to the treatment in progress in that region.

When asked whether they would repeat the treatment, one of the patients answered that she would not repeat the PDT treatment due to the pain, which she considered very intense, and to the inflammatory reaction on the following days.

The assessment of the aesthetic results did not show any hyperpigmentation, hypopigmentation, atrophy, or scarring in the treated areas. Two patients – one treated with imiquimod and the other with PDT – had mild persistent erythema in the hemifaces.

Patient satisfaction was graded with scores from 0 to 10 (total improvement, reduction of lesions, cosmetic results, and adverse effects). The scores of the first three items were significantly higher for PDT (Table 4). Regarding the subjective analysis of adverse effects, there was a trend toward higher scores for imiquimod, nonetheless without statistical significance.

Patients were asked about their preference regarding the two treatments. Of the 12 patients, 10 (83%) preferred PDT, with a statistical significance of ($p = 0.03$).

Table 4: Patients' subjective satisfaction (scores from 0 to 10)

Considered aspects (mean score ± 2SD)	PDT	Imiquimod	P
Complete improvement	9.6 ± 0.9	8.8 ± 1.4	0.022
Partial improvement	9.6 ± 0.9	8.8 ± 1.5	0.032
Aesthetic results	9.7 ± 0.7	9.0 ± 1.1	0.040
Adverse effects	6.9 ± 3.0	7.9 ± 2.8	0.053

SD = Standard Deviation

DISCUSSION

The present study was mainly aimed at evaluating the therapeutic response and patients' preference regarding the imiquimod and PDT treatments for AK.

Interestingly, each patient in this study served as her own control, ensuring the accuracy of the comparison. PDT offers a relatively selective and noninvasive therapy, which can be performed at an ambulatory clinic, ensuring adherence to the treatment. This provides benefits regarding patient adherence when compared to topical treatments that require prolonged use at home, especially those whose therapeutic effect are based on the inflammation of the skin.[14]

The present study offers the intention to treat results including all patients, independently of the cases where patients withdrew during the follow-up.

The therapeutic response rate – the study's main objective – was similar to those reported for other therapeutic modalities, including cryotherapy and 5-fluorouracil cream.[8, 15] It is important to highlight that there was a decrease in the size of residual lesions with both treatment methods. Re-treatment with both modalities could further reduce residual lesions or completely cure the condition.

The results also showed that the patients preferred the PDT-based treatment. The study's intra-individual design offered a benefit in the comparison of the efficacy and patient preference between the two treatment options, in the same individual.

Both the PDT and the imiquimod treatments offer advantages over other treatments, especially when there is diffuse actinic damage.[16]

Due to the high frequency of AK and its potential for development into invasive squamous cell carcinoma, it is important that treatments not only be effective but also straightforward, with tolerable adverse effects and good aesthetic outcomes.[17]

Although the present study offered important information on the treatment of AK with PDT and imiquimod, it had some limitations, such as the small sample size and the lack of long follow-up periods with patients after the treatment. In addition, the patient sample was composed only of women, not reflecting the typical population of patients bearing AK.[18]

Although the skin discomfort with PDT occurred only during the week following the treatment, while that caused by imiquimod lasted for 4 months, they were comparable as for their intensity.

Despite the patients' subjective evaluation regarding adverse effects not being statistically significant, it tended to benefit imiquimod – probably due to the acute pain during the PDT session.

In conclusion, the results of the present study showed that both imiquimod and PDT were effective and well tolerated in the treatment of AK. However, patients overwhelmingly preferred PDT, probably due to the rapid improvement of lesions and because of its practicality. In addition, PDT was the first method to be performed, and patients may have had greater motivation to begin the treatment. Furthermore, patient motivation may also have been greater with PDT due to the fact that the application was carried out by physicians, while imiquimod was applied by the patient at home.

The present study was a pilot program. Future studies with greater numbers of patients and longer-term monitoring can confirm the outcomes. ●

REFERENCES

1. Lee PK, Harwell WB, Loven KH, Phillips TJ, Whiting DA, Andres KL, et al. Long-term clinical outcomes following treatment of Actinic Keratosis with imiquimod 5% cream. Dermatol Surg. 2005;31(6): 659-64.
2. Chamberlain AJ, Kurwa HA. Photodynamic Therapy. Is it a valuable treatment option for actinic keratoses. Am J Clin Dermatol. 2003;4(3):149-55.
3. Sotirou E, Spalla Z, Maliamani F, Zaparas N, Panagiotidou D, Ioannides D. Intraindividual, right left comparison of topical 5-aminolevulinic acid photodynamic therapy vs. 5% imiquimod cream for actinic keratoses on the upper extremities. J Eur Acad Dermatol Venereol. 2009;23(9):1061-5.
4. Lima HC. Fatos e mitos sobre imunomoduladores. An Bras Dermatol. 2007;82(3):207-21.
5. Stockfleth E, Meyer T, Benninghoff B, Salasche S, Papadopoulos L, Ulrich C, et al. A Randomized, Double-blind, Vehicle-Controlled Study to Assess 5% Imiquimod Cream for the Treatment of Multiple Actinic Keratoses. Arch Dermatol. 2002; 138(11):1498-502.
6. Zeichner JA, Stern DWK, Uliasz A, Itenberg S. Placebo-controlled, double-blind, randomized pilot study of imiquimod 5% cream applied once per week for 6 months for the treatment of actinic keratoses. J Am Acad Dermatol. 2009;60(1):59-62.
7. Lehmann P. Methyl aminolaevulinate-photodynamic therapy: a review of clinical trials in the treatment of actinic keratoses and nonmelanoma skin cancer. Br J Dermatol. 2007;156(5):793-801.
8. Alomar A, Bichel J, McRae S. Vehicle-controlled, randomized, double-blind study to assess safety and efficacy of imiquimod 5% cream applied once daily 3 days per week in one or two courses of treatment of actinic keratoses on the head. Br J Dermatol. 2007;157(1):13341.
9. Ferrandiz C. Update on actinic keratosis in clinical trial experience with imiquimod. Br J Dermatol. 2007; 157(Suppl 2): 32-33.
10. Wulf HC, Pavel S, Stender I, Wensveen CAB. Topical Photodynamic Therapy for Prevention of New Skin Lesions in Renal Transplant Recipients. Acta Derm Venereol. 2006;86(1):25-8.
11. Freeman M, Vinciullo C, Francis D, Spelman L, Nguyen R, Fergin P, et al. A comparison of photodynamic therapy using topical methyl aminolevulinate (metvix®) with single cycle cryotherapy in patients with actinic keratosis: a prospective, randomized study. J Dermatolog Treat. 2003;14(2):99-106.
12. Bjerring P, Funk J Poed- Petersen J. Randomized double blind study comparing photodynamic therapy (PDT) with Metvix® to PDT with placebo cream in actinic keratosis. Abstracts in the 29th Nordic Congress of Dermatology and Venereology. [cited 2014 Dec 17]. Available from: http://medicaljournals.se/forum/articles/6/Supplement%202/Suppl2.pdf
13. Lebwohl M, Dinehart S, Whiting D, Lee P, Tawfik N, Jorizzo J, et al. Imiquimod 5% cream for the treatment of actinic keratosis: Results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. J Am Acad Dermatol. 2004;50(5):714-21.
14. Morton CA. Methyl aminolevulinate (metvix®) photodynamic therapy - pratical pearls. J Dermatolog Treat. 2003;14(Suppl 3):23-6.
15. Wiegell SR, Haedersdal M, Philipsen PA, Eriksen P, Enk CD, Wulf HC. Continuous activation of PpIX by daylight is as effective as and less painful than conventional photodynamic therapy for actinic keratoses; a randomized, controlled, single-blinded study. Br J Dermatol. 2008; 158(4):740-6.
16. Vatve M, Ortonne J, Machin MAB, Gupta G. Management of field change in actinic keratosis. Br J Dermatol. 2007;157(Suppl 2):21-4.
17. Stockfleth E, Ferrandiz C, Grob JJ, Leigh I, Pehamberger H, Kerl H. Development of a treatment algorithm for actinic keratoses: a European Consensus. Eur J Dermatol. 2008;18(6): 651-9.
18. Merk HF. Topical diclofenac in the treatment of actinic keratoses. Int J Dermatol. 2007;46(1):12-18.

Original Articles

Artigo 4 - 539

Management of periocular tumors with Mohs micrographic surgery

Manejo dos tumores perioculares com cirurgia micrográfica de Mohs

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ABSTRACT

Introduction: Due to the risk of invasion of the orbital cavity and involvement of noble structures, the periocular region requires specific knowledge related to the anatomy and biological behavior of tumors in this region.

Objective: To present the particularities and complexity of the approach to periocular tumors, through the analysis of cases treated at a Mohs micrographic surgery specialist center.

Methods: A retrospective, observational, cross-sectional study was carried out based on data collected through a review of medical records, operative records, and photographic archives. Thirty-four cases were analyzed between April 2010 and April 2014.

Results: Thirty-one basal cell carcinomas, two squamous cell carcinomas, and one sebaceous carcinoma were operated. Of these, 22 (64.70%) were primary tumors, and 12 (35.29%) were recurrent or incompletely excised. The nodular was the most common type of basal cell carcinoma (38.70%), followed by the micronodular (25.80%), the infiltrating (22.58%), the sclerodermiform (6.45%), the superficial (3.22%) and the adenoid (3.22%). Most of the lesions affected the lower eyelid (44.11%), followed in number by the internal canthus (41.17%), the upper eyelid (11.76%), and the external canthus (2,94%). There was only one recurrence following Mohs micrographic surgery.

Conclusions: Most tumors had an aggressive histological subtype, especially those located in the internal canthus. Despite the study's limitations, the strict histological control of Mohs micrographic surgery, combined with the multidisciplinary approach to patients, provided excellent oncological, functional, and cosmetic results.

Keywords: Mohs surgery; carcinoma, basal cell; carcinoma, squamous cell; eyelid neoplasms; orbit evisceration.

RESUMO

Introdução: *Pelo risco de invasão da cavidade orbitária e comprometimento de estruturas nobres, a região periocular exige conhecimento específico relacionado à anatomia e ao comportamento biológico dos tumores dessa região.*

Objetivo: *Apresentar as particularidades e complexidade da abordagem dos tumores perioculares por meio da análise dos casos operados em um centro de referência em cirurgia micrográfica de Mohs.*

Métodos: *Estudo retrospectivo, observacional, transversal, com dados colhidos por revisão de prontuários, ficha operatória e arquivo fotográfico. Analisados 34 casos entre abril de 2010 e abril de 2014.*

Resultados: *Foram operados 31 carcinomas basocelulares, dois carcinomas espinocelulares (CEC), e um carcinoma sebáceo (CS). Desses, 22 (64,70%) tumores primários, e 12 (35,29%) recidivados ou incompletamente excisados. O CBC nodular foi o mais frequente (38,70%), seguido do micronodular (25,80%), infiltrante (22,58%), esclerodermiforme (6,45%), superficial (3,22%) e adenoide (3,22%). A maioria dos tumores acometia pálpebra inferior (44,11%), seguida do canto interno (41,17%), da pálpebra superior (11,76%) e do canto externo (2,94%). Após CMM, houve somente uma recidiva.*

Conclusões: *A maioria dos tumores apresentava subtipo histológico agressivo, especialmente os localizados em canto interno. Apesar das limitações do estudo, o rigoroso controle histológico da CMM, aliado a abordagem multidisciplinar dos pacientes, propiciou excelente resultado oncológico, funcional e cosmético.*

Palavras-chave: *cirurgia de Mohs; carcinoma basocelular; carcinoma de células escamosas; neoplasias palpebrais; exenteração orbitária.*

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INTRODUCTION

The periocular region is often affected by malignant skin tumors, with basal cell carcinoma (BCC) being the most frequent, followed by squamous cell carcinoma (SCC), and less commonly by sebaceous carcinoma (SC) and Merkel cell carcinoma. Basal cell carcinoma is responsible for 80-90% of all malignant neoplasms of the eyelids.[1] It mainly affects the lower eyelid (50-60%), followed by the medial canthal region (25-30%), and to a lesser extent by the upper eyelid and lateral canthal region.[1,2] In the literature, the mortality rate is variable, estimated at 1.5 to 11%,[3,4] and in general is precipitated by intracranial invasion. Tumors involving the medial canthal region are correlated to an increased risk of intraorbital and intracranial invasion.[1,2]

Although less common, SCC has a more aggressive biological behavior due to its metastatic potential. It is estimated that there is a 24% risk of metastasis to regional lymph nodes secondary to palpebral SCC, and an 8% risk of perineural invasion.[1,2,5]

Perineural invasion can result in a worse prognosis, due to an increased risk of orbital invasion, and an increased recurrence rate. Intermittent or continuous pain, and prickling are symptoms that are often associated with perineural invasion.[1,5]

Sebaceous carcinoma is often undertreated, due to the fact that it often mimics benign diseases such as blepharoconjunctivitis or chalazion. It can simulate a BCC or a SCC, and has great potential to metastasize and be lethal.[5,6] It originates in the meibomian glands in the tarsal plate, or in the Zeiss glands, which are related to the eyelashes. It is more frequent in the upper eyelid, but may cause multifocal lesions, with an estimated orbital invasion of around 15-19% of cases. Metastases can occur in 17% of cases, and mortality is estimated at 6%.[5,6]

Although rare, Merkel cell carcinoma may arise on the eyelids. It has great lethality, grows rapidly, and primarily affects elderly female patients. Metastases may occur early, having a negative affect on the prognosis for recovery. Other malignant neoplasms in this region are even rarer.[1,5]

The surface anatomy of the periocular region classically comprises four anatomical subunits: upper eyelid, lower eyelid, lateral canthal region, and medial canthal region.[2]

Periocular tumors constitute a challenge to the dermatologic surgeon who, while minimizing the functional impairment of the eyelids,[7] should pay attention to the fact that this region is located over the embryonic cleft area, and is therefore less resistant to tumoral spread.[1,8,9] The risk of orbital invasion is greater with biologically aggressive tumors, such as SC and SCC. Although rare in occurrence, it is estimated that the risk of a periorbital BCC invading the orbits varies from 0.8 to 3.6% of cases.[8-10] Among the risk factors are histologic sclerodermiform, micronodular, and infiltrating subtypes, recurrent tumors, development duration in excess of one year, compromise of the medial or lateral canthus, and neural invasion.[9-11] The signs and symptoms that are most frequently linked to orbital invasion are adherence of the tumor to the orbital bone, limitation of the ocular motility, diplopia, displacement of the eyeball due to mass effect, palpebral ptosis and, more rarely, proptosis.[1,12] The tumor spreads through the periosteum of the orbital cavity, but rarely invades the eyeball.[1,11] Intracranial involvement usually takes place via neural invasion through the superior orbital fissure,[13,14] which is the path of the oculomotor (III cranial nerve) and abducens nerves (VI cranial nerve), and lacrimal and frontal branches of the ophthalmic nerve – which in turn is a branch of the trigeminal nerve (V cranial nerve). A multidisciplinary approach, with the presence of an ophthalmologist, and/or head and neck surgeon is essential in such cases.

Mohs micrographic surgery (MMS) is considered the gold standard treatment for periocular tumors due to the fact that it enables accurate histological control of surgical margins, ensuring a higher cure rate, with lower recurrence rates.[10,15,16] An additional advantage of the Mohs' technique is that it allows for a greater economy of the healthy tissue around the tumor, favoring the preservation of important structures and the surgical closure.[9-11]

Although some periocular tumors are easily handled, most of them are difficult to approach due to their size, location, and aggressive biological behavior. Salashe[17] notes that for these tumors, there should ideally be a multidisciplinary team prepared to deal with any tumor size, complex surgical reconstructions, and the management of any possible complications.

The present study is aimed at presenting the particularities and challenges of approaching periocular tumors, through analysis of cases where operations were performed at a Mohs micrographic surgery reference center.

METHODS

A retrospective, observational, cross-sectional study was carried out through a review of medical records, operative records, and a vast photographic archive.

Thirty-four periocular tumors were studied in 33 patients operated on between April 2010 and April 2014, and who were followed up with until September 2014. The patients analyzed had Fitzpatrick skin phototypes II and III. The tumors had the following distribution: 6 in men and 28 in women, 22 were primary tumors, 10 were recurrent, and 2 were incompletely excised.

All patients who underwent surgery had previous biopsies, with paraffin specimens and reports issued by pathologists. Tumors were divided according to histologic type and classified according to the previous biopsy report or the histological analysis performed during surgery (where it was possible to detect remaining tumors in the evaluated margins). In case of an inconsistency between histological subtypes observed in the biopsy reports and those observed in the slides analyzed during surgery, the latter was chosen for the study. This happened in three cases: the previous reports recorded the nodular BCC subtype in two cases and the sclerodermiform BCC subtype in one case; during surgery all three were found to be of the infiltrating BCC type.

In two BCC cases there was no classification of the histological subtype in the report of the incisional biopsy issued by the pathologist. In such cases, the histological slide was requested

and analyzed by the Mohs surgeon, with both having been classified as nodular BCC subtype.

The tumors were still classified into primary, recurrent and incompletely excised, and those that had had their surgical safety margin compromised. This was done according to the histological report drafted after the previous conventional surgery and in consideration of those that were referred to Mohs micrographic surgery for a widening of margins.

The anatomical features of this region impose difficulties for dermoscopic visualization, by hampering the delimitation of margins through dermoscopy. Therefore, a choice was made to delimit margins with the naked eye. In all cases an initial surgical margin was marked based on the clinically apparent boundaries of the lesion. A 2 mm margin was used for nodular BCCs, while a 3 mm margin was used for other BCC subtypes, SCCs, and SCs.

Patients with recurrent or aggressive histological subtype tumors, or with tumors located in the medial or lateral canthal region underwent computerized tomography (CT) with contrast and fine cuts in the topography of the orbit. In all, 10 patients with an increased risk of subclinical invasion of the intraorbital structures were operated on with the participation of an ophthalmologist specializing in ocular plastic. One patient with recurrent SC also had the participation of a head and neck surgeon.

All patients with lesions in the medial canthal region underwent a probing of the upper and/or lower lacrimal canaliculus aimed at minimizing the risk of injury during the tumor resection (Figure 1).

Only two cases were operated on under general anesthesia; the others received tumescent local anesthesia and sedation.

Most tumors operated on were located in the lower eyelid or internal canthus.

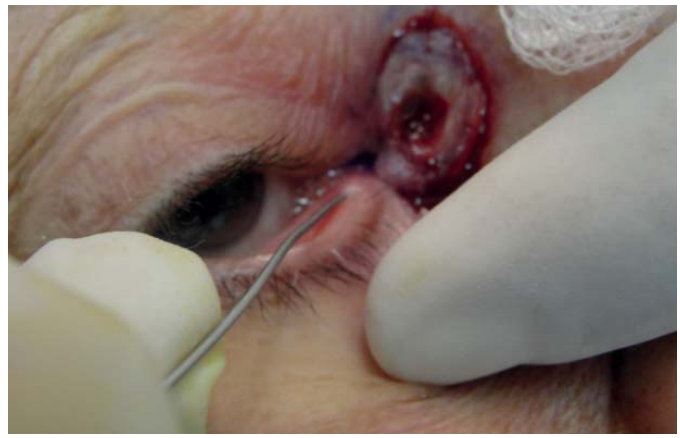
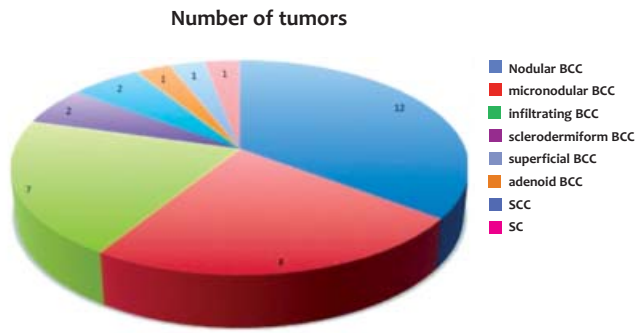


Figure 1: Probing of the lower lacrimal canaliculus. This maneuver was always used in tumors located in the inner canthus in order to minimize the risk of sectioning the lacrimal canaliculus



Graph 1: Histological types of operated tumors

RESULTS

BCC was the most frequent tumor, at 31 cases, with the nodular subtype found in 12 patients, followed by the micronodular (8 cases), infiltrating (7 cases), sclerodermiform (2 cases), superficial (1 case) and one with adenoid differentiation. Other

If the most aggressive histological BCC subtypes (micronodular, infiltrating and sclerodermiform) are added to the SCC and SC cases, it is possible to notice a high incidence of aggressive tumors, as compared with subtypes considered less aggressive

Table 1: Histological type of the tumor & location

type of tumor	Upper eyelid	Lower eyelid	Internal canthus	External canthus	Column 6	Recurrent / Including excised	1 phase 1	2 phases	3 phases	4 phases	Total number of tumors
nodular BCC	0	8	4	0	11	1	9	3	0	0	12
micronodular BCC	1	3	4	0	3	5	1	3	3	1	8
infiltrating BCC	1	3	2	1	5	2	4	0	2	1	7
CBC esclerodermiforme	0	0	2	0	1	1	0	1	1	0	2
superficial BCC	1	0	0	0	0	1	0	1	0	0	1
adenoid BCC	0	0	1	0	1	0	0	1	0	0	1
SCC	0	1	1	0	1	1	1	1	0	0	2
SC	1	0	0	0	0	1	1*	0	0	0	1
Total	**4**	**15**	**14**	**1**	**22**	**12**	**16**	**10**	**6**	**2**	**34**

Note the high incidence of recurrent tumors, especially micronodular BCCs.

Note: *Exenteration of SC performed by head and neck surgeon.

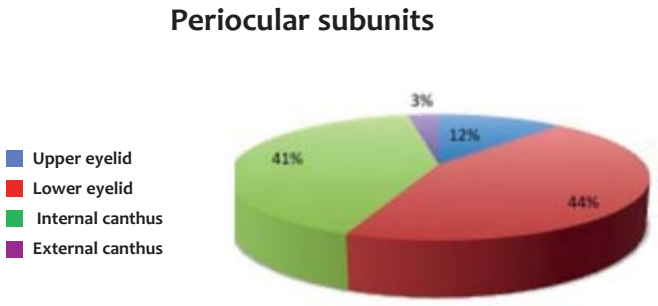


Gráfico 2: Anatomical location of tumors operated on

Most tumors operated on were located in the lower eyelid or internal canthus

tumors operated on were: SCC (2 cases) and one recurrent SC in the upper eyelid (Graph 1).

None of the patients had an image compatible with the invasion of the orbital cavity under CT.

The most affected periocular subunit was the lower eyelid (15 cases), followed by the internal canthus (14 cases), the upper eyelid (4 cases), and external canthus (1 case) (Table 1 and Graph 2).

Regarding the number of stages/phases needed to achieve free margins, only 16 were free of neoplasms, given the initial margin of 2-3 mm. In 10 cases, 2 expansion phases were required; 6 cases needed 3 phases; and 2 cases required 4 phases. (Table 2)

Surgical closure was highly variable according to the size of the surgical defect and location. In lower eyelid tumors, 7 inferior rotation flaps were performed, 1 upper eyelid transposition flap, 1 primary closure, and 6 ear helix chondro-perichondrial grafts.[5] The simple skin graft was used in 9 tumors in the internal canthus, skin flaps were used in 3 cases, and primary closures were used in 2 cases. In the upper eyelid, skin flaps were used in 2 cases, a graft was used in 1 case, and the orbital exenteration was used in 1 case of recurrent SC. In the single case of an external canthus lesion, the tumor occupied 1/3 of the upper eyelid and half of the lower eyelid (Figure 2). An ear helix chondro-perichondrial graft was used for the reconstruction of the inferior tarsus and a periosteal flap for the reconstruction of the superior tarsus, followed by the performance of a lateral advancement skin flap for the closure of the upper eyelid.

The follow-up time ranged from 5 to 48 months, with 1 to 4 years in 26 patients (76.5%) and shorter than 1 year in 8 patients (23.5%). One female patient had recurrence of an extensive micronodular BCC in the nose and internal canthus (Figure 3). Having previously undergone PDT in 2012, she was advised by a dermatologist physician to seek care at the authors' dermatologic service, when the lesion recurred. She then underwent MMS in January 2013, through surgical reconstruction with a simple skin graft. After 8 months a tumor recurrence was identified at the graft's superior border, and she underwent a new MMS in November 2013. The patient had no signs of recurrence up to the date this paper was submitted (10 months of follow-up).

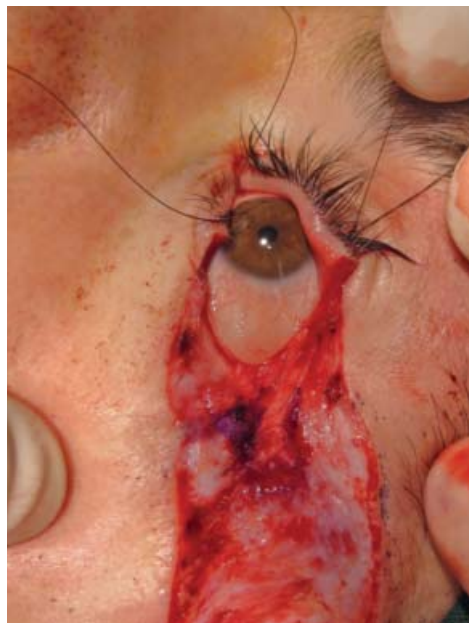


Figure 2: In the single case of a tumor in the orbit's external canthus, the final surgical defect shows a loss of full thickness in 1/3 of the upper eyelid, in 1/2 of the lower eyelid, and of tissue in the temporal region

Table 2: Histological type of the tumor/ number of Mohs stages

	1 phase	2 phases	3 phases	4 phases	Total
nodular BCC	0	8	4	0	11
micronodular BCC	1	3	4	0	3
infiltrating BCC	1	3	2	1	5
sclerodermiform BCC	0	0	2	0	1
superficial BCC	1	0	0	0	0
adenoid BCC	0	0	1	0	1
SCC	0	1	1	0	1
SC	1*	0	0	0	0
Total	**4**	**15**	**14**	**1**	**22**

There was a trend for the aggressive histologic subtypes to need additional expansion phases in order to achieve tumor-free surgical margins.
* SC with invasion of the bulbar conjunctiva was referred to ocular enucleation.

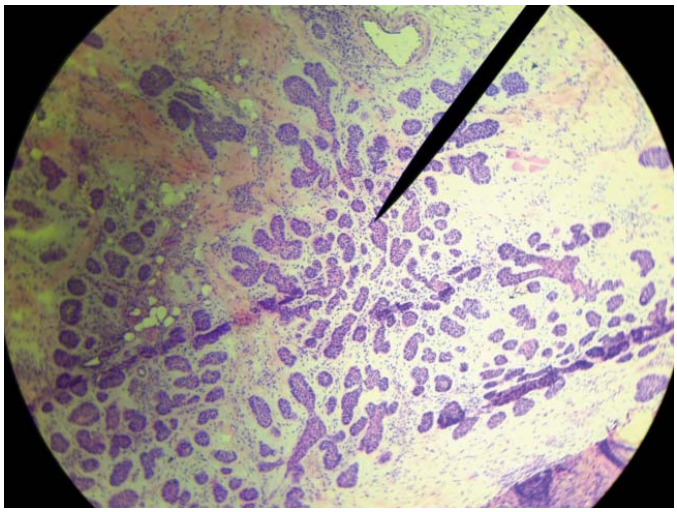


Figure 3: Photomicrography of the recurrent micronodular BCC. It is possible to notice several islets of tumor cells, which are responsible for the high recurrence rate of this histologic subtype.[25]

Regarding complications in the post-operative period, 1 patient had a lower lacrimal canaliculus injury due to tumor infiltration, which progressed to epiphora, and was then referred to the ophthalmologist for evaluation for a possible connective tissue surgery (dacryocystorhinostomy) six months after the CMM. In 5 lower eyelid tumor cases there was a slight scleral show, without relevant functional or aesthetic compromise. One case progressed with chondrite in the donor area of the chondro-perichondrial graft in the ear helix, which was easily resolved with oral corticosteroids.

DISCUSSION

In line with the international literature, BCC was the most common tumor (91.17% of the patients).[12] Considering the fact that the BCC's more aggressive histological subtypes are the sclerodermiform, micronodular and infiltrating[1,3,] the present study will have come across a large number of aggressive tumors (54.83%) – higher than the average found in the literature.[1,8,10] This may be explained by the fact that they were sourced at a reference center for MMS, where most cases have a high complexity level, which also explains the large number of recurrent or incompletely excised tumors, with 12 cases (35.29%) having been operated on during the study's period.

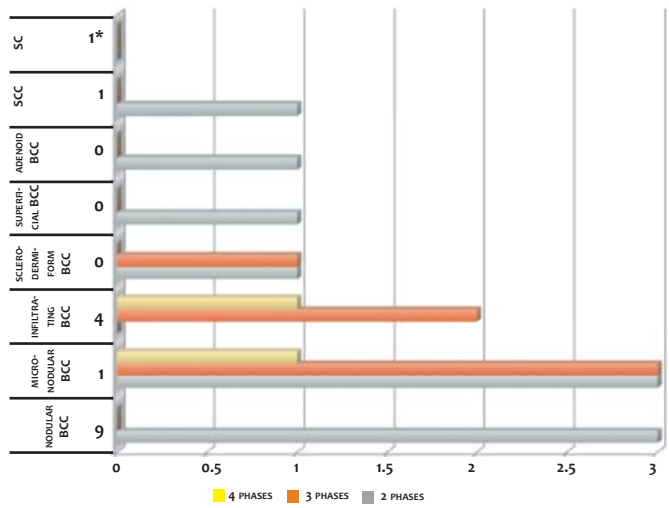
As compared to BCCs, tumors located in the internal canthus have a higher incidence of aggressive subtypes,[1,6,16] with 4 micronodular, 2 infiltrating and 2 sclerodermiform tumors (Table 1). That was also the location of the only case of recurrence after MMS. This confirms data from the literature, which point to internal canthus tumors as having greater invasiveness and a poorer prognosis.[18,19]

As for the location of the lesions, the data from the present study is aligned to the literature,[1,2] with a predominance in the lower eyelid (44.11%), followed by the internal canthus (41.17%), the upper eyelid (11.76%) and the external canthus (2.94%) (Graph 2).

Large surgical margins imply larger surgical defects, requiring complex reconstructions. Most authors recommend using the smallest possible safety margin, sufficient only to completely remove the tumor without generating excessively large defects, thereby minimizing the functional and cosmetic deficits. Hsuan et al.[20] demonstrated that 2 mm margins were insufficient for the complete removal of nodular BCC from the eyelid in about 18% of cases. Chadha et al.[21] recommend 2 mm margins in clearly delimited BCCs, having found incompletely excised surgical margins in approximately 13% of cases and a recurrence rate of 3.3%. Other studies recommend 3-5 mm surgical margins for tumors in the area.[8, 11, 22]

Although the surgical margins recommended for the treatment of BCC with conventional surgery are variable and depend on the histological type and the affected area,[23] in general, most authors consider surgical margins between 2-5mm reasonable for the eyelids.[11, 19-21] With MMS, the authors used an initial margin of 2-3mm, which was not enough to excise the tumor in most studied cases, since 52.94% of tumors needed more than 1 phase of surgical expansion (Figure 3). This finding demonstrates the importance of the histological control of margins through MMS.

Although some authors question the use of MMS for the treatment of SC,[24] the strict histological control achieved by the Mohs technique was important in the management of a case of recurrent SC in the upper eyelid in which a bulbar conjunctival invasion was identified during the procedure. In this case a choice was made for an orbital exenteration during the same surgical event, with the involvement of a head and neck surgeon (Figures 4 and 5). After the exenteration, a new perioperative histological analysis of the margins was performed, in which the tumor was not observed, making it unnecessary to perform a new surgical approach to extend the exenteration. The patient's



Graph 3: Correlation between the histological types of tumors that required more than one phase of margin expansion, and the number of phases to achieve tumor-free surgical margins

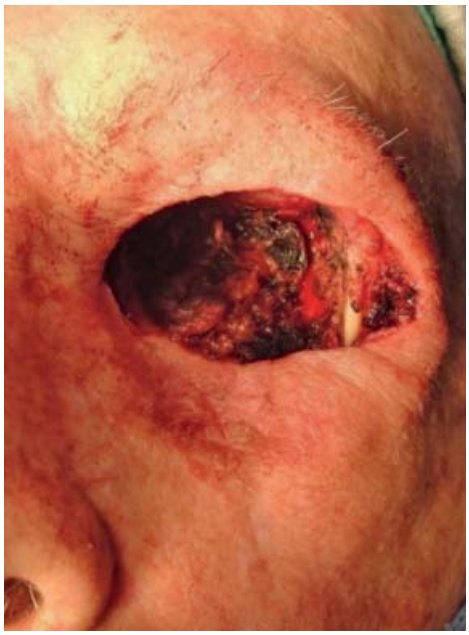


Figure 4: Surgical defect after orbital exenteration, including surgical removal of the eyelids for the treatment of recurrent SC. A choice was made for exenteration after histological confirmation of extensive conjunctival compromise

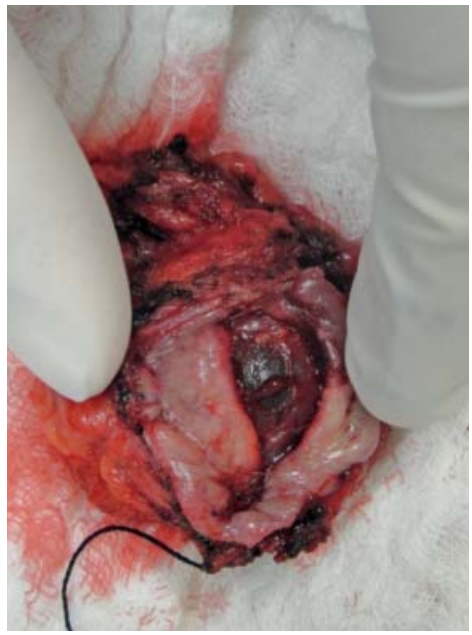


Figure 5: Anatomical specimen containing eye and eyelids, after orbital exenteration for the treatment of a SC. Histological analysis by MMS showed an absence of residual tumor in the surgical margins

follow-up was carried out by the Head and Neck Surgery and Radiotherapy Departments, with no recurrence having been found as of the submission date of the present paper.

The multidisciplinary team effort, which included the contribution of an ophthalmologist and a head and neck surgeon, was critical to the success of the most complex cases, allowing a better approach to deep soft tissues in the orbit and assisting in complex surgical reconstruction and post-operative management.

Notwithstanding the short follow-up time, which ranged from 1 to 4 years in 76.5% of patients – and shorter than 1 year in 23.5% - there was a low recurrence rate, with only one case (2.94%) to date.

Regarding the type of surgical reconstruction, several techniques were used according to the surgical defect's location and size. Five patients developed slight scleral show, with minimal aesthetic impact, and an absence of any recorded cases of ectropion, entropion, or infection.

CONCLUSIONS

The complex anatomy and the peculiar biological behavior of tumors affecting the periorbital region require a specific knowledge on the part of the dermatologic surgeon and the support of a multidisciplinary team.

Most tumors operated on had aggressive histologic subtypes, with roughly 1/3 being recurrent or incompletely excised, evidencing the high degree of difficulty of treating these tumors.

Regarding BCCs, tumors located in the internal canthus showed more aggressive biological behavior, coinciding with the literature data.[1,16,19] This was also the location for the only case of recurrence after MMS – one micronodular BCC, which had a large subclinical size – a fact aligned with the literature that deems this subtype as highly recurrent.[25]

Although surgical margins of 2-3 mm have been performed in all tumors by numerous authors,[18,20,21,22] and considered reasonable for the treatment of primary BCC, most cases in the present study required successive expansion phases in order for neoplasia-free margins to be achieved (Table 2). This datum demonstrates the importance of strict histological control of surgical margins achieved by MMS.

Of the 20 tumors with subtypes considered aggressive, 13 (65%) required more than one expansion phase. Of the 14 less aggressive tumors, only 5 (35.7%) demanded more than 1 expansion phase, demonstrating the relationship between aggressive histological types and subclinical invasion.

Despite the limited size of the sample and the short follow-up time, MMS yielded a high cure rate and a low recurrence rate to date.

The multidisciplinary approach to periocular tumors provided an excellent oncologic management, with maximum functional and aesthetic preservation. ●

REFERENCES

1. Kourt G, Martin P. Eyelid and Periocular Skin Tumors. In: Zeynel A. Karcioglu, editors. Orbital Tumors: Diagnosis and Treatment. New York: Springer; 2005. p. 233-44.
2. Spinelli H M, Jelks GW. Periocular Reconstruction: A systematic approach. Plast. Reconstr. Surg. 1993;91(6):1017-24.
3. Wang JK, Liao SL, Jou JR, Lai PC, Kao SC, Hou PK, et.al. Malignant eyelid tumours in Taiwan. Eye (Lond). 2003;17(2):216-20.
4. Margo CE, Waltz K. Basal cell carcinoma of the eyelid and periocular skin. Surv Ophthalmol. 1993;38(2):169-92.
5. Faustina M, Diba R, Ahmadi MA, Esmaeli B. Patterns of regional and distant metastasis in patients with eyelid and periocular squamous cell carcinoma. Ophthalmology. 2004;111(10):1930-2.
6. Robert P, Taylor MC, James A, Lehman MC. Sebaceous Adenocarcinoma of the Meibomian Gland Presentation of a Case and Review of the Literature. Arch Ophthalmol. 1969;82(1):66-8.
7. Sanchez FH, Eduardo L. Reconstrução palpebral com enxerto condro-pericondral de hélice de orelha. Experiência de um centro de referência em cirurgia micrográfica de Mohs. Surg Cosmet Dermatol. 2013;5(4):324-9.
8. Amjadi M, Coventry B, Greenwood J. Surgical Treatments of Non-Melnaoma Skin Cancers: A Review. The Internet J Plast Surg. 2010;7(2). [Cited 2014 Aug 10]. Available from:: https://ispub.com/IJPS/7/2/9861 .
9. Muller FM, Dawe RS, Moseley H, Fleming CJ. Randomized comparison of Mohs micrographic surgery and surgical excision for small nodular basal cell carcinoma: tissue-sparing outcome. Dermatol Surg, 2009;35(9):1349-54.
10. Tüzün Y, Kutlubay Z,Engin B, Serdaroğlu S. Basal Cell Carcinoma. In: Xi Y, editor. Skin Cancer Overview. Croatia: InTech; 2011. [Cited 2014 Aug 10]. Available from: http://www.intechopen.com/books/skin-cancer-overview/basal-cell-carcinoma .
11. Telfer NR, Colver GB, Morton CA. Guidelines for the management of basal cell carcinoma. Br J Dermatol. 2008;159(1):35-48.
12. D Naidu D, R Salas, K Lee, W Payne. Cutaneous Non-Melanoma Malignancies with Retrobulbar Extension. The Internet J Plast Surg. 200;4(2). [Cited 2014 Aug 10]. Available from: https://ispub.com/IJPS/4/2/5185 .
13. Wood LD, Ammirati CT. An overview of mohs micrographic surgery for the treatment of basal cell carcinoma. Dermatol Clin. 2011;29(2):153-60.
14. Cumberland L, Dana A, Liegeois, N. Mohs micrographic surgery for the management of nonmelanoma skin cancers. Facial Plast Surg Clin North Am. 2009;17(3):325-35.
15. Ratner D, Lowe L, Johnson TM, Fader, DJ. Perineural spread of basal cell carcinomas treated with Mohs micrographic surgery. Cancer. 2000;88(7):1605-13.
16. Litwin AS1, Rytina E, Ha T, René C, Woodruff SA. Management of periocular basal cell carcinoma by Mohs micrographic surgery. J Dermatolog Treat. 2013;24(3):232-4.
17. Salasche SJ, Shore JW, Olbricht SM. Periocular tumors. Dermatol Clin. 1992;10(4):669-85.
18. Ishi LA, Pereira LC, Schellini SA, Marques MEA, CR. Padovani. Carcinoma basocelular da pálpebra - fatores relacionados com a recidiva tumoral. An bras Dermatol.2004; 79(4):423-30.
19. Jankovic I, Visnjic M, Binic I, Kovacevic P, Jankovic D, Jankovic A. Does incomplete excision of basal cell carcinoma of the eyelid mean tumor recurrence? An. Bras Dermatol. 2010;85(6):872-7.
20. Hsuan JD, Harrad RA, Potts MJ, Collins C. Small margin excision of periocular basal cell carcinoma: 5 year results. Br J Ophthalmol. 2004; 88(3):358-60.
21. Chadha V, Wright M. Small margin excision of periocular basal cell carcinomas. Br J Ophthalmol. 2009; 93(6):803-6.
22. Margo CE, Waltz K. Basal cell carcinoma of the eyelid and periocular skin. Surv Ophthalmol. 1993;38(2):169-92.
23. Takenouchi T, Nomoto S, Ito M. Factors influencing the linear depth of invasion of primary basal cell carcinoma. Dermatol Surg. 2001;27(4):393-6.
24. While B1, Salvi S, Currie Z, Mudhar HS, Tan JH. Excision and delayed reconstruction with paraffin section histopathological analysis for periocular sebaceous carcinoma. Ophthal Plast Reconstr Surg. 2014; 30(2):105-9.
25. Hendrix JD Jr, Parlette HL. Micronodular basal cell carcinoma. A deceptive histologic subtype with frequent clinically undetected tumour extension. Arch Dermatol 1996;132(3):295-8.

Hyaluronidase: a necessity for any dermatologist applying injectable hyaluronic acid

Hialuronidase: uma necessidade de todo dermatologista que aplica ácido hialurônico injetável

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ABSTRACT

Introduction: Injectable hyaluronic acid is regarded as the gold standard treatment in the aesthetic correction of wrinkles, loss of contour, and restoration of facial volume. However, it is expected that consequentially adverse – sometimes severe – reactions will arise concomitant with the growth in use of hyaluronic acid-based cutaneous fillers.

Objective: To evaluate the application of hyaluronidase in the treatment of adverse effects of injectable hyaluronic acid, as well as possible reactions to the intradermal injection of that enzyme.

Methods: A retrospective study was carried out with 50 patients who underwent the application of hyaluronidase aimed at correcting complications or unaesthetic effects following hyaluronic acid-based filling procedures in the face.

Results: Twenty-three patients had some type of adverse effect (restricted to the injection site) ranging from erythema, burning sensations, and mild edema, during or after the application, with spontaneous improvement. There were no cases of moderate to severe edema. Most patients reported regression of excess hyaluronic acid a few hours after the injection.

Conclusions: Hyaluronidase is an extremely effective tool both in acute adverse events and in the reversal of unsatisfactory results, and in the dilution of biofilm. All those who use hyaluronic acid when treating their patients should have technical mastery of hyaluronidase application.

Keywords: hyaluronic acid; enzymes; accidents.

RESUMO

Introdução: *O ácido hialurônico injetável é considerado o padrão ouro na abordagem estética para correção de rugas, perda de contorno e reposição de volume facial. No entanto, é de esperar que, concomitante ao aumento do uso de preenchedores à base de ácido hialurônico, estes sejam implicados com efeitos indesejáveis, às vezes graves.*

Objetivo: *avaliar a aplicação da hialuronidase no tratamento de efeitos adversos do ácido hialurônico injetável, assim como possíveis reações à injeção intradérmica dessa enzima.*

Métodos: *foi realizado estudo retrospectivo de 50 pacientes submetidos à aplicação de hialuronidase para correção de complicações ou efeitos inestéticos após preenchimentos à base de ácido hialurônico na face.*

Resultados: *23 pacientes apresentaram algum tipo de efeito adverso, restrito ao local de injeção, variando de eritema, ardência a edema leve, durante ou após a aplicação, com melhora espontânea. Não houve nenhum caso de edema moderado a grave. A maioria dos pacientes relatou regressão do excesso de ácido hialurônico após poucas horas da injeção de hialuronidase.*

Conclusões: *a hialuronidase é ferramenta extremamente eficaz, tanto nos episódios adversos agudos como na reversão dos resultados insatisfatórios e diluição de biofilme, e sua aplicação deveria ser de domínio técnico de todos aqueles que aplicam o ácido hialurônico em seus pacientes.*

Palavras-chave: *Ácido hialurônico; enzimas; acidentes.*

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INTRODUCTION

Injectable hyaluronic acid (HA) is currently considered the gold standard treatment for the aesthetic correction of wrinkles, loss of facial contour, and for volume replacement. According to the American Society of Plastic Surgeons some two million procedures using dermal fillers were carried out in 2012, 5% more than in 2011 and 205% more than in 2000. Second only to botulinum toxin type A, these two minimally invasive and non-surgical cosmiatric procedures were the most commonly performed during the study period.[1] Data from the American Society of Dermatologic Surgeons shows a similar trend, and a study carried out from 2001 to 2007 showed that the procedure that has had the greatest increase (of those performed by dermatologists) was dermal filling, with an impressive growth of 405% (70% of which were HA-based filling products). HA's popularity is attributed to its accessibility, quality, and relative safety, and to its rapid and significant clinical results.[2-4] However, as the use of HA-based fillers grows, it is expected that they will become the most commonly implicated source for undesirable – and sometimes severe – side effects.[5] Despite it being a substance that can be broken down by the human body, and that the majority of adverse effects are only unaesthetic, some complications require fast and aggressive treatment in order to reduce the risk of sequelae or morbidity. Therefore, dermatologists should be able to control these events by applying an enzyme that specifically degrades HA: hyaluronidase.

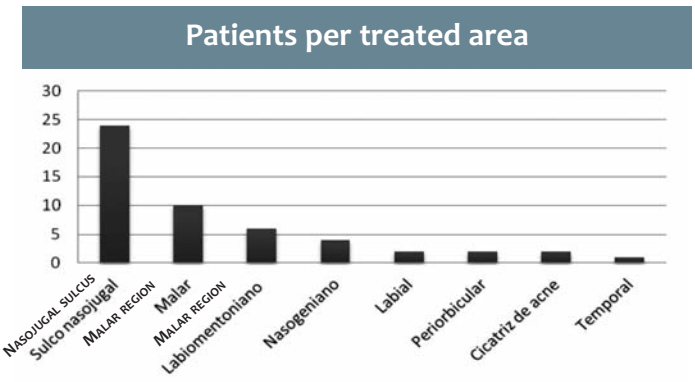
MATERIALS AND METHODS

A retrospective study was carried out with 51 patients who underwent an application of hyaluronidase (Hyalozima® 2,000UTR - Apsen) to correct complications or unaesthetic effects after injectable HA-based dermal filling in the face. The cases were selected from those treated at a private practice from January 2012 to August 2014, and included all patients who underwent dermal filling at the practice and those referred by other physicians, regardless of the brand of HA that was used. Based on the analysis of medical and photographic records, the following data were evaluated: age, gender, anatomical subunits involved, number of sessions, volume of hyaluronidase used, and adverse effects after the application of the enzyme. These reactions were rated by the study team according to the presence or absence of a burning sensation and/or erythema, mild edema (only in the application site), moderate edema (in the treated anatomic subunit), severe edema (across the face or angioedema), and anaphylaxis. All patients were photographed before and after the application and informed about the procedure, including about the possible adverse effects of hyaluronidase. During the interview, patients were questioned about their knowledge of any allergic reaction to bee and/or wasp stings in their medical history. Intradermal testing was not carried out due to the fact that it was not part of the practice's clinical protocol. In the four cases where there was a clinical suspicion of local infection by biofilm, antibiotic therapy was started with macrolide and quinolone for seven days, with hyaluronidase only then being applied. After the procedure, the antibiotic therapy was continued for one week. The routine established for each application was: skin asepsis with cleansing lotion followed by 0.5% alcoholic chlorhexidine solution. The total content of a 2,000UTR hyaluronidase lyophilisate powder vial (Hyalozima®) was dissolved in 5.0 ml of the diluent supplied with the product, generating a 400UTR/ml solution. The application was carried out using a BD Ultra-fine 30U or 50U syringe, and 6.00 mm x 0.25 mm needles (31G).

RESULTS

The study evaluated 51 patients (2 men and 49 women), aged between 27 and 61 years. The standard dose used was 0.1 ml of 400UTR/ml Hyalozima® solution per cm^2 area to be corrected. The total doses applied ranged from 0.05 to 0.4 ml (20-160UTR) per treated anatomical subunit per session. The regions treated, in order of frequency were: nasojugal, malar, mentolabial sulcus, nasolabial, lips, acne scars, periorbicular and temporal (Graph 1). The maximum and minimum doses applied per anatomical subunit are in Table 1.

Regarding the enzyme's possible adverse effects, 28 patients had not had any type of effect with hyaluronidase, while 23 reported some type of symptom or local sign: erythema, burning sensation, or mild edema, during or after the application. Symptoms typically decreased spontaneously within min-



Graph 1: Number of patients treated with hyaluronidase per treated subunit

Table 1: Dose used per area as a fraction of 400 U/ml hyaluronidase solution.

Treated areas	Doses used (ml)
Nasojugal sulcus	0,05-0,4
Malar region	0,03-0,2
Mentolabial sulcus	0,05-0,1
Nasogenian sulcus	0,05-0,2
Lips	0,05-0,1
Periorbicular region	0,2
Acne scars	0,15 - 0,3
Temporal region	0,1

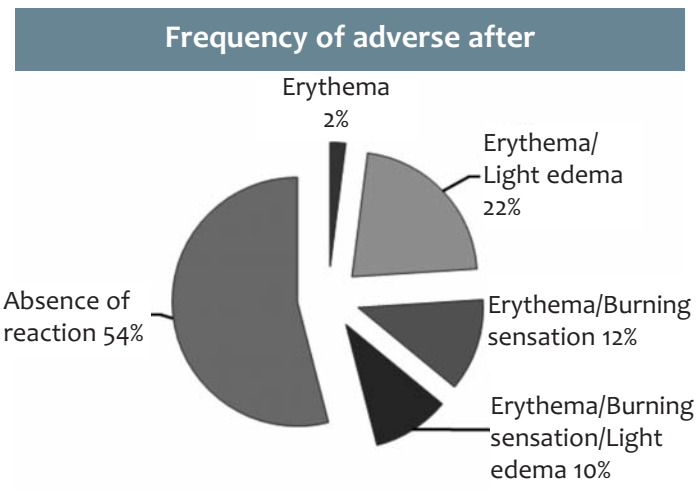
utes or a few hours, and lasted no more than 24 hours, without the need for any additional medication (Graph 2). There were no cases of moderate to severe edema or anaphylaxis. Most patients reported that the regression of excess HA began a few hours after the injection of hyaluronidase. Cases with complete resolution after a single session also reported complete dilution of the HA within 24-48 hours (Figures 1 to 3). Five patients required two sessions, and in only one case did a patient require three sessions to be carried out. In these cases the 15-day interval between applications was observed.

DISCUSSION

Hyaluronidase is an enzyme that occurs naturally in the dermis and acts by depolymerization of HA, which is a viscous mucopolysaccharide, an essential component of the extracellular matrix that is responsible for maintaining cell adhesion by acting as a cement. In this manner, hyaluronidase decreases the intercellular viscosity and temporarily increases the tissue's permeability and absorption. The US Food and Drug Administration (FDA) endorses three indications for the medical use of hyaluronidase: (1) as an adjuvant to increase the absorption and diffusion of other injected drugs, in the clinical practice it is commonly used in retrobulbar anesthesia block in ophthalmic surgery; (2) in hypodermoclysis, consisting of the administration of fluids and/or drugs subcutaneously, an alternative route in cases of mild to moderate dehydration mainly in elderly patients receiving care in the home; (3) to enhance the resorption of radiopaque agents in subcutaneous urography, especially in children and young adults, when intravenous administration can not be performed. Its use in dermatology to dissolve HA is off-label and, although growing, still little discussed.[6]

The hyaluronidase fillings are extracted from cattle and sheep testicles, and a new formulation from a human recombinant enzyme has already been commercially distributed in the US. Table 2 presents the characteristics of the enzymes currently marketed in the US and Europe. Some formulations may contain preservatives and other substances, such as thimerosal (present in Amphadase®), lactose (present in Hylenex®), and albumin (in the most recently preparation, purified from recombinant human DNA, in the Vitrase®). In Brazil, bovine hyaluronidase (Hyalozima®) is available. The different sources, formulations, and concentrations generate great controversy regarding the possibility of side effects and allergic events resulting from the use of hyaluronidase.[6-9]

In practice, however, adverse effects after the use of hyaluronidase are rare, transient, and most frequently reported in the body site where it was applied. The symptoms are mainly local, with edema, heat, erythema, pruritus, and pain, which



Graph 2: Frequency of adverse events after intradermal injection of hyaluronidase for correcting HA-based filler complications.

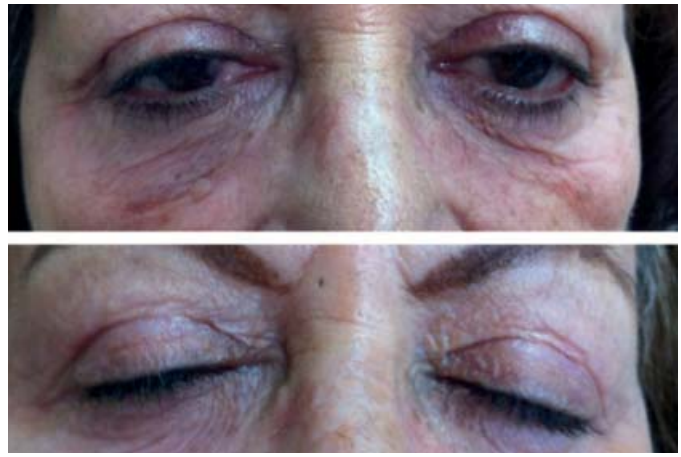


Figure 1: Patient with tyndalization in the right nasojugal groove after injectable HA-based filling and complete regression after application of hyaluronidase.

Figure 2: Patient with nodules in the right nasojugal groove after injectable HA-based filling and complete regression after application of hyaluronidase.

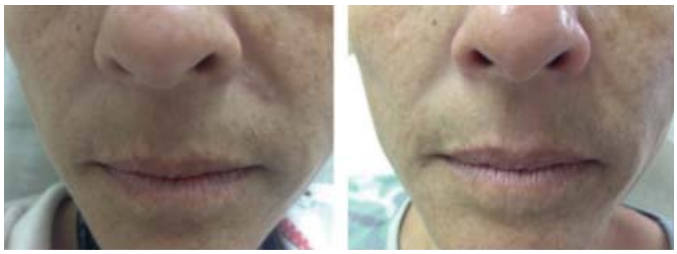


Figure 3: Patient with superelevation in left nasolabial groove after injectable HA-based filling and complete regression after the application of hyaluronidase

respond to the use of oral corticosteroids and antihistamines.[10-17] Less than 0.1% of the treated patients have urticaria or angioedema, and most cases found in the literature are related to the combined use of anesthetics, ophthalmic surgery, analgesia, and chemotherapy.[6,18] These occur mainly due to immediate hypersensitivity, with some reports of patients with delayed reactions, starting within minutes, hours, or even days after exposure.[12-14, 19] This wide range in the onset of symptoms suggests that type I reactions (IgE mediated) and IV (cellular – T lymphocytes) can contribute to the immune response.[10, 11, 19]

It is worth noting that in many of the reports of adverse effects, the patients already had a history of prior exposure to the enzyme in ophthalmic surgery, using hyaluronidase in retrobulbar anesthesia, analgesia and/or old chemotherapy sessions or had an allergy to bees or wasps. Cases of anaphylaxis have been reported after retrobulbar anesthesia block, analgesia for the control of chronic pain, and when combined with chemotherapy for the treatment of CNS tumors in children. In these cases, the doses of hyaluronidase are much higher than those used in the correction of cutaneous fillers and are usually administered intravenously or intrathecally, ranging from 1,500IU and up to 200,000IU, as reported by Szeâpfalusi et al. for the use in CNS tumors chemotherapy. Support with intravenous or intramuscular epinephrine, intravenous or oral corticosteroids, antihistamines and volemic replacement have reversed the reaction picture.[20-23] Thus, several authors have questioned the importance of sensitization as a risk factor for developing hypersensitivity, as well as the route of administration and the dose injected. In this manner, performing an intradermal test prior to the use of the medication, in order to assess the presence of hypersensitivity to hyaluronidase or to one of the solution's components is still a controversial issue for the authors, and was not considered in this study protocol. The discussion regarding the test is centered on the fact that it does not exclude either the presence of allergic hypersensitivity in patients with no previous exposure nor a possible dose-dependent toxicity, yet it is still able to function as sensitizer. The test consists of an intradermal injection of 0.02 ml (3U) of 150U/ml solution. A positive result leads to the appearance of linear erythematous-edematous plaques arising five minutes after the application and persisting for 20-30 minutes, associated with pruritus. Only local erythema or transient vasodilation do not indicate a positive test result. A positive test as well as a history of hypersensitivity to bee and wasp stings contraindicate the use of hyaluronidase, since the enzyme is active in the venom. In addition, enzymes of animal origin should not be used if there is a known allergy to ovine or bovine derived products, or even to excipients present in the solution.[6, 7, 18, 24]

The use of hyaluronidase to dissolve HA-based fillers is relatively recent. Few cases of hypersensitivity were found in the dermatological literature – most of which were restricted to the studied location, ranging from pruritus at the injection time to edema, erythema, and warmth, as observed in the present study.[24-27] A single case of facial angioedema was described by Pierre et al. without mucosal or upper airway involvement, arising minutes after the completion of ovine hyaluronidase injection. The patient had a history of asthma and atopic dermatitis, however denied a hypersensitivity to bee or wasp stings and previous use of the enzyme. The picture was reversed with immediate intravenous corticosteroids and follow-up with oral corticosteroids.[28] There were no reports of anaphylaxis after subepidermal applications for the correction of HA-based filling.[6,19] The authors believe that this is due to the use of much lower doses of the product when compared to other indications.

In addition to being used to treat unaesthetic complications, when used early on in cases of intra-arterial injection of HA, hyaluronidase has been demonstrated to be capable of reducing this complication, with greater benefits when performed in the first 24 hours after the ischemic event. The intra-arterial injection of fillers causes pain, color change, and tissue necrosis.[25,26,29,30] Recent articles have demonstrated that hyaluronidase injections in the treatment of biofilms with HA favor the degradation of the substrate matrix, facilitating the

Table 2: Hyaluronidase trade marks currently marketed in the United States, Europe and Brazil

Trade mark ®	Source	Preservative	Other ingredients	Available formulation	Available source countries	Units
Amphadase®	Bovine	Thimerosal	-	Solution	EUA	150/ml
Vitrase®	Ovine	-	Lactose	Solution	EUA	200/ml
Hylenex®	Recombinante humana	-	Albumina	Solution	EUA	150/ml
Hylase Dessau®	Bovine	-	-	Pó	Germany	150,300,1500/frasco
Desinfiltral®	Ovina	-	-	Solução	England	1500/frasco
Hyalozima®	Bovine	-	Mannitol benzalkonium chloride	Pó	Brazil	2000/frasco (400/ml) 20000/frasco (4000/ml)

migration of macrophages and the penetration of antibiotics.[3,31] Some authors have reported a favorable response to the use of hyaluronidase in resistant inflammatory reactions after dermal filling, regardless of the material used.[32]

The authors based the guidance for the application based on the review of recent literature on the role of hyaluronidase in HA depolymerization and on the authors' own experience. The dilution of the lyophilic powder contained in a 2,000UTR Hyalozima® vial is carried out in 5.0 ml of solvent that comes with the product, generating a 400UTR/ml solution (Video 1). The volume to be injected depends on the amount of HA to be corrected. This avoids high doses in a single application, which could lead to atrophic and unaesthetic results – due to suspicions about the possibility of hydrolysis of the native HA[5,8] – in addition to lowering the probability of allergic reaction. Nonetheless, amounts equivalent to 40 U (0.1 ml) per cm^2 of the area to be corrected are usually sufficient and should be injected only in the nodules of the product to be diluted (Video 2). In case there is an unsatisfactory result, further doses may be offered within 10 to 15 days. There is no evidence that the addition of lidocaine or epinephrine is useful, and they have not been used by the authors. Patients should be informed that erythema, edema, and warmth are possible and expected reactions after the injection, and do not indicate an allergic reaction to the medicament. Cases of hypersensitivity to hyaluronidase should be dealt with according to their severity.

Furosemide, epinephrine, benzodiazepines, heparin, and phenytoin are incompatible with hyaluronidase. Patients using salicylates, corticosteroids, estrogens, adrenocorticotropic hormones, and antihistamines may require higher doses, as these medications seem to increase the tissues' resistance to the effect of hyaluronidase. The enzyme should not be used to increase the absorption of dopamine or alpha-agonists and should not be injected into the infected areas or in the presence of inflammation due to the risk of dissemination of the infection. Local malignancy is also considered as a contraindication. Hyaluronidase is classified as a category C drug during pregnancy.[6,33]

In most of the reported cases, patients had already begun to notice that the HA nodules started to decrease a few minutes after the injection of hyaluronidase, with approximately 50% of the mass regressing after 1 hour and complete resolution in 24 hours, without inflammation.[33,34]

CONCLUSION

The authors of the present study had as their aim to share their experience with the use of hyaluronidase for correcting the unaesthetic effects of HA, which, according to their findings, is consistent with the medical literature. Given that hyaluronidase is an extremely effective tool both in acute adverse events and in the reversion of unsatisfactory results, as well as in the dilution of biofilm, the application of the enzyme and its side effects should be technically mastered by all those who apply HA in their patients.

Video 1: http://www.sgponline.com.br/scd/sgp/downloadvideo.asp?cod_video=21&cod_fluxo=557
Video showing the dilution of the lyophilic powder in a 2,000UTR Hyalozima® vial in 5.0 ml of the solvent supplied with the product, generating a 400UTR/ml solution.

Video 2: http://www.sgponline.com.br/scd/sgp/downloadvideo.asp?cod_video=22&cod_fluxo=557
Video demonstrating the application of hyaluronidase to dissolve nodules that formed in the nasojugal region of a patient after a filling procedure with injectable HA.

REFERENCES

1. American Society of Plastic Surgeons [Internet]. 2012 plastic surgery procedural statistics. [Cited 2014 Jul 20]. Available from: http://www.plasticsurgery.org/news/plastic-surgery-statistics/2012-plastic-surgery-statistics.html .
2. Tierney EP, Hanke CW. Recent trends in cosmetic and surgical procedure volumes in dermatologic surgery. Dermatol Surg. 2009;35(9):1324-33.
3. Ozturk CN, Li Y, Tung R, Parker L, Piliang MP, Zins JE. Complications following injection of soft-tissue fillers. Aesthet Surg J. 2013;33(6):862-77.
4. Crocco EI, Alves RO, Alessi C. Eventos adversos do ácido hialurônico injetável. Surg Cosmet Dermatol 2012;4(3):259-63.
5. Park TH, Seo SW, Kim JK, Chang CH. Clinical experience with hyaluronic acid-filler complications. J Plast Reconstr Aesthet Surg. 2011;64(7):892-96.
6. Lee A, Grummer SE, Kriegel D, Marmur E. Hyaluronidase. Dermatol Surg. 2010;36(7):1071-77.
7. Rzany B, Becker-Wegerich P, Bachmann F, Erdmann R, Wollina U. Hyaluronidase in the correction of hyaluronic acid-based fillers: a review and a recommendation for use. J Cosmet Dermatol. 2009;8(4):317-323.
8. Neri SRNG, Addor FASA, Parada MB, Schalka S. Uso de hialuronidase em complicações causadas por ácido hialurônico para volumização da face: relato de caso. Surg Cosmet Dermatol 2013;5(4):364-6.
9. Pirrello RD, Ting Chen C, Thomas SH. Initial experiences with subcutaneous recombinant human hyaluronidase. J Palliat Med. 2007;10(4):861-4.
10. Borchard K, Puy R, Nixon R. Hyaluronidase allergy: a rare cause of periorbital inflammation. Australas J Dermatol. 2010;51(1):49-51.
11. Zamora-Alejo K, Moore S, Leatherbarrow B, Norris JH, Lake DB, Goggin M, et al. Hyaluronidase toxicity: a possible cause of postoperative periorbital inflammation. Clin Experiment Ophthalmol. 2013;41(2):122-6.
12. Kim TW, Lee JH, Yoon KB, Yoon DM. Allergic reactions to hyaluronidase in pain management -A report of three cases-. Korean J Anesthesiol. 2011;60(1):57-9.
13. Feighery C, McCoy EP, Johnston PB, Armstrong DK. Delayed hypersensitivity to hyaluronidase (Hyalase) used during cataract surgery. Contact Dermatitis. 2007;57(5):343.
14. Kirby B, Butt A, Morrison AM, Beck MH. Type I allergic reaction to hyaluronidase during ophthalmic surgery. Contact Dermatitis. 2001;44(1):52.
15. Dieleman M, Bettink-Remeijer MW, Jansen J, Hoppenreijs VP, van der Pol R, Baarsma S, et al. High incidence of adverse reactions to locoregional anaesthesia containing hyaluronidase after uneventful ophthalmic surgery. Acta Ophthalmol. 2012;90(3):245-6.
16. Agrawal A, McLure HA, Dabbs TR. Allergic reaction to hyaluronidase after a peribulbar injection. Anaesthesia. 2003;58(5):493-4.
17. Ahluwalia HS, Lukaris A, Lane CM. Delayed allergic reaction to hyaluronidase: a rare sequel to cataract surgery. Eye (Lond). 2003;17(2):263-6.
18. Hirsch RJ, Brody HJ, Carruthers JD. Hyaluronidase in the office: a necessity for every dermasurgeon that injects hyaluronic acid. J Cosmet Laser Ther. 2007;9(3):182-5.
19. Kim JH, Choi GS, Ye YM, Nahm DH, Park HS. Acute urticaria caused by the injection of goat-derived hyaluronidase. Allergy Asthma Immunol Res. 2009;1(1):48-50.
20. Ebo DG, Goossens S, Opsomer F, Bridts CH, Stevens WJ. Flow-assisted diagnosis of anaphylaxis to hyaluronidase. Allergy. 2005;60(10):1333-4.
21. Lee HK, Choi EJ, Lee PB, Nahm FS. Anaphylactic shock caused by the epidurally-administered hyalurinidase. Korean J Pain. 2011;24(4):221-5.
22. Lyall DA, McQueen M, Ramaesh K, Weir C. A sting in the tale: cross reaction hypersensitivity to hyaluronidase. Eye (Lond). 2012; 26(11):1490.
23. Szépfalusi Z, Nentwich I, Dobner M, Pillwein K, Urbanek R. IgE-mediated allergic reaction to hyaluronidase in paediatric oncological patients. Eur J Pediatr. 1997 Mar;156(3):199-203.
24. Vartanian AJ, Frankel AS, Rubin MG. Injected hyaluronidase reduces restylane-mediated cutaneous augmentation. Arch Facial Plast Surg. 2005;7(4):231-7.
25. Hilton S, Schrumpf H, Buhren BA, Bölke E, Gerber PA. Hyaluronidase injection for the treatment of eyelid edema: a retrospective analysis of 20 patients. Eur J Med Res. 2014;19:30.
26. Sclafani AP, Fagien S. Treatment of injectable soft tissue filler complications. Dermatol Surg. 2009;35 (Suppl 2):1672-80.
27. Soparkar CN, Patrinely JR, Tschen J. Erasing restylane. Ophthal Plast Reconstr Surg. 2004;20(4):317-8.
28. Andre P, Fléchet ML. Angioedema after ovine hyaluronidase injection for treating hyaluronic acid overcorrection. J Cosmet Dermatol. 2008;7(2):136-8.
29. Kim DW, Yoon ES, Ji YH, Park SH, Lee BI, Dhong ES. Vascular complications of hyaluronic acid fillers and the role of hyaluronidase in management. J Plast Reconstr Aesthet Surg. 2011;64(12):1590-5.
30. Hirsch RJ, Cohen JL, Carruthers JDA. Successful Management of an Unusual Presentation of Impending Necrosis Following a Hyaluronic Acid Injection Embolus and a Proposed Algorithm for Management with Hyaluronidase. Dermatol Surg. 2007;33(3):357-60.
31. Cox SE. Clinical experience with filler complications. Dermatol Surg. 2009;35 (Suppl 2) :1661-6.
32. Dayan SH, Arkins JP, Brindise R. Soft tissue fillers and biofilms. Facial Plast Surg. 2011;27(1):23-8.
33. Brody HJ. Use of hyaluronidase in the treatment of granulomatous hyaluronic acid reactions or unwanted hyaluronic acid misplacement. Dermatol Surg. 2005;31(8 Pt 1):893-7.
34. Pierre A, Levy PM. Hyaluronidase offers an efficacious treatment for inaesthetic hyaluronic acid overcorrection. J Cosmet Dermatol. 2007;6(3):159-62.

Artigo Original

The benefits of using a compound containing Polypodium leucotomos extract for reducing erythema and pigmentation resulting from ultraviolet radiation

Benefícios do uso de um composto contendo extrato de polypodium loucotomos na redução da pigmentação e do eritema decorrentes da radiação ultravioleta

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ABSTRACT

Introduction: Solar radiation can produce erythema and pigmentation in the skin, interfering with pigmentary dermatoses such as melasma. Photoprotection is essential in the treatment or prevention of hyperpigmentation. The use of Polypodium leucotomos extract was effective in reducing the damage resulting from solar radiation, through antioxidant and immunomodulatory mechanisms.

Objective: To evaluate the efficacy of Polypodium leucotomos extract in reducing the erythema and pigmentation following exposure to solar radiation.

Methods: Twenty volunteers were exposed to UVB and UVA radiation emitted by a solar simulator. The reading of the minimum pigmentary and erythema doses were performed after two and 24 hours of exposure, respectively. After seven, 14 and 28 days use of Polypodium leucotomos extract (1,000 mg daily), the minimum pigmentary erythema doses were re-assessed.

Results: There was an increase in mean values for the minimum pigmentary and erythema doses in all visits, with a statistical significance of ($p < 0.05$) after 28 days for the minimum pigmentary dose and after 14 and 28 days for the minimum erythema dose.

Conclusions: The continued use of a compound containing Polypodium leucotomos extract was effective in increasing individual resistance to pigmentation and erythema resulting from UV radiation, meaning it can contribute to the treatment of skin pigmentation disorders such as melasma.

Keywords: chemexfoliation; antioxidants; cosmetics; efficacy; shikimic acid.

RESUMO

Introdução: *A radiação solar é capaz de produzir eritema e pigmentação na pele, interferindo em dermatoses pigmentares como o melasma. A fotoproteção é essencial no tratamento ou prevenção da hiperpigmentação. A utilização do extrato de Polypodium leucotomos demonstrou ser efetiva na redução dos danos decorrentes da radiação solar, através de mecanismos antioxidantes e imunomoduladores.*

Objetivo: *Avaliar a eficácia do uso de extrato de Polypodium leucotomos na redução do eritema e pigmentação após exposição à radiação solar.*

Métodos: *20 voluntários foram expostos à radiação UVB e UVA, através do uso de simulador solar. A leitura da dose pigmentária mínima e da dose eritematosa mínima foram realizadas após duas e 24 horas da exposição, respectivamente. Após o uso durante sete, 14 e 28 dias do extrato de Polypodium leucotomos (1000mg ao dia), novas determinações da dose pigmentária mínima e dose eritematosa mínima foram realizadas.*

Resultados: *Observou-se aumento das médias da dose pigmentária mínima e dose eritematosa mínima em todas as visitas, com significância estatística ($p<0,05$) após 28 dias para a dose pigmentária mínima e após 14 e 28 dias para a dose eritematosa mínima.*

Conclusões: *O uso continuado de um composto contendo extrato de Polypodium leucotomos foi eficaz no aumento da resistência individual à pigmentação e eritema decorrente da radiação UV, podendo cooperar no tratamento de transtornos pigmentares da pele, como o melasma.*

Palavras-chave: *raios ultravioleta; queimadura solar; pigmentação da pele; substâncias protetoras.*

INTRODUCTION

With a more intense or prolonged exposure to ultraviolet radiation, cutaneous tissue will react – to a greater or lesser extent, depending on individual's susceptibility – [1] presenting a clinical picture of erythema and pigmentation, as seen in Table 1.

Erythema – or sunburn – is more evident in fair-skinned individuals, beginning after a period of two to four hours of exposure to sunlight, and reaches its greatest intensity after around 24 hours. Its onset results from vasodilation and the subsequent migration of polymorphonuclear leukocytes, characterizing an acute inflammatory reaction. UVB radiation is the main determinant of the onset of erythema.[1]

Solar pigmentation can be immediate, persistent, or late. Immediate and persistent pigmentations are due to the action of UVA radiation. Resulting from photo-oxidation of the preformed melanin and from melanin transfer from the melanocytes to keratinocytes, these pigmentations are more apparent in darker skinned individuals, arising a few minutes after exposure to sunlight, reaching their peak in two hours and regressing around 72 hours after the exposure.

On the other hand, late pigmentation results from the increased production of melanin due to the action of UVB and UVA, and also affects darker or dark-skinned individuals. Its onset begins three days after exposure to sunlight and can last for months.

The ability to respond to solar radiation through skin pigmentation (tanning) or the production of erythema (sunburn) is genetically determined by ethnic characteristics of individuals.[2]

Fairer-skinned individuals respond predominantly with sunburn, while darker-skinned individuals willexperience a more intense pigmentation rather than erythema.[1]

To quantify an individual's susceptibility to erythema and/or pigmentation, visual measurements, such as the minimal erythemal dose (MED) and the minimum pigmentary dose (MPD), can be used.

The MED can be defined as the smallest amount of effective erythematogenic energy, enough to produce the first perceptible erythema reaction with clearly defined borders.[3] For its determination, an individual must be exposed to increasing doses of UV radiation (through a device called solar simulator, whose radiation spectrum is similar to that of the sun). The reading of the erythema and MED are carried out 24 hours after.[3]

Similarly, Moyal et al.[4,5] described the MPD as the lowest UV dose required for producing an area of persistent pigmentation. For this determination, an individual must be exposed only to UVA radiation in the solar simulator, with the reading of the MPD being carried out after 2 hours.

The greater the MED or MPD, the greater the resistance of an individual to the production of erythema or pigmentation, respectively.

Prevention of erythema is desirable for individuals with acute exposure to the sun, due to the evident discomfort it causes during leisure or work activities. It was in search of a solution for this problem that the first sunscreens were developed early in the last century.

Conversely, prevention of pigmentation is particularly relevant for individuals predisposed to develop pigmentary dermatosis, such as melasma and post-inflammatory hyperchromia. In these situations, the use of topical sunscreens is also recommended, specifically those that have protection against UVA.

In addition to topical sunscreens, some oral use agents with photoprotective action have been developed more recently, with an aim at interfering with the molecular and cellular mechanisms linked to the development of acute and chronic actinic damage.

Among these agents, the Polypodium leucotomos extract (PLE), rich in phenolic derivatives, enjoys an extensive bibliography demonstrating its benefits as a photoimmunomodulator agent capable of reducing acute and chronic actinic damage.[6]

The effect created by the aqueous extract of Polypodium leucotomos leaves is intrinsically related to its antioxidant and anti-inflammatory activity, reducing the erythematogenic response triggered by solar radiation and the phototoxic reaction triggered by the use of psoralen associated with the exposure to UVA radiation-emitting devices.[7]

Furthermore, there is evidence that the systemic use of PLE is capable of preventing the depletion of epidermal antigen presenting cells (Langerhans cells).[7]

The combination of these effects has demonstrated the extract's photoprotective capacity for the prevention of the erythematogenic and phototoxic response to solar radiation.

A study by González et al.[8] was considered a milestone in the establishment of the mechanisms of action of that phytoextract. The authors evaluated a group of 21 volunteers who received topical or oral PLE and were exposed to varying doses of natural solar radiation, with or without psoralen ingestion for triggering a phototoxic reaction. Twelve patients were treated orally with PLE, four of which had received psoralens and eight who had not. The results showed that the use of topical and sys-

Table 1: Características dos principais efeitos agudos da radiação solar

	Erythema (sunburn)	Immediate + persistent pigmentation	Late pigmentation
Responsible wavelength	UVB	UVA	UVB + UVA
More frequently affected individuals	(I a III) = Lower phototypes (I to III)	Higher phototypes * (III to VI)	Higher phototypes * (III to VI)
Etiopathogenic mechanisms	Acute inflammatory reaction	Photooxidation of preformed melanin	Increased production of melanin
Onset	2 to 4 hours	Minutes	From 72 hours
Peak	24 hours	2 hours	
Duration	48 hours	72 hours	From days to weeks

*Phototype classification according to the Fitzpatrick scale.[2]

temic PLE promoted in their respective groups a statistically significant increase in MED and MPD in the non-sensitized group and a significant increase in the minimum phototoxic dose (MFD) in the photosensitized group.

Other studies published subsequently[9,10] have demonstrated that the use of oral PLE in varied doses and administered in an acute fashion a few hours before exposure to UV radiation, was capable of raising the MED, increasing the volunteers' individual resistance to UV-induced erythema.

Moreover, the effect of PLE's in the treatment of pigmentary dermatosis – such as melasma – has been proposed through antioxidant mechanisms (bearing in mind that the pigment is derived from the photo-oxidative process of melanin) and anti-inflammatory mechanisms.

Two studies[11,12] have demonstrated that patients with melasma showed clinical and colorimetric improvement of lesions with continued use of PLE after 12 weeks of treatment.

OBJECTIVES

Primary Objective: To evaluate, by determining the MPD, the effectiveness of the continued use of a formulation containing Polypodium leucotomos extract in reducing pigmentation.

Secondary objectives: To evaluate, by determining the MED, the effectiveness of the continued use of a formulation containing Polypodium leucotomos extract in reducing sunburn.

To evaluate the tolerability to the product after continued use.

METHODS

Study design

Clinical, open, monocentric study with clinical evaluations.

Study population

After having been granted approval by the Research Ethics Committee (REC), the study took place in the period from June to August 2013. Twenty female volunteers were initially recruited and included in the study (ages between 18 and 60 years old, skin phototypes II and III, absence of active skin condition, absence of continuing use of systemic medication). All volunteers signed the Free and Informed Term of Consent (FITC) before undergoing any procedures described in the study's protocol.

In addition to the required characteristics of the population and in order to ensure the eligibility of each of the volunteer, none of the following criteria could be met: pregnancy or potential risk of pregnancy, lactation, use of anti-inflammatory medications and/or topical or systemic immunosuppressants, use of antihistamines for up to 15 days before the beginning of the study, atopic or allergic history, active skin conditions (local and/or disseminated) that could impact the results of the study, conditions that could cause immune suppression, intense exposure to sunlight up to 15 days prior to the inclusion in the study, and other conditions considered to be reasonable for disqualification by the investigator.

Methodological procedures

After initial clinical evaluation for verification of eligibility criteria, each volunteer was referred to the demarcation of test areas and subsequent irradiation. One of the demarcated areas received UVA irradiation, and the other, UVB irradiation.

In the irradiated areas, UV radiation exposures were performed in six subsites (six gates) with areas of 50cm² each. The irradiations emitted by the solar simulator were delivered with progressive doses.

For the UVA irradiated area, these doses were predetermined by a UVA radiation detector, with each being 25% higher than the previous one, according to a geometric progression – the series of six UVA irradiation doses should cover the range 8J / cm² to 25J / cm².

For the UVB irradiated area, the doses were predetermined by a UVB radiation detector, with each dose being 12% higher than the previous one, according to a geometric progression.

After the exposure, each volunteer had to wait for 15 additional minutes in order that any immediate reaction to the UV radiation, such as tanning, reflection erythema, and vesicant eruption could be observed. Any possible reaction was recorded in the medical record accordingly.

After 2 and 24 hours of the irradiation, readings of the areas irradiated with UVA and UVB were carried out with an aim at determining the MPD and the MED, respectively.

MPD's values are expressed in joules per square centimeter (J / cm²).

MED is defined as the amount of radiant energy required to produce the first perceptible erythematous reaction with clearly defined borders, observed at between 16 and 24 hours after the exposure to UV radiation. It is expressed in millijoules per square centimeter (mJ / cm²).

After determining the pre-treatment MPD and MED, the volunteers were released to start the treatment.

During a 28-day period the volunteers made use of the compound containing PLE (Fernblock®, Melora, São Paulo, Brazil), with a daily dose of 4 capsules of 250 mg each (1,000 mg / day) – 2 capsules taken at 9:00 and 2 capsules taken at 13:00.

After 7, 14, and 28 days of medication use, the volunteers returned to the study center for new measurements of the MPD and MED.

On the days of the intermediate exposures (D7 and D14), the volunteers came to the study center and received the UVA and UVB doses before taking the first capsule of the day (at 9:00). This ensured that the last ingestion of the complex had taken place at least 19 hours prior to exposure to the UVR.

These procedures were repeated in new areas of each volunteer's dorsum.

The results were tabulated and the statistical analysis performed using the Student's t-test for paired samples.

RESULTS

All of the 20 included volunteers completed the study, with none having presented a picture characterized by a serious adverse event. Notwithstanding, one volunteer had an adverse

event with mild abdominal colic, which regressed spontaneously and did not require early withdrawal from the study.

MPD PROGRESSION THROUGHOUT THE VISITS

Graph 1 shows the percentage change between the mean values of MPD at the experimental times D0, D7, D14, and D28. It is possible to notice that the studied product provided a statistically significant increase ($p = 0.021$) on MPD values after 28 days of continuous use, suggesting preventive action against UVA-caused photodamage. In particular there was preventive action by stimulation of production of persistent solar pigmentation.

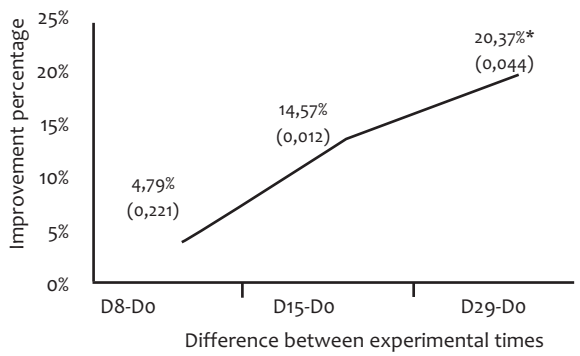
The percentage change shows a gain of up to 17.41% in the MPD, i.e. an increase in the individual resistance to the production of pigmentation.

MED PROGRESSION THROUGHOUT THE VISITS

Graph 2 shows that the studied drugs provided a statistically significant increase in MED values, after 15 days ($p = 0.012$) and 29 days ($p = 0.044$) of continuous use, thus demonstrating the presence of a preventive action against photodamage caused by UVB, particularly in preventing solar erythema.

The percentage change indicates a gain of up to 20.37% in MED, meaning increased individual resistance to the production of solar erythema.

Graph 1: Percentage change in MED at different experimental times regarding the baseline (p-value) * statistical significance ($p < 0.05$)



Graph 2: depicts the percentage change between mean values of MED at the experimental times D1, D8, D15 and D29

DISCUSSION

Photoprotection can be conceptualized as a set of measures aimed at reducing or minimizing the harmful effects of solar radiation on the skin.

Of these harmful effects, the development of sunburn and pigmentation has the most acute onset and usually becomes the primary motivation for the establishment of photoprotection measures.[1,4,5]

Among pigmentary dermatoses, melasma is the most common, and is a frequent complaint in dermatologic practices, constituting one of the main motivations for prescribing photoprotective measures.

It is known that immediate and persistent pigmentation results from the photo-oxidation of the preformed melanin, making it therefore an oxidative phenomena triggered by UVA radiation and visible light, that has an intrinsic correlation with the etiopathogeny of the melasma.[1]

Thus, the introduction of new oral photoprotective active principles, capable of providing a reduction in UV-caused pigmentation through antioxidant and immunomodulatory action, is desirable.

PLE was proven to have significant antioxidant and immunomodulatory capacity in laboratory experiments.[6] In addition, previous clinical studies have indicated that intense use of PLE can produce an increase in MED, showing a clear photoprotective effect.[7-10]

More recently, two clinical studies with melasma patients indicated that the continued use of PLE can produce clinical and colorimetric reduction of lesions, confirming its effectiveness as a therapeutic option in the treatment of this condition.[11,12]

A study evaluating the effect of the continued use of PLE in preventing solar pigmentation (i.e. in the increase of MPD) had not been published to date, and the experimental model employed in the present study is widely used in photobiology to demonstrate the photoprotective efficacy of sunscreen against UVA radiation. Also, there is an absence of studies proving the effectiveness of continued use of PLE in the prevention of solar erythema (i.e. in the increase of MED).

The present study was aimed at evaluating the effects of the continued use of PLE in reducing solar pigmentation, by evaluating the MPD, and the reduction of solar erythema by evaluating the MED changes between experimental times.

The findings have demonstrated that the continued use of a compound containing PLE, at 1,000 mg / day dose produced a positive effect on the increase of MPD, leading to an improved resistance to pigment production due to exposure to solar radiation.

The authors observed a positive effect already at the evaluation on D14, with an improvement greater than 11%. Nevertheless, it was at the evaluation on D28 that the best result was observed, with a statistically significant improvement in excess of 17%.

As already mentioned, the increase in MPD produced by the use of PLE generates a higher resistance to pigmentation and, therefore, a greater photoprotective action against pigmen-

tation – a development that is particularly desirable in patients suffering from pigmentary dermatoses, such as melasma.

It was also possible to note that continued use produces better effects, which reinforces the observation of previous clinical studies showing results in the treatment of melasma within 12 weeks of use.[11,12] Regarding the production of erythema, the authors of the present study observed a similar behavior, though with different numbers.

In the evaluation after 15 days of use, the authors observed a statistically significant increase of roughly 15% in MED, which increased to the even higher level of 20% (with statistical significance) after 29 days of use.

Prior studies to evaluate protection against erythema by determining the MED were aimed at verifying the effect of the intensive use of PLE.[8-10]

Middelkamp-Hup MA et al.[10] carried out a study with clinical assessments of erythema and histological evaluations in volunteers irradiated with solar simulator before and after receiving acute doses of PLE up to a maximum of 24 hours prior to exposure.

The assessment of erythema was not based on the determination of MED, but on the use of a scale to evaluate erythema, which makes comparisons with the results of the present study difficult. It is, however worth noting that the authors found a statistically significant reduction in erythema in irradiated sites after taking PLE up to 2 hours after the ingestion of the last dose of the extract. In the present study, the objective was not to identify the acute effect linked to the ingestion of PLE, but rather to identify some continued benefit regardless of the time of ingestion of the doses (as mentioned above, the volunteers received UVA and UVB doses after at least 19 hours had passed since the last ingestion of the investigated product), which is of particular interest for the understanding of the benefits found in patients with chronic photodermatoses, such as melasma.

The results found in the present study demonstrate that the continued use of PLE provides a slow and gradual increase of MPD and basal MED. This is not exactly a cumulative effect, but a gradual increase in the individual's tolerance to pigmentation and erythema triggered by UV.

CONCLUSION

The continued use of a compound containing PLE produced a significant reduction in MED within 14 days of use, and a significant reduction of MPD within 28 days of use, after exposure to solar simulator irradiation. This has demonstrated the presence of the positive effect in the anti-erythematogenic and anti-pigmentary actions following ultraviolet exposure. This compound can provide benefits to users who bear photodermatoses or dermatoses that may be exacerbated by exposure to UV radiation, such as melasma.●

REFERENCES

1. Hönigsmann H. Erythema and pigmentation. Photodermatol Photoimmunol Photomed. 2002;18(2):75-81.
2. Fitzpatrick TB. The validity and practicability of sun-reactive skin types I through VI. Arch Dermatol. 1988;124(6):869-71.
3. U.S. Food and Drug Administration, Department of Health and Human Services, FDA, USA. Sunscreen Drug Product for Over-The-Counter Human Use, Final Monograph. Federal Register vol. 64, Nº 98; pp 27689-27693, 1999.
4. Moyal D, Chardon A, Kollias N. Determination of UVA protection factors using the persistent pigment darkening (PPD) as the end point (part 1):calibration of the method. Photodermatol Photoimmunol Photomed. 2000;16(6):245-49.
5. Moyal D, Chardon A, Kollias N. UVA protecion efficacy of sunscreens can be determinated by the persistent pigment darkening (PPD) method (part 2). Photodermatol Photoimmunol Photomed. 2000;16(6):250-5.
6. Gonzalez S, Gilaberte Y, Philips N, Juarranz A.. Fernblock: A nutritional with photoprotective properties and potential preventive agent for skin photoaging and photoinduced skin cancers. Int J Mol Sci. 2011;12(12): 8466-75.
7. González S, Pathak MA. Inhibition of ultraviolet-induced formation of reactive oxygen species, lipid peroxidation, erythema and skin photosensitization by polypodium leucotomos. Photodermatol Photoimmunol Photomed. 1996;12(2):45-56.
8. González S, Pathak MA, Cuevas J, Villarrubia VG, Fitzpatrick TB. Topical or oral administration with an extract of Polypodium leucotomos prevents acute sunburn and psoralen-induced phototoxic reactions as well as depletion of Langerhans cells in human skin. Photodermatol Photoimmunol Photomed. 1997;13(1-2):50-60.
9. Middelkamp-Hup MA, Pathak MA, Parrado C, Garcia-Caballero T, Rius-Díaz F, Fitzpatrick TB, et al. Orally administered Polypodium leucotomos extract decreases psoralen-UVA-induced phototoxicity, pigmentation, and damage of human skin. J Am Acad Dermatol. 2004;50(1):41-9.
10. Middelkamp-Hup MA, Pathak MA, Parrado C, Goukassian D, Rius-Díaz F, Mihm MC, et al. Oral Polypodium leucotomos extract decreases ultraviolet-induced damage of human skin. J Am Acad Dermatol. 2004;51(6):910-8
11. Martin LK, Gables C, Caperton C. A randomized double-blind placebo controlled study evaluating the effectiveness and tolerability of oral Polypodium leucotomos in patients with melasma. J Am Acad Dermatol. 2012;66(4): AB21.
12. Ahmed A, Lopez I, Perese F, Vasquez R, Hynan LS, Pandya AG. Oral Polypodium leucotomos extract as an adjuvant to sunscreen in the treatment of melasma. Poster at WCD Seoul 2011.

A succesful topical therapy for cellulite

Uma terapia tópica bem sucedida para a celulite

Artigo Original

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ABSTRACT

Introduction: The present article offers a brief review of the demographics and etiology of cellulite. It shows that cellulite is a true clinical entity, with multi-factorial causes, and that it may affect more than 90% of all post-pubertal women.

Objective: A clinical trial aimed at assessing the effects of a special topical formulation (containing retinol, caffeine, vitamin C, and vitamin E, in an optimized delivery system) on the visible signs of cellulite.

Methods: A topical formulation was used by 25 female patients every evening for 17 weeks. In order to assess its efficacy, the clinical trial employed before and after photographs, self-assessment, and a specific rating system to measure cellulite severity.

Results: The photographs, the self-assessment, and the objective assessment carried out by the expert evaluator, all showed a reduction in the visible signs of cellulite severity. It was possible to observe improvement at the 4th week of treatment, with continued improvement for 17 weeks and beyond.

Conclusion: The results showed that the product tested in the present study in fact led to the reduction of the visible signs of cellulite severity.

Keywords: cellulite, retinol, caffeine, delivery system

RESUMO

Introdução: *O presente artigo apresenta uma breve revisão dos dados demográficos e etiologia da celulite. Demonstra que a celulite é de fato uma entidade clínica verdadeira, com causas multifatoriais, e que pode afetar mais de 90% de todas as mulheres pós-púberes.*

Objetivo: *Um ensaio clínico foi conduzido com o objetivo de avaliar os efeitos de uma formulação tópica especial (contendo retinol, cafeína, vitaminas C e E, em um veículo otimizado), sobre os sinais visíveis da celulite.*

Métodos: *A formulação tópica foi utilizada por 25 pacientes do sexo feminino, todas as noites, durante 17 semanas. A fim de avaliar a sua eficácia, o ensaio clínico empregou imagens fotográficas comparativas e questionários de auto-avaliação, além de um sistema de classificação específico para medir a gravidade da celulite.*

Resultados: *As fotografias, a auto-avaliação e a análise objetiva realizada pelo avaliador especialista indicaram uma redução dos sinais visíveis da gravidade da celulite. Foi possível observar melhora na 4ª semana de tratamento, com melhoria contínua por 17 semanas ou mais.*

Conclusão: *Os resultados mostram que o produto testado no presente estudo, de fato levou à redução dos sinais visíveis da gravidade da celulite.*

Palavras-chave: *celulite, retinol, cafeína, sistema de entrega*

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INTRODUCTION

Cellulite is a colloquial term for deposits of fat and fibrous tissue that cause a dimpling appearance on the skin. The medical term for this condition is *edematous fibrosclerotic panniculopathy*.[1] It was first described in the 17th century, and was simply attributed to an accumulation of fat. It was only recently that it was in fact recognized as a clinical entity.[2]

Cellulite occurs almost exclusively in post-pubertal women and is in fact present in some form in 80-95% of women. [3] Cellulite is much more complex than a simple accumulation of fat. The key factor is the presence of estrogen,[4] which influences a vascular factor, and in turn controls the whole process. The sequence, which begins with a vascular component, is mediated by a specific factor. The final step in the process is the formation of dimpled islands of fat.

It is well known that estrogen plays an important role in the regulation of the skin's blood vessels, as evidenced by the flushed appearance and the telangiectasia seen with rosacea, as well as by the telangiectasias and severed vessels observed elsewhere in the skin, especially in the legs. With the increase in the number of vessels caused by estrogen, and due to the effects of gravity and pressure, vessel rupture occurs, resulting in blood release. This leads to the additional release of proteases, peptides and growth factors, resulting in swelling and inflammation, which triggers the healing process and subsequent fibrosis.

The cell that is primarily involved in wound healing is obviously the fibroblast, which promotes increased production of collagen and the altered synthesis of glycosaminoglycans. Due to the increase in peptides and growth factors, adipocytes increase in size and number, and become trapped in the regrowth of fibrous tissue.

In sum, the vessels weaken and rupture when under the influence of estrogen,[5] the lipocytes accumulate and expand, the fibroblasts are activated and there is a remodeling of the subcutaneous space, which results in islands of fat surrounded by a newly synthesized fibrous network.

While it is a fact that almost all women will have cellulite at some point in their lives,[2] this may occur to varying degrees, including only simple changes that do not have an impact on the personal appearance and may or may not develop into more serious alterations.

Based on many years of clinical observation, the following severity scale for cellulite was developed:

Grade I: The skin appears to be normal, however it displays an "orange peel" effect when pinched.

Grade II: The "orange peel" effect is visible even when the skin is not pinched.

Grade III: Horizontal depressions and dimples are visible on the skin, however there is no clear compartmentalization.

Grade IV: Clearly visible compartments, depressions, and dimples.

Grade V: Final stage of development; in addition to the compartmentalization and dimples, there is also skin overlapping.

There are many treatment modalities in use that are aimed at changing the appearance of cellulite. These include massage, endermologie, liposuction, laser, diet, and physical exercise. Since diet and physical exercise have proven ineffective, certain procedures – such as IPL (Intense Pulsed Light), vacuum massage systems, VelaSmoothTM, AlmaAccent®,[6] RF System, Thermage® ThermaCoolTM,[7] and Smooth ShapesTM[8] 100 among others – have become more prevalent. None of these methods has a significant amount of research ratifying its proposals. Invasive therapies – such as ultrasonic liposuction, smart lipo, subcision, and mesotherapy – have also not proven to be significantly beneficial in improving the appearance of cellulite, whether in the short, or long term.

Topical therapies with formulations containing methylxanthines – such as caffeine and theophylline, retinoids,[9] and compounds that can affect blood circulation, such as Ginko Biloba and papain – were also tested and found minimally effective, perhaps due to their formulation.

An effective therapy should ideally act on all stages of the process that leads to cellulite formation. Furthermore, the results should be apparent to the physician and the patient, additional clinical damage must be avoided and, finally, the treatment should demonstrate efficacy and safety in appropriate clinical trials.

The objective of the trial described in the present paper was to evaluate the effects of a special topical formulation on the visible signs of cellulite, one that contains retinol, caffeine, vitamin C, and vitamin E in an optimized vehicle.

METHODS

Effectiveness of the clinical trial described

The results of a clinical trial performed with a new topical treatment are presented below. Following the study protocol, a formulation containing the following ingredients was used: retinol (to improve the texture of the skin's surface and to stimulate glycosaminoglycans, collagen, and elastin), caffeine (to improve microcirculation and fat metabolism), vitamin C (to help in the synthesis of new collagen) combined with vitamin E (to provide antioxidant action). A patented system of topical delivery (Accudel™)[10] was used to improve the transmission of the ingredients to the skin. The test material (CELLURASE® Renewal Cream) was provided by resolutionMD, LLC.[11]

Accudel[12] is a patented delivery system with a lipid matrix that stabilizes high concentrations of active ingredients, allowing fast and controllable transportation through the stratum corneum while minimizing systemic exposure. It is biocompatible, biodegradable, and non-immunogenic. This system is currently undergoing independent clinical trials for optimal topical delivery of ketoprofen for pain management.

The present study was designed with the purpose of determining the safety and beneficial effects of a formulation that uses the above-mentioned delivery system and ingredients to reduce the visible signs of cellulite. The study duration was 17 weeks. Twenty-five female patients aged between 25 and 60 years participated and were instructed to apply the test-cream every night before going to sleep. They were also instructed to

apply a conventional moisturizer every morning after the removal of the test-cream.

EVALUATIONS

The patients were evaluated after 2, 4, 8, 12, and 17 weeks of treatment. Evaluations consisted of digital photographs of the affected areas. The same precise body site was photographed in each evaluation, with carefully standardized lighting and positioning.

At each experimental point, the patients were asked to answer a questionnaire about product safety, aesthetic attributes and, especially, on their perception of the effectiveness of the treatment.

At the end of the study, two clinical evaluators rated the photographs independently using a 6-point subjective scale, where "0" corresponded to the absence of any signs of cellulite and "5" corresponded to severe cellulitis (Grade V in the described in severity scale).

RESULTS

A) Subjective evaluation (self-evaluation)

No undesirable effects were reported except for a slight dryness in the affected areas, which decreased with the use of a common moisturizer.

In general, efficacy was noticed from Week 4 and at the end of the study. Over 90% of participants noticed an improvement in the visible aspects of cellulite (Graph 1).

In Week 4, 33.4% of patients agreed with the statement "I have noticed improvement in the cellulite", with 4.8% strongly agreeing and 28.6% agreeing partially. Of the total group, 52.4% neither agreed nor disagreed and the 14.3% remaining did not notice improvement.

In Week 8, 68.5% of the patients agreed with the statement "I have noticed improvement in the cellulite", with 21.1% strongly agreeing and 47.4% partially agreeing. A total of 26.3% neither agreed nor disagreed and the 5.3% remaining did not notice improvement.

In Week 12, 81.8% of the patients agreed with the statement "I have noticed improvement in the cellulite", with 27.3% strongly agreeing and 54.5% agreeing partially. At this point in the study, 9.1% neither agreed nor disagreed and the remaining 9.1% did not notice improvement.

In Week 17, 100.0% of the patients agreed with the statement "I have noticed improvement in the cellulite", with 90.0% strongly agreeing and 10.0% agreeing partially.

B) Objective evaluation (performed by clinical evaluators)

The two independent evaluators noticed a gradual overall improvement, reflected in the decreasing cellulite scores in each of the evaluation sessions. When the two independent assessments of the severity of the cellulite were normalized, a gradual improvement as compared to the baseline was observed regarding the appearance of the cellulite. (Graph 2), with a maximum value of 68.6% in Week 17, at the end of the study.

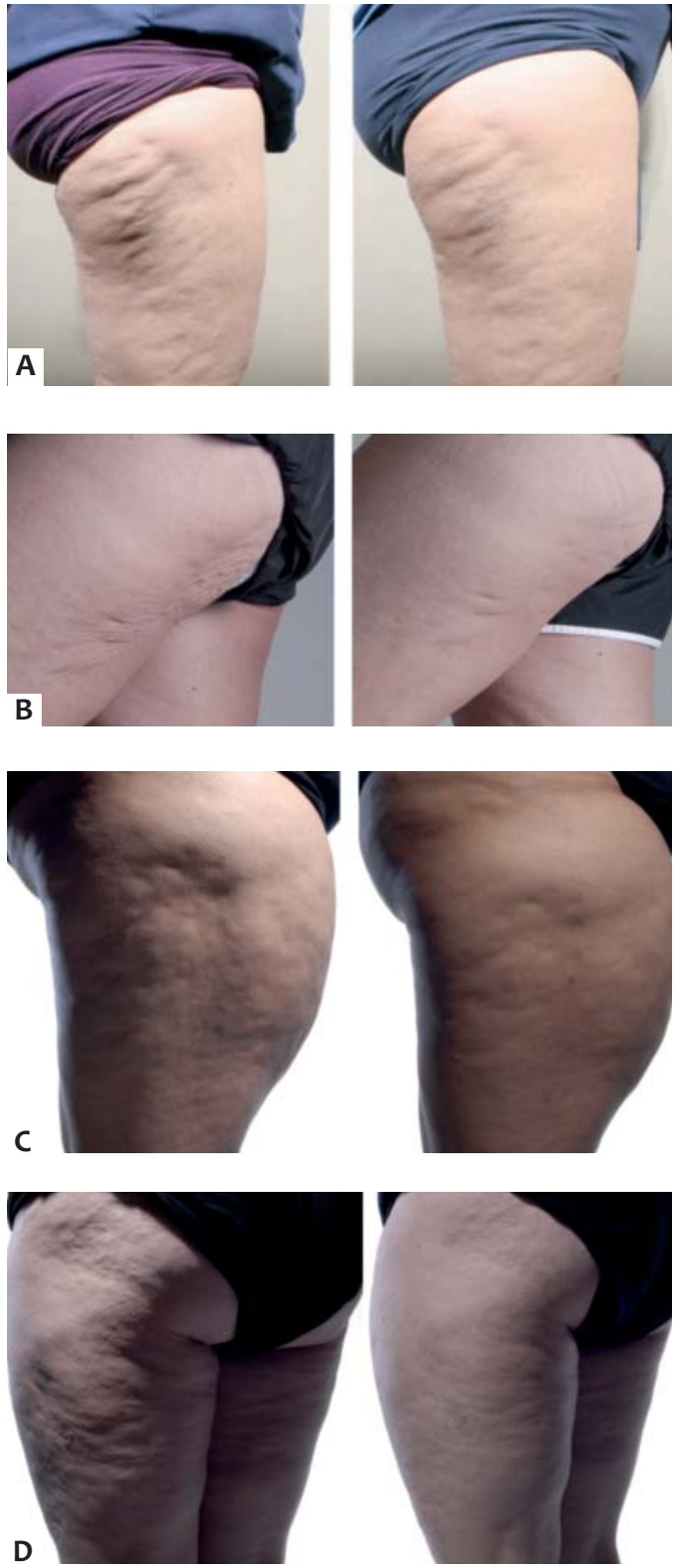
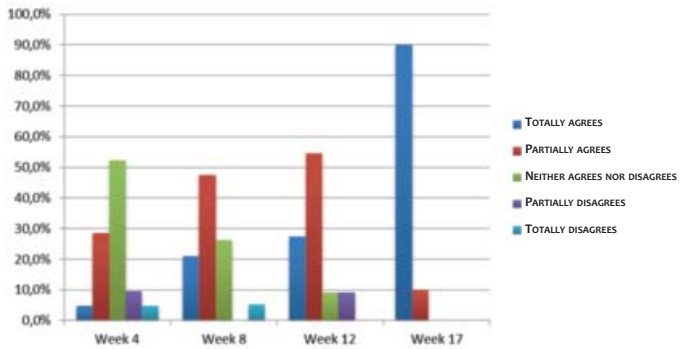


Figure 1: A. Baseline vs. Week 12 (Patient 1); **B.** Baseline vs. Week 12 (Patient 2); **C.** Baseline vs. Week 12 (Patient 3); **D.** Baseline vs. Week 12 (Patient 4).



Graph 1: Percentage of individuals who noticed an improvement in their cellulite condition over time ("I noticed improvement in the cellulite")

Graph 2: Improvement in the severity of cellulite over time

C) Photographic records

The following "before and after" photographs in pairs show the levels of improvement that were typically observed in the clinical trial. The baseline picture is always on the left hand side (Figure 1).

DISCUSSION

The evaluation of the various factors responsible for the development of cellulite allows for the conclusion that cellulite is a real clinical entity (and not simply an accumulation of fat), with a multifactorial cause, and that it should be treated as such.[13]

A substantial number of physical treatments for cellulite are commercially available, however the results are often unpredictable – and even if they are effective, the improvement does not last for long.

During the last twenty years, dozens of companies have sold cellulite-reducing creams,[14] mainly based on the potential lipolytic activity of xanthines – caffeine in particular. None of these products has achieved significant marketplace success, probably due to their minimal effectiveness, even when retinol is added to the xanthines.

Many clinical studies have used a reduction in thigh circumference, or simply weight loss, as measures of efficacy. However, it is a well-known fact that body mass itself does not correlate to the presence or severity of cellulite. In the U.S. the Federal Trade Commission regulatory body has explicitly stated that claims of improvement to cellulite based on any of these measures are unacceptable, and severe fines have been levied to companies that make such claims.

Despite the apparent lack of commercial success with these ingredients (xanthines and retinol), there are reports of their beneficial effects, and, taking into account the changes in the subcutaneous tissue when cellulite is present, it can be expected that, if properly formulated, some retinol, xanthines, and vitamin combinations can reduce the external signs of cellulite.

CONCLUSIONS

The results obtained in the described clinical study indicate that topical therapy to treat the visible manifestations of cellulite can be effective when the appropriate ingredients are selected and incorporated into a topical delivery system designed to improve penetration into the skin. In addition, both patients and evaluators observed without difficulty an improvement in the cellulite, and remarkable improvement was observed after four weeks. Finally, the improvement was gradual, persisting for more than 17 weeks. ●

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REFERENCES

1. Avram MM. Cellulite: a review of its physiology and treatment. J Cosmet Laser Ther. 2004; 6(4): 181-5.
2. Numberger F. Muller G. So-called cellulite: an invented disease. J Dermatol Surg Oncol. 1998;4(3):221-9.
3. Pavicic T., Borella C, Kooting HC. Cellulite—the greatest skin problem in healthy people? An Approach. J Dtsch Dermatol Geo. 2006;4(10):861-70.
4. Wanner M, Avram M. An evidence-based assessment of treatments of cellulite. J Drugs Dermatol. 2008;7(4):341-5.
5. Mendelsohn ME, Kress RH. Estrogen and the blood vessel wall. Curr Opin Cardiol. 1999;9(5):619-26.
6. Alma Lasers [Internet]. Alma LasersTMUS, Buffalo Grove, IL 60084. [cited 2014 Dec 18]. Available from: http://www.almalasers.com/int/
7. Red Spot Interactive [Internet] Jupiter, FL 33458. [cited 2014 Dec 18]. Available from: http://www.redspotinteractive.com/
8. Kligman AM, Pagnoni A. Topical retinol improves cellulite. J Dermat Treatment. 1999;10(2):119-25.
9. PatentBuddy [Internet]. U.S. Patent No. 5,837,289 [cited 2014 Dec 08]. Available from: http://www.patentbuddy.com/Patent/5837289
10. Resolution MD [Internet]. Resolution MD, LLC, Henderson, NV 89074. [cited 2014 Dec 08]. Available from: http://www.trademarkia.com/resolutionmd-85740709.html
11. Imprimis Pharmaceuticals [Internet]. Imprimis Pharmaceuticals, Inc., San Diego, CA 9213. [cited 2014 Dec 08]. Avaiable from: http://imprimispharma.com/
12. Khan MH, Victor F, Rao B, Sadick NS. Treatment of cellulite: Part II. Advances and controversies. J Am Acad Dermatol. 2010:62(3):373-384.
13. Greenway FL, Bray GA, Heber D. Topical Fat Reduction. Obes Res. 1995;3 Suppl 4:561S-568S.
14. Dickinson B, Gora-Harper ML. Aminophylline for Cellulite Removal. Ann Pharmacother. 1996; 30(3):292-3.

Hypodermis and subcutaneous adipose tissue - two different structures

Hipoderme e tecido adiposo subcutâneo: duas estruturas diferentes

Artigo de Revisão

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ABSTRACT

In the literature there is significant confusion between the terms hypodermis and subcutaneous adipose tissue, which are often used interchangeably. They are however two distinct and independent structures, with independent metabolic responses. The distinction between these two layers and the knowledge of their behavior is of crucial importance for choosing the appropriate treatment. The objective of the present study was to review the existing literature on the topic, in order to demonstrate the anatomical and histological differences between the two tissues.

Keywords: subcutaneous fat; adipose tissue; subcutaneous tissue.

RESUMO

Na literatura há uma grande confusão entre os termos hipoderme e tecido adiposo subcutâneo, muitas vezes utilizados como sinônimos. Designam, porém, duas estruturas distintas, independentes e com respostas metabólicas diversas. A distinção entre essas camadas e o conhecimento de seu comportamento são de fundamental importância na escolha do tratamento adequado. Este estudo teve como objetivo uma revisão bibliográfica do tema, com o intuito de demonstrar as diferenças anatômicas e histológicas entre esses dois tecidos.

Palavras-chave: *gordura subcutânea; tecido adiposo; tela subcutânea.*

INTRODUCTION

Development of technologies for use with autologous adipose tissue has drawn attention to fat deposits, which represent an almost unlimited reservoir of stem cells accessible through minimally invasive procedures. Some of these deposits have until this point never been investigated. A growing number of experimental studies have demonstrated the potential of adipose stem cells 1 for neoangiogenesis and immunomodulatory action, as well as their use in treating ischemic and autoimmune diseases. The absence of scientific evidence corresponds to a hurdle in choosing a location for collecting samples.[1]

Moreover, the so called subcutaneous adipose tissue has recently been the object of growing interest since new surgical and non-surgical techniques have been proposed for their removal. These facts call for a deep knowledge of the embryological origin structure within the mesoderm, whose functions are storing energy, protecting against mechanical shock, enabling mobility in deeper structures, and acting as insulation. It also has a cosmetic effect, helping to shape the contours of the body.[2]

Adipose tissue has been empirically assumed by surgeons to be composed of two layers of fat (with differences between

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its lobules) divided by a membranous tissue layer. Its terminology varies according to atlases and textbooks, with the term *fascia superficialis* being the more frequently used (although improperly and inconsistently).[3] Knowledge of the anatomy of superficial and deep fat tissue, called by some authors the *superficial fascial system* (SFS), allows for more well thought out and effective procedures to be conducted, though their terminology varies from author to author.[4, 5] Based on studies of the anatomy of the abdominal wall, several authors have demonstrated that it is organized into the following layers, starting from the surface: skin (epidermis and dermis), superficial adipose or areolar tissue (SAT), a fibrous horizontal layer of connective tissue (membranous layer or fascia superficialis), deep adipose or lamellar tissue (DAT), deep fascia, and the abdominal wall muscles.[3-5]

With the macroscopic dissection of the abdominal wall of 10 fresh cadavers of different physical structure (4 men and 6 women aged 48-93 years, mean age = 69 years), Lancerotto et al. identified a thin layer of adipose tissue underneath the dermis (Superficial Adipose Tissue) formed by fatty lobules and interspersed with fibrous septa, with a structure similar to that of honeycombs and which had a uniform distribution throughout the tissue. These septa (reticula cutis superficialis) were well defined and oriented perpendicularly towards the surface, and were strongly anchored to the dermis. (Figure 1)[6] The fat lobules were organized into single or multiple layers, depending on the fat content of each individual's SAT thickness, and had no clear difference in the distribution both in the caudal and cranial directions, towards the thorax. It was possible to observe that the SAT was highly stable both in its structure and in its elastic properties, returning to its initial position after distention in the compression test.[3] The SAT was histologically characterized by fibrous septa connecting the dermis with the fascia superficialis. These septa were composed of elastic and collagen fibers, which defined oval-polygonal lobules of fat cells,[3] forming what Sbarbati called peri-adipocyte collagen network, with compartments well vascularized by capillaries.[1] This structure plays an important role in preserving cellular integrity and can therefore influence the outcomes of autologous fat transplants (Figure 2).[1]

According to this description, it is possible to observe that this is the layer that is commonly defined as the hypodermis. Despite the clear anatomical distinction between dermis and hypodermis, both are structurally and functionally integrated via the network of vessels and nerves and via the presence of epidermal appendages.[2] SAT or areolar tissue virtually covers the entire body in a layout with vertical compartments, distributed perpendicularly to the skin's more superficial layers. When there is weight gain, it increases in thickness.[5, 6] With advancing age and in the presence of photodamage, it stretches and relaxes (like the dermis), resulting in the ptosis of soft tissue and in the formation of deformities due to pseudo deposits of fat.[4]

After removing the SAT, Lancerotto et al. observed a fibrous layer with a membranous appearance, apparently continuous and macroscopically well organized, with different thicknesses along the abdominal wall and thicker in the lower abdomen. This membrane merged medially with the linea alba,

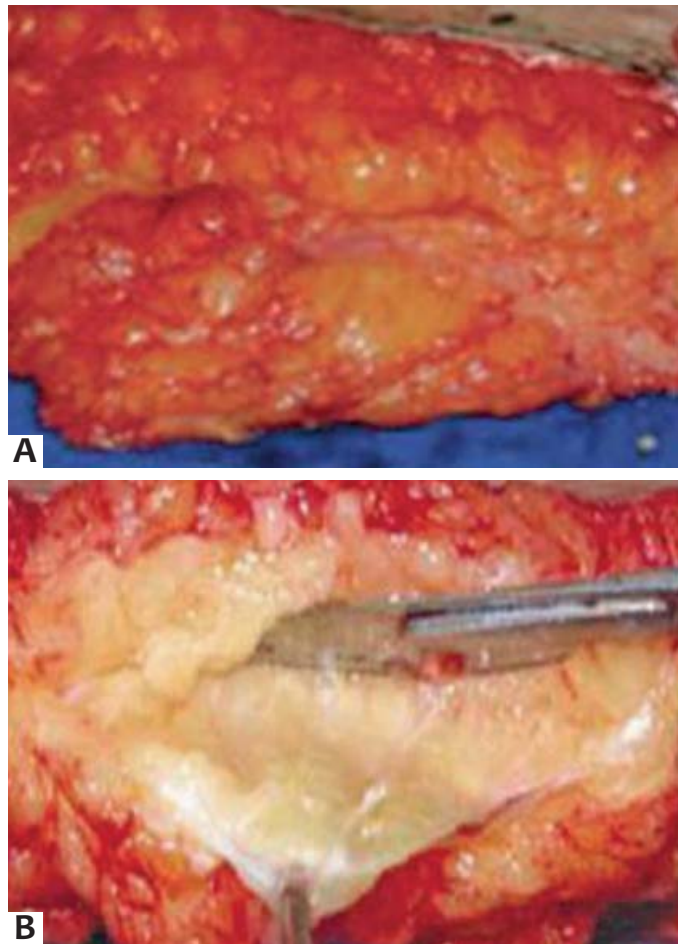

Figure 1: (A) Cross-section of a woman's abdominal skin showing fat lobules. **(B)** Dissected fascia superficialis and superficial and deep layers of adipose tissue.[6]

in the caudal direction with the inguinal ligament and with the bone prominences of the iliac crest; in the cranial direction it continued towards the thorax.[3] Histologically, this membranous layer had multiple sub-layers of fibroelastic tissue consisting of collagen bands distributed in different directions, with intersection points between them and with fine irregular islands of adipose cells, located between the collagen fibers and with the appearance of lamellae.[3, 5]

After removing the fibrous layer, Lancerotto et al. observed yet another layer of adipose tissue (deep adipose tissue – DAT), which Gasperoni et al. called the lamellar layer. It differs from SAT in appearance: it has larger, flattened, and less defined fat lobules, with less evident fibrous septa, and in general obliquely oriented and connected to the membranous layer of the deep fascia of the abdominal wall muscles.[3] Sbarbati et al. describe this layer from the peri-adipocyte collagen network as incomplete, extremely fragile and finely adherent, with few vascular components, which apparently characterizes it as an area of high lipid deposition (Figure 3).[1]

The DAT layer or lamellar tissue overlays the deep fascia

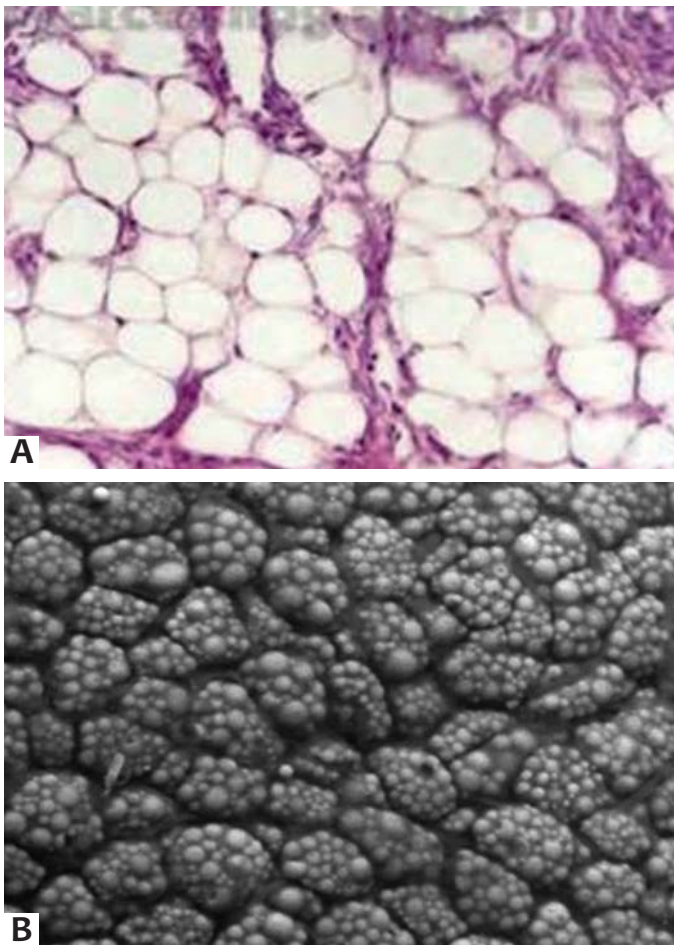

Figure 2: SAT's or hypodermis' adipocytes with well-defined collagen network - **(A)** optical microscope, **(B)** Scanning Electron microscopy (Scale bars: 50 µm).

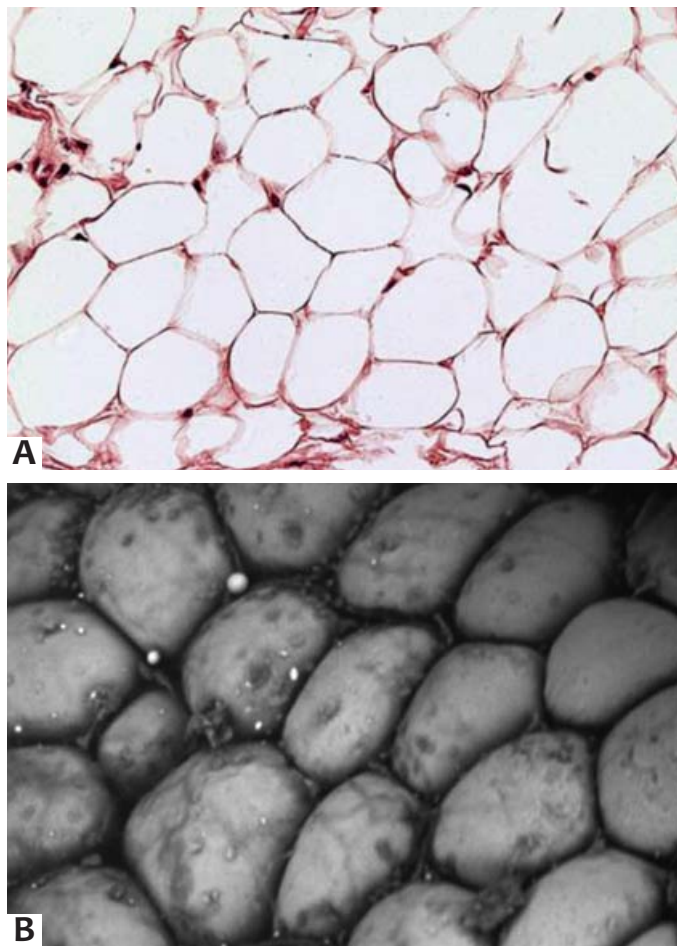

Figure 3: DAT's adipocytes characterized by large adipocytes and poor collagenous component - (A) optical microscope, **(B)** Scanning Electron microscopy (Scale bars: 50 µm).

and the abdominal muscles, with significant variation in thickness. In the adhesion layers of the fibrous areas (inguinal ligament, linea alba and bone prominences) it is thinner due to the reduction of the fat component. Its thickness varied in fat content and mechanical strength among the studied individuals. The septa's oblique distribution, its limited elastic properties when stretched, and its low resistance under explain the sliding of this subcutaneous tissue over the deep fascia.[3,5]

The DAT is present only in certain body sites: abdomen, flanks, trochanteric region, knees, back of the arms, and the upper third of the inner face of the thighs. In the instance of weight gain, it is responsible for localized deformations, when its thickness increases disproportionally more than that of the SAT.[5]

Lancerotto et al. also observed that SAT and DAT behave differently depending on the site of accumulation. In SAT, the thickness was almost uniform around the trunk. DAT tended to be thin in the anterior part, especially anterolaterally over the external oblique muscle, showing maximum thickness posterolaterally at the level of the flanks, where an accumulation was found.[3] In addition, the thickness of both SAT and DAT varied among individuals: in the obese, the average thickness measured for SAT was 17.18 mm and for DAT 18.50 mm; in individuals with normal weight those values were 3.66 mm and 3.14 mm respectively. In both the obese and normal weight individuals, DAT's thickness increased progressively in the T10 – femoral head direction, while the thickness of SAT increased in the same direction only in the obese.[3]

In this manner, studies highlight that the distribution of the superficial and deep adipose tissue (SFS) varies in different body sites and from individual to individual, according to weight and gender. In certain sites it consists of several layers of fat and with obesity its distribution is almost indistinct. Anatomy differentiates body sites with both layers (SAT and DAT) and body regions that have SAT only. Inter-gender SFS variations entail differences in body contour and location of fat deposits. In the lower limbs of both genders, for instance, SAT was observed only in the anterior part of the thighs; in the inner, outer, and posterior parts of the medial portion of the thighs, in the ankles and in the anterior part of the arms. On the other hand, the trochanteric region of the female anatomy has a unique architecture, with the DAT's fibrous septa being firm and dense, and the fat being compact – resembling that of the SAT,

in which lipids are mobilized at a slower rate and synthesized at a higher rate than in the abdominal region. [5] As a result, women have 51% of their DAT in the abdomen while men have 66%.[7] In some body sites, SFS is firmly attached to the fascia or periosteum of the adjacent muscles, forming areas of adhesions, such as in the anterior and posterior middle line of the trunk, and in the inframammary and inguinal grooves and in the gluteus. In men, SFS is firmly adhered to the iliac crest region, while in women the zone of adherence is several centimeters below, determining the contour differences of the trunk region.[5] For some authors, the polymorphism of the adipose tissue can determine different entities, depending on its location. Data from groups of patients with different ages indicate that the adipocytes' specialization and their metabolism can be partly related to the individual's life style. Weight loss is accompanied by an increase in the mobilization rate and a decrease in the fat synthesis rate in all tissues, although this change is more evident in abdominal fat than in the femoral fat.[1] Regarding the resistance to insulin, the abdomen's DAT expresses a strong connection to the key aspects that define the insulin resistance syndrome, in a pattern similar to that observed for visceral adiposity,[7] making it a major contributor to the metabolic consequences of obesity.[8]

CLINICAL IMPLICATIONS

In restorative therapies based on the implantation of cells, the structural morphology of the peri-adipocyte network and the presence of stem cell-rich microcirculation make SAT the optimal tissue for donor areas, particularly in places where the collagen network is thin, as in the trochanteric region and in the inner part of the knees.[1]

Traditional liposuction treats the deep adipose layer or DAT, avoiding the superficial layer, whose removal causes irregularities in the contour (Figure 4). On the other hand, the thickness of the SAT decreases with weight loss.[5]

Cellulite or gynoid lipodystrophy (GLD) is a pathology specific to women due to the anatomical characteristics of SAT. In men, the fibrous septa are smaller and arranged in oblique planes with small fat lobules, whereas in women these lobules are larger and have parallel septa (Figure 5). These conditions exist from birth, however with the hormonal changes of puberty, greater storage of fat occurs along with interstitial fluid retention, and the fat lobules become enlarged due to the hypertrophy of the adipocytes, secondary to vascular alterations[9,10] (Figure 6).[8]

In the female, the fat lobules are larger and have parallel septa. In the male, the lobules are smaller and arranged in oblique planes.

CONCLUSION

Adipose tissue should and needs to be divided into two distinct layers: hypodermis (SAT) and subcutaneous cellular tissue (DAT), for these layers have a completely different anatomy, histology, and metabolism (Charts 1 and 2).

The identification of novel aspects of the physiology of adipocytes and their established peculiarities are related not only to the skin's biology, but also become of paramount importance

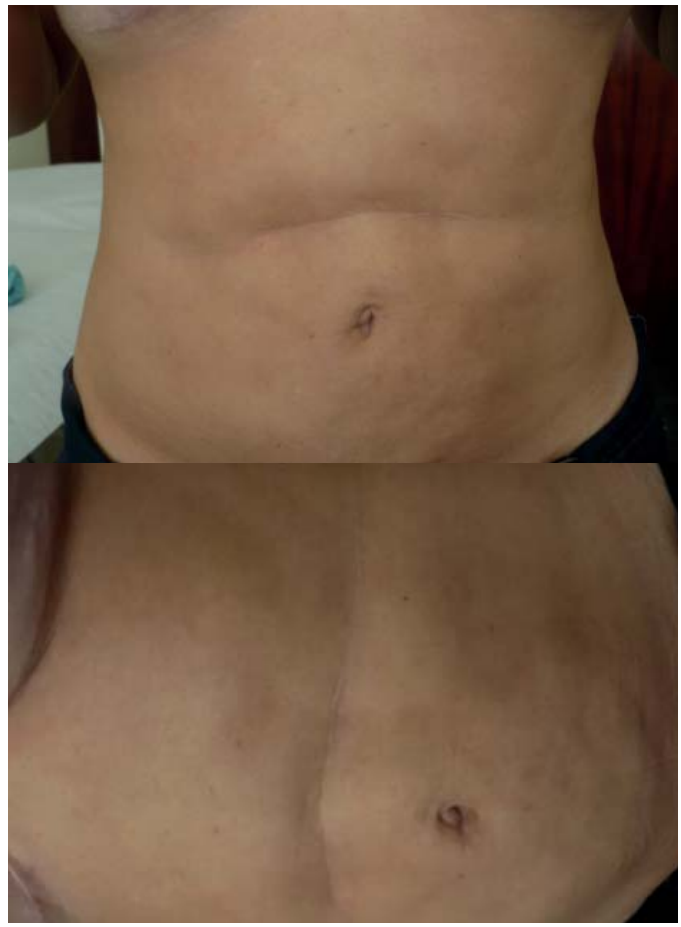

Figura 4: irregularidades de contorno da parede abdominal após lipoaspiração do SAT

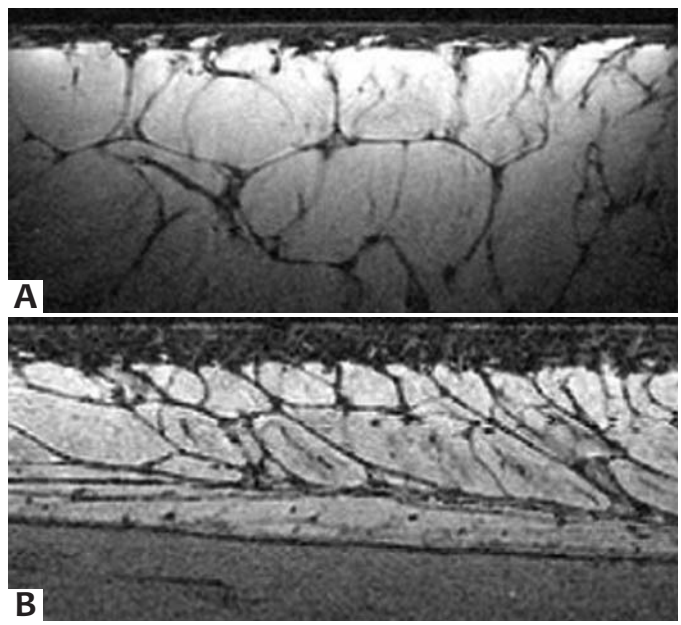

Figura 5: (A) - Pele de mulher sem celulite - **(B)** - Pele de homem. Na mulher os lóbulos de gordura são maiores e com septos paralelos. No homem os lóbulos são menores e arranjados em planos oblíquos.

Figura 6: Desenho esquemático do tecido adiposo normal e na LDG.[8]

to better understand the dynamics of weight loss and localized fat deposition. When some researchers refer to the subcutaneous fat or adipose layer without precise observation of what is being anatomically and histologically described, it becomes impossible to discern which tissue the reference concerns.[11]

Quadro 1: Características anatômicas e histológicas da hipoderme (TAS)

- reveste praticamente todo o corpo
- lóbulos adiposos ovais-poligonais bem organizados
- septos fibrosos conectados à derme
- adipócitos menores envoltos por tecido conectivo denso e bem vascularizados
- alta estabilidade estrutural e nas propriedades elásticas
- diminui de espessura com o emagrecimento

Quadro 2: Características anatômicas e histológicas do tecido adiposo subcutâneo (TAP)

- sua distribuição depende do sexo e da idade
- presente somente em determinadas áreas do corpo: abdômen, flancos, região trocantérica, parte interna do terço superior das coxas, joelhos e parte posterior dos braços
- lóbulos de gordura maiores, achatados e pouco definidos com menor vascularização
- septos fibrosos conectados à fascia muscular
- adipócitos maiores envoltos por tecido conectivo frouxo
- baixa estabilidade estrutural e nas propriedades elásticas
- os lipídeos são mobilizados numa taxa menor durante o emagrecimento
- determina as diferenças de contorno corporal de acordo com o sexo

Further studies will undoubtedly reveal previously unknown concepts of the pathophysiology of adipocytes, and their ultrastructural and metabolic differences, which will lead to a better understanding of their behavior according to body site and consequently allowing a more precise determination of the best therapeutic approach. ●

REFERÊNCIAS

1. Sbarbati A, Accorsi D, Benati D, Marchetti L, Orsini G, Rigotti G. et al. Subcutaneous adipose tissue classification. Eur J Histochem. 2010; 54(4):226-30.
2. Chu, DH. Development and Structure of Skin. In: Wolff K, Goldsmith L, Katz S, Gilchrest BA, Gilchrest B, Paller A, et al. Editors. Fitzpatrick,s Dermatology in General Medicine, 7th ed. New York: The MacGraw-Hill Companies.Inc; 2008. p. 57-72.
3. Lancerotto L, Stecco C, Macchi V, Porzionato A, Stecco A, De Caro R. Layers of the abdominal wall: anatomical investigation of subcutaneous tissue and superficial fascia. Surg Radiol Anat. 2011; 33(10):835-42.
4. Lookwood TE. Superficial Fascial System (SFS) of the trunk and extremities: a new concept. Plast Reconst Surg. 1991; 87(6):1009-18.
5. Gasperoni G, Salgarello M. Rationale of Subdermal Superficial Liposuction related to the anatomy of subcutaneous fat and the Superficial Fascial System. Aesth Plast Surg. 1995; 19(1):13-20.
6. Silva SL. Variações anatômicas do tecido celular subcutâneo pós-perda ponderal. Rev Bras Cir Plast. 2010; 25(4):130-5.
7. Kelley DE, Thaete FL, Troost F, Huwe T, Goodpaster BH. Subdivisions of subcutaneous abdominal adipose tissue and insulin resistance. Am J Physiol Endocrinol Metab. 2000; 278(5):E911-8.
8. Smith SR, Lovejoy JC, Greenway F, Ryan D, deJonge L, de la Bretonne J, et al. Contribuitions of total body fat, abdominal subcutaneous adipose tissue compartments, and visceral adipose tissue to the metabolic complications of obesity. Metabolism. 2001; 50(4):425-35.
9. Paschoal LHC, Cunha MG, Ciporkin H. Fisiopatologia e Atualização Terapêutica da Lipodistrofia Ginóide - Celulite. 2ª ed. revisada e ampliada. São Paulo: Di Livros Editora Ltda; 2012. p.79-110.
10. Mirrashed F, Sharp JC, Krause V, Morgan J, Tomanek B. Pilot study of Dermal and Subcutaneous Fat Structures by MRI in Individuals that differ in Gender, BMI, and Cellulite Grading. Skin Res Technol. 2004;10(3):161-8.
11. Driskell RR, Jahoda CA, Chuong CM, Watt FM, Horsley V. Defining dermal adipose tissue. Exp. Dermatol. 2014; 23(9):629-31.

Dermoscopy of an uncommon lesion in the umbilicus

Dermatoscopia de lesão incomum na cicatriz umbilical

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ABSTRACT

The present article discusses the importance of differential diagnosis with lesions located in the umbilicus. A case of verrucous nevus is described in this location, emphasizing the role of dermoscopy in the diagnosis.

Keywords: melanoma, epidemiology, skin neoplasms.

RESUMO

Discute-se neste artigo a importância do diagnóstico diferencial das lesões localizadas no umbigo. É relatado caso de nevo verrucoso nessa localização, ressaltando-se o papel da dermatoscopia na elucidação diagnóstica.

Palavras-chave: *umbilicus; dermoscopy; nevus*

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INTRODUÇÃO

A cicatriz umbilical é sede de afecções inflamatórias, infecciosas e tumorais, sendo a endometriose umbilical e o nódulo irmã Maria José, as mais "clássicas".[1] Entretanto, outras mais raras, como o nevo epidérmico verrucoso, também deve ser lembrado ao avaliar essa região.

O nevo epidérmico verrucoso é malformação congênita a partir da hiperplasia da camada basal da epiderme, surgindo em 80% dos casos no primeiro ano de vida.[2]

Pode localizar-se em segmento cefálico, região cervical, tronco e membros, sendo estes dois últimos os locais mais frequentes.[3,4]

Relatamos caso de nevo epidérmico verrucoso, de localização atípica, e os achados dermatoscópicos.

RELATO DO CASO

Mulher, 27 anos, apresentando lesão hiperqueratósica com projeção cônica central e área verrucosa adjacente, em cicatriz umbilical há 10 anos. Lesão firme, áspera, indolor e não aderida a planos profundos (Figura 1). À dermatoscopia, áreas de coloração amarelo-alaranjada no centro, lesões verrucosas na parede da cicatriz umbilical e debris. Além disso, fina rede pigmentada regular nas margens da lesão (Figura 2).

O estudo histológico demonstrou hiperqueratose laminar, acantose e papilomatose, achados compatíveis com o diagnóstico de nevo epidérmico verrucoso (Figuras 3, 4, 5).

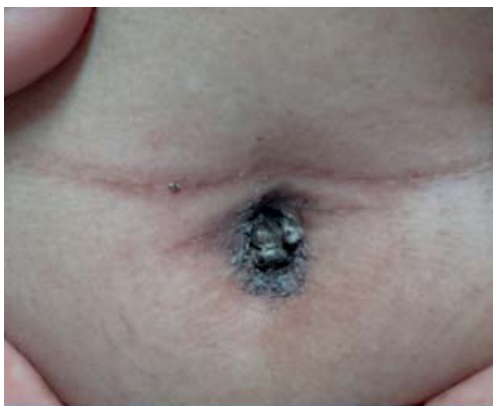

Figura 1: Lesão hiperqueratósica com projeção cônica central e área verrucosa adjacente, em região umbilical

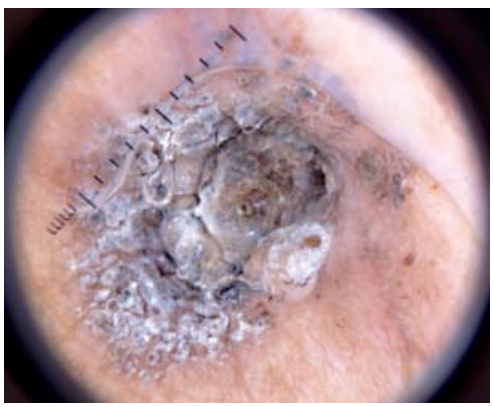

Figura 2: Dermatoscopia; presença de áreas amarelo-alaranjadas em região central, com lesões verrucosas periféricas

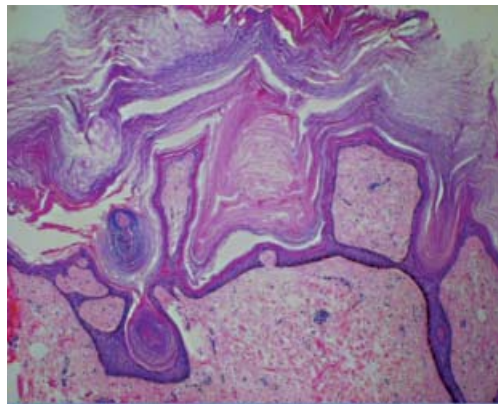

Figura 3: Aspecto histológico da lesão (HE – 40X); hiperplasia epidérmica com papilomatose e hiperqueratose laminar

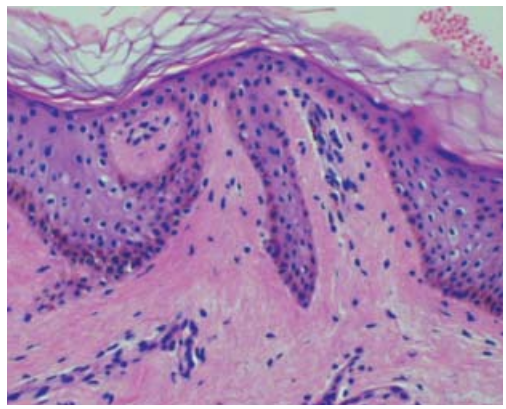

Figura 4: Aspecto histológico da lesão (HE – 200X); queratinócitos com aumento da pigmentação melânica na camada basal

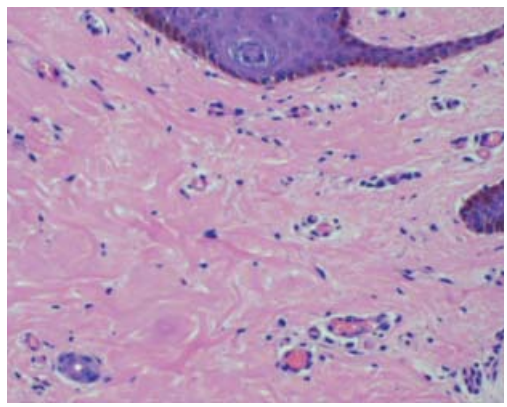

Figura 5: Aspecto histológico da lesão (HE – 200X); fibrose da derme correspondendo à cicatriz umbilical

DISCUSSÃO

O nevo epidérmico verrucoso se apresenta como pápulas e/ou placas únicas ou múltiplas, hiperqueratósicas, ou francamente verrucosas, hiperpigmentadas e bem delimitadas, com predomínio em tronco e membros. Embora não haja sido descrito padrão dermatoscópico específico, o encontro de áreas amarelo-alaranjadas nos sugeriu a presença de queratina, indicando processo de proliferação queratinocítica. A ausência de achados dermatoscópicos típicos de outras lesões nos auxiliou a afastar alguns diagnósticos diferenciais.

Na suspeita de queratose seborreica observaríamos a presença de pseudocomedões (estruturas marrom-amareladas),

pseudocistos (estruturas branco-amareladas) e área amorfa de coloração amarelada. Na verruga viral, haveria pápulas normocrômicas e vasos trombosados. Nos angioqueratomas, são descritos três padrões: lacunas escuras, vinhosas ou véu esbranquiçado, eritema periférico e crostas hemorrágicas.[5]

Complicação extremamente rara, porém importante, é a transformação neoplásica do nevo verrucoso em carcinoma basocelular ou carcinoma espinocelular. Sangramento, ulceração e espessamento podem ser sinais clínicos de transformação maligna.[2] No caso aqui relatado não foram encontradas alterações dermatoscópicas ou histológicas sugestivas de malignidade.

Ressaltamos com este caso a singularidade da localização e a importância da dermatoscopia na elucidação diagnóstica, e no monitoramento da rara transformação maligna.

REFERÊNCIAS

1. Kluger N. Dermatoses ombilicales et péri-ombilicales. Ann Dermatol Venereol. 2014;141:224-35.
2. Elder DE, Elenitsas R, Johnson BL Jr, Murphy GF, Xu G. Lever's Histopathology of the Skin. 10th ed. Lippincott Williams & Wilkins; 2008.
3. Noronha L, Neto JF, Nones RB, Taniguchi K. Nevo epidérmico: análise clínica e histológica de seis casos. An Bras Dermatol. 1999;74(1):259-62.
4. Kim R, Marmon S, Kaplan J, Kamino H, Pomeranz MK. Verrucous epidermal nevus [Internet]. Dermatol Online J. 2013;19(12):20707.
5. Kim JH, Kim MR, Lee SH, Lee SE. Dermoscopy: a useful tool for the diagnosis of angiokeratoma. Ann Dermatol. 2012; 24(4):468-71.

Hemostatic enclosure: pre-incision surgical technique

"Cerquinha" hemostática: técnica pré-incisão cirúrgica

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ABSTRACT

With an aim at reducing surgical complications, the authors describe an innovative technique – the hemostatic enclosure – performed with simple interrupted surgical stitches. The technique is indicated for lesions of any size, due to its simple implementation and because it results in the increased safety of surgical procedures.

Keywords: hemostasis; hemostasis, surgical; ambulatory surgical procedures; sutures.

RESUMO

Preocupados em diminuir as complicações cirúrgicas, os autores descrevem técnica inovadora, a "cerquinha" hemostática realizada com pontos cirúrgicos simples interrompidos. Está indicada para lesões de qualquer dimensão, sendo de simples execução e resultando em aumento da segurança do ato cirúrgico.

Palavras-chave: *hemostasia; hemostasia cirúrgica; procedimentos cirúrgicos ambulatórios; suturas.*

INTRODUÇÃO

Para todos os cirurgiões a hemostasia é sempre uma preocupação pertinente, tendo sido descritas várias técnicas hemostáticas na literatura.[1-3] Paralelamente, nos últimos anos tem sido constatado aumento no número de tumores malignos cutâneos, principalmente entre pacientes imunossuprimidos,[4] com indicação de retirada cirúrgica. Essas lesões frequentemente se localizam em áreas muito irrigadas, como o couro cabeludo,[5] e podem ter grandes dimensões[6] e incidir em portadores de distúrbios de coagulação[7] ou em uso de anticoagulantes.

Para auxílio nessas situações, descreve-se uma nova técnica de hemostasia profilática, útil na ressecção de lesões que possam oferecer risco de sangramento intenso. A proposta dos autores é a realização de sutura com pontos simples separados, próximos entre si e distribuídos de maneira a circundar externamente a margem de segurança da lesão a ser excisada. A essa técnica foi atribuída pelos autores a denominação "cerquinha" hemostática.

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MÉTODO

Inicialmente faz-se a marcação da lesão com margem de segurança adequada. A anestesia local é então realizada de modo que a infiltração do anestésico ocorra em linha que se localiza 5mm além da área programada para a "cerquinha"; se for possível, procede-se a anestesia regional por bloqueio para evitar edema no local. Iniciamos a realização da "cerquinha", que é colocada externamente à margem de segurança. São executados pontos simples interrompidos, lado a lado, com espaço entre si suficiente para que não ocorra sangramento significativo sem interromper a nutrição sanguínea local. No couro cabeludo e em lesões grandes o ideal é fio de náilon 2-0 com agulha de 3cm. O ponto deve ser passado com a agulha em posição perpendicular à pele (no couro cabeludo o ponto deve atingir a gálea aponeurótica), e o nó deve estar bem firme; para tanto, o auxiliar deve segurá-lo com o porta-agulhas. O comprimento da agulha (3cm) é mais importante do que a espessura do fio, posto que ela deve atravessar a pele em toda a sua espessura, o que não seria possível com agulhas mais curtas. A agulha passa profundamente na pele, surge mais adiante, seguindo-se os nós de um ponto simples. Pontos contínuos não são eficientes, por resultar em menor pressão do que a obtida com pontos interrompidos.

Prossegue-se então com a retirada do tumor, estando agora a hemostasia facilitada. Nos casos de fechamento da ferida cirúrgica borda a borda, a "cerquinha" hemostática pode permanecer até a remoção de todos os pontos. Quando se realizam retalhos locais, são retirados os pontos localizados no trajeto de sua incisão; se houver sangramento a "cerquinha" poderá ser ampliada para a região externa à marcação do retalho. Essa técnica pode também ser realizada após o início da cirurgia; em casos de sangramentos significativos, interrompe-se a retirada da lesão e colocam-se os pontos hemostáticos retomando-se a seguir o tempo cirúrgico. As suturas hemostáticas devem permanecer durante duas ou três semanas.

RESULTADOS

Observa-se importante redução do sangramento durante o ato cirúrgico. A presença da "cerquinha" hemostática não provoca necrose ou sofrimento das bordas. A utilização dessa técnica em enxertos resulta, sete dias depois, em seu melhor aspecto do que quando empregadas outras técnicas hemostáticas (Figuras 1, 2 e 3).

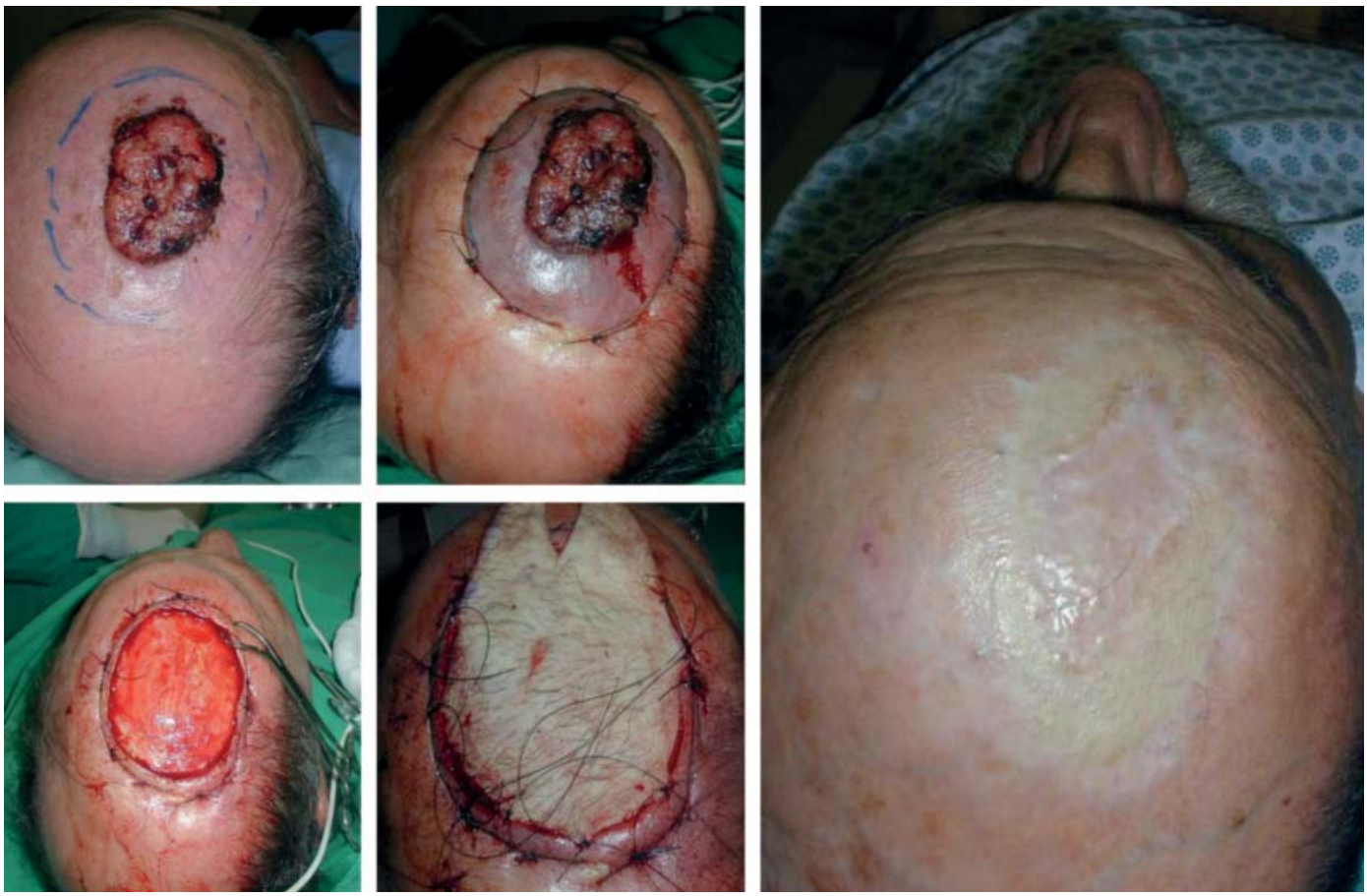

Figura 1: "Cerquinha" hemostática pré-cirúrgica contornando lesões de carcinoma espinocelular no couro cabeludo de paciente transplantado renal

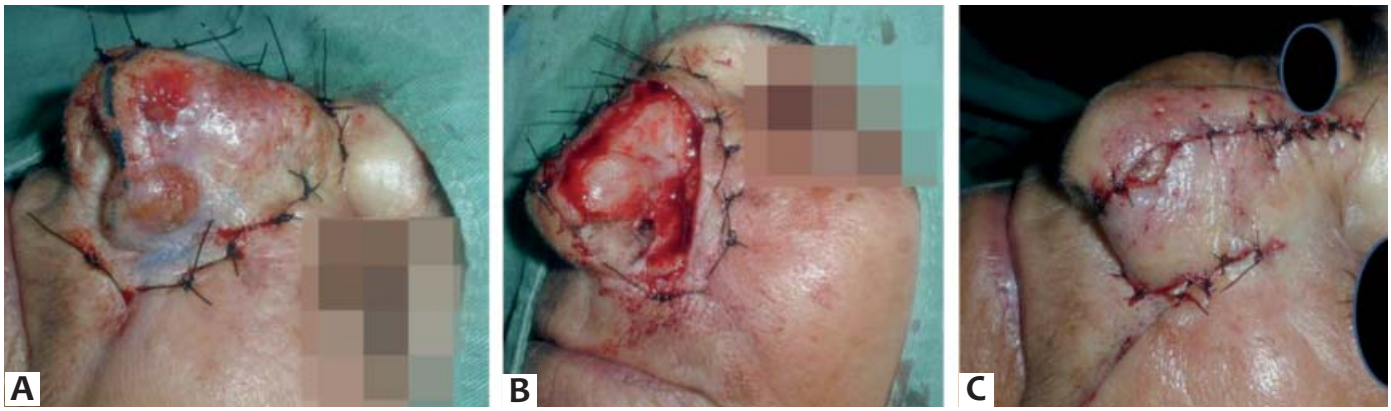

Figura 2 A-B-C: "Cerquinha"hemostática facilitando a retirada de grande área da região nasal

DISCUSSÃO

A "cerquinha" hemostática é indicada em todos os casos em que já se pressupõe que haverá alto risco de sangramento, como, por exemplo, lesões extensas no couro cabeludo ou nariz. Pode ser também realizada mesmo após o início da cirurgia se ocorrer sangramento acima da expectativa. Existem outras maneiras de fazer hemostasia no couro cabeludo, tais como o uso de soro fisiológico com vasoconstritores, compressão manual, pinças *kelly* comprimindo vasos que sangram, ligadura de vasos, descolamento abaixo da gálea e colocação de grande quantidade de gaze.[1,2]

Com a colocação da "cerquinha", no entanto, não há necessidade de controlar a quantidade de gaze utilizada ou o volume de anestésico injetado, o que aumenta a segurança dos procedimentos.

Procedimento similar foi realizado em neurocirurgia em que se utilizou a hemostasia com pontos contínuos feitos antes da incisão.[8] Os autores da presente técnica propõem a realização da sutura com pontos simples separados e distribuídos de maneira a fazer um cercado externo à margem de segurança da lesão a ser excisada. Com esse procedimento o sangramento diminui muito, embora não cesse. Isso é uma vantagem, porque podem ser deixados os pontos do cercado, sem que ocorra risco de necrose ou sofrimento da pele. Além disso, essa técnica pode ser realizada também para a remoção de pequenas lesões cutâneas, incluídas as biópsias de couro cabeludo, com pouco sangramento e desfecho rápido. Cigna et al. descreveram método utilizando o anel da tesoura, que, entretanto, só pode ser utilizado para lesões pequenas, além de ocupar uma das mãos do cirurgião,[9] diferentemente do método que descrevemos, no qual, após sua realização efetivamente não mais se observa sangramento profuso; é eficiente para qualquer tamanho de lesão e seu emprego redunda em conforto e segurança para o cirurgião no decorrer do ato cirúrgico.

Devemos entender que esse procedimento é prévio à cirurgia propriamente dita e não deve ser confundido com a "bolsa de tabaco" (marsupialização), que é feita depois da remoção da lesão e cuja função é diminuir a ferida cirúrgica.[10] Na técnica descrita, os pontos são dados antes da remoção da lesão.

Utilizando-se essa técnica, observamos diminuição significativa do sangramento. Os pontos devem permanecer durante duas ou três semanas após o ato cirúrgico, pois sua retirada precoce pode levar a sangramento significativo, demandando nova

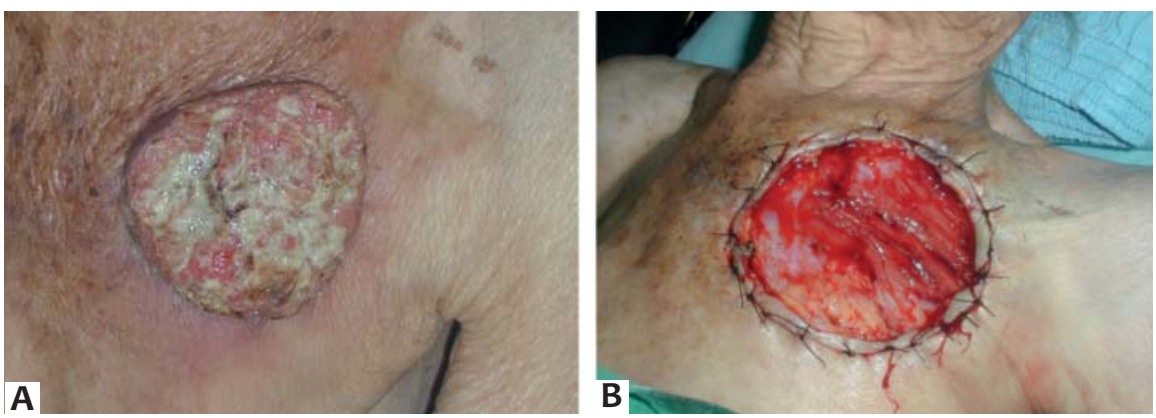

Figura 3: A. Carcinoma espinocelular **B.** Lesão retirada após hemostasia com a "cerquinha"; observa-se pouco sangramento; são removidos apenas os pontos que possam atrapalhar no fechamento da ferida

sutura. Essa técnica, além de ser útil para cirurgias de couro cabeludo, face, tronco, enfim locais que possam apresentar sangramento significativo, evita complicações decorrentes de outros métodos, como reações granulomatosas,[1] ou preocupação com pacientes portadores de marcapasso no caso de uso da eletrocirurgia.[2] Outra vantagem da técnica é diminuir a chance de complicações isquêmicas por hematomas devido à realização de sua profilaxia. O método mostrou importantes inovação e auxílio para cirurgiões dermatológicos.

CONCLUSÃO

A "cerquinha" hemostática é solução simples que aumenta a segurança na retirada de lesões cutâneas. Essa estratégia permite retirar grandes áreas de couro cabeludo, principalmente em pacientes transplantados, em uso de medicações anticoagulantes e que apresentem várias lesões confluentes na mesma região. ●

REFERÊNCIAS

1. Howe N, Cherpelis B. Obtaining rapid and effective hemostasis: Part I. Update and review of topical hemostatic agents. J Am Acad Dermatol. 2013;69(5): 659.e1-659.e17.
2. Howe N, Cherpelis B. Obtaining rapid and effective hemostasis: Part II. Electrosurgery in patients with implantable cardiac devices. J Am Acad Dermatol. 2013;69(5): 677.
3. Glick JB, Kaur RR, Siegel D. Achieving hemostasis in dermatology-Part II: Topical hemostatic agents. Indian Dermatol Online J. 2013;4(3):172-6.
4. Ho WL, Murphy GM. Update on the pathogenesis of post-transplant skin cancer in renal transplant recipients. Br J Dermatol. 2008;158(2): 217-24.
5. Ulrich C, Schmook T, Sachse MM, Sterry W, Stockfleth E. Comparative epidemiology and pathogenic factors for nonmelanoma skin cancer in organ transplant patients. Dermatol Surg. 2004;30(4 Pt 2):622-7.
6. Panajotovic L, Dordevic B, Pavlovic MD. A giant primary cutaneous melanoma of the scalp--can it be that big? J Eur Acad Dermatol Venereol. 2007; 21(10):1417-8.
7. Leonard AL, Hanke CW, Greist A. Perioperative management of von Willebrand disease in dermatologic surgery. Dermatol Surg. 2007;33(4):403-9.
8. Sakhai H. Hemostatic control of scalp incisions. Technical note. J Neurosurg. 1989;70(1):142.
9. Cigna E, Buccheri EM, Monarca C, Scuderi N. Hemostasis in skin surgery. Aesthetic Plast Surg. 2008;32(4):702.
10. Cohen PR, Martinelli PT, Schulze KE, Nelson BR. The purse-string suture revisited: a useful technique for the closure of cutaneous surgical wounds. Int J Dermatol. 2007;46(4):341-7.

Rhinophyma: practical and safe treatment with trichloroacetic acid

Rinofima: tratamento prático e seguro com ácido triclcoroacético

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ABSTRACT

The authors introduce a method for the treatment of different intensities and scales of rhinophyma, with trichloroacetic acid. This is a safe process, created and performed by the authors for five decades, with an absence of descriptions of adverse effects.

Keywords: trichloroacetic acid; rhinophyma; therapeutics.

RESUMO

Apresentamos método de tratamento com ácido tricloroacético para casos de rinofima de diferentes intensidades e extensões. Trata-se de processo seguro, que criamos há cinco décadas e desde então vimos executando, sem nenhum efeito adverso.

Palavras-chave: *ácido tricloroacético; rinofima; terapêutica.*

INTRODUÇÃO

O rinofima é desordem desfigurante e progressiva da pele nasal, caracterizada pela hiperplasia de glândulas sebáceas, com oclusão de ductos e fibrose dérmica, afetando preferentemente homens brancos de meia-idade ou mais.

Esse processo ocorre mais comumente acompanhando quadros de rosácea, podendo afetar a região frontal (metophyma) ou em casos mais raros, orelhas (otophyma), pálpebras (blepharophyma) ou mento (gnatophyma).

A evolução do processo é progressiva e deformante; em alguns pacientes é possível ocorrer processo inflamatório intermitente, o que pode culminar em aspectos cicatriciais, fibrosos.

O processo de remoção do tecido hiperplásico através de cirurgia incisional,[1-6] eletrocirurgia,[7-8] ou laser[5, 9-13] é sempre trabalhoso, demandando eficiente preparo do dermatologista e apresenta sempre substancial risco de cicatriz.

Os autores descrevem método para tratamento de rinofima, criado por Gaspar NK há cinco décadas e executado em inúmeros pacientes, sem qualquer complicação.

O objetivo desta publicação é demonstrar a aplicabilidade do método.

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MÉTODO

Para a seleção dos pacientes não houve restrição de idade, sexo ou doença somática. Esse processo só não é indicado para os poucos pacientes que apresentam aspecto cicatricial, xerótico e brancacento.

O paciente deverá ser avisado de que haverá formação de crosta espessa e escura que permanecerá durante período de sete a dez dias e que deverá ter descolamento espontâneo e não traumático.

É necessária a administração de acyclovir oral aos pacientes com história de herpes simples e de tetraciclina e ibuprofeno àqueles com processo inflamatório muito intenso. Procede-se ao esvaziamento dos comedões por expressão vigorosa, para que não ocorra processo inflamatório sob as crostas.

O procedimento inicia-se com o desengorduramento da pele com acetona imediatamente antes e consiste na aplicação de ácido tricloroacético (ATA) 70% ou 90%, com bastão envolvido em chumaço de algodão (formando cotonete plano), até o intenso branqueamento local, que ocorre alguns segundos após a aplicação (Figuras 1 e 2). Nas lesões muito exuberantes e hipertróficas, a aplicação deve ser mais intensa, duas ou mais vezes seguidas (Figura 3). As áreas de pele normal ou com lesões atróficas devem ser sempre poupadas (Figura 4).

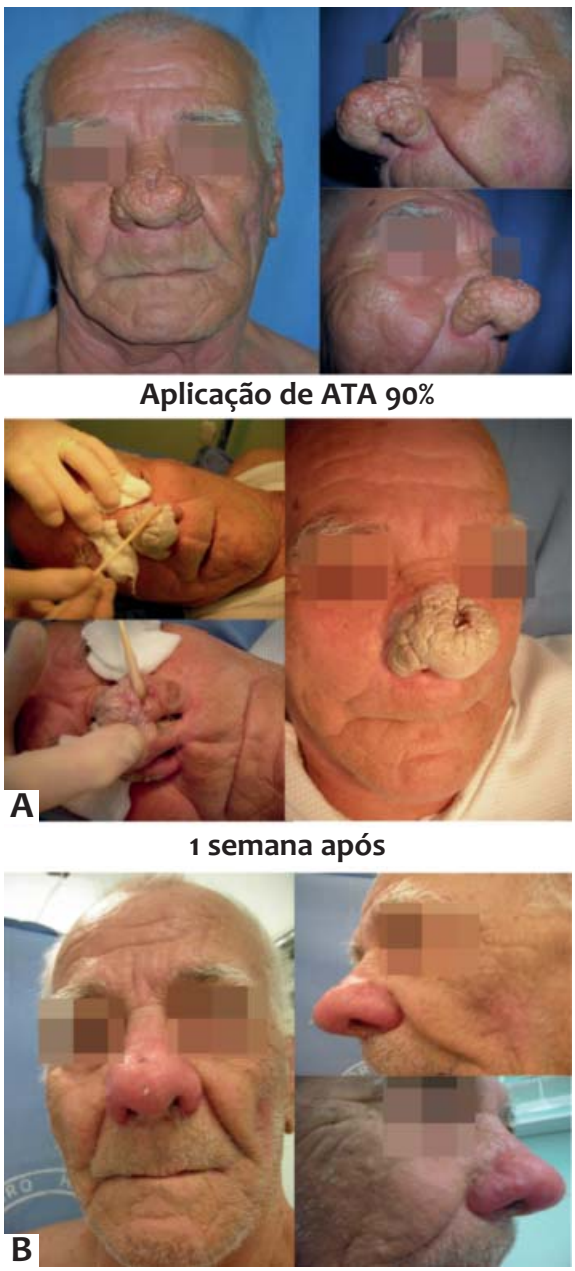

Figura 1: A. Modo de aplicação de ATA 90% em torno aos tubérculos lesionais até branqueamento total; **B.** Uma semana após

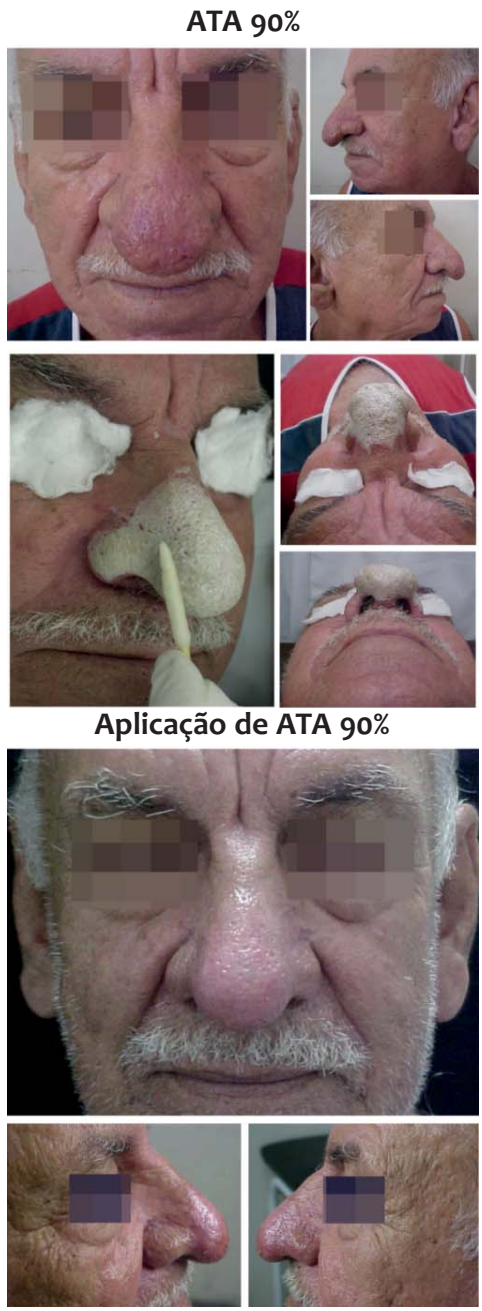

Figura 2: ATA a 90% com grande redução do volume nasal

Figura 3: A. ATA 90% com aplicação mais profícua sobre áreas exuberantes; **B.** Um mês após

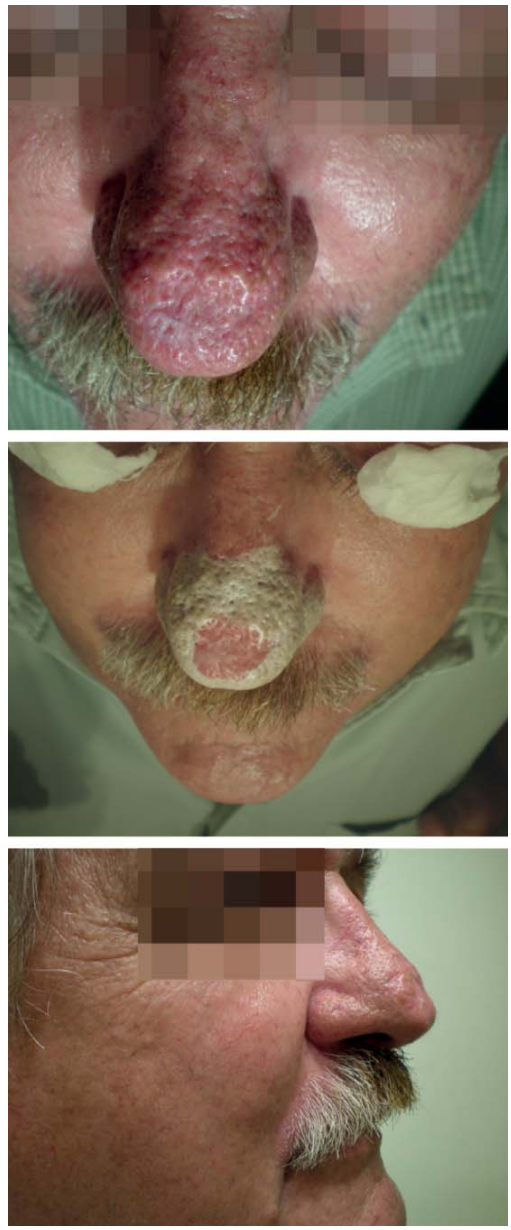

Figura 4: ATA 90% em rinofima circundando cicatriz

Quando o rinofima é parcial o tratamento deve abranger apenas as áreas hipertróficas (Figura 5).

As lesões que se estendem a outras regiões também poderão ser tratadas imediatamente (Figura 6).

Se necessária nova aplicação nos pontos que permanecerem com alguma hipertrofia, poderá ser realizada logo que as crostas se soltem.

Após 30-60 minutos o aspecto branqueado é substituído por eritema discreto.

Pacientes do sexo feminino apresentam lesões geralmente muito discretas, devendo ser tratadas com concentração baixa de ATA (35%) em única passada do bastão, que não deverá conter grande quantidade do ácido (Figura 5).

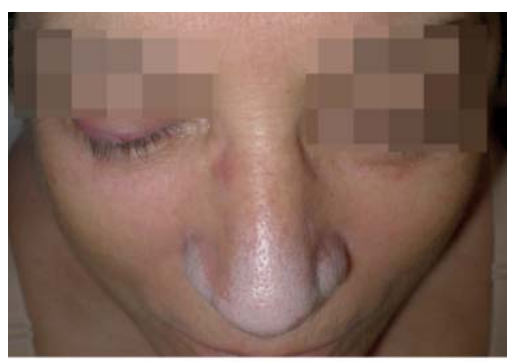

Figura 5: ATA 35% em paciente do sexo feminino, apenas em discreta área lesional

Figura 6: ATA 90%, uma semana após; tipo de crosta

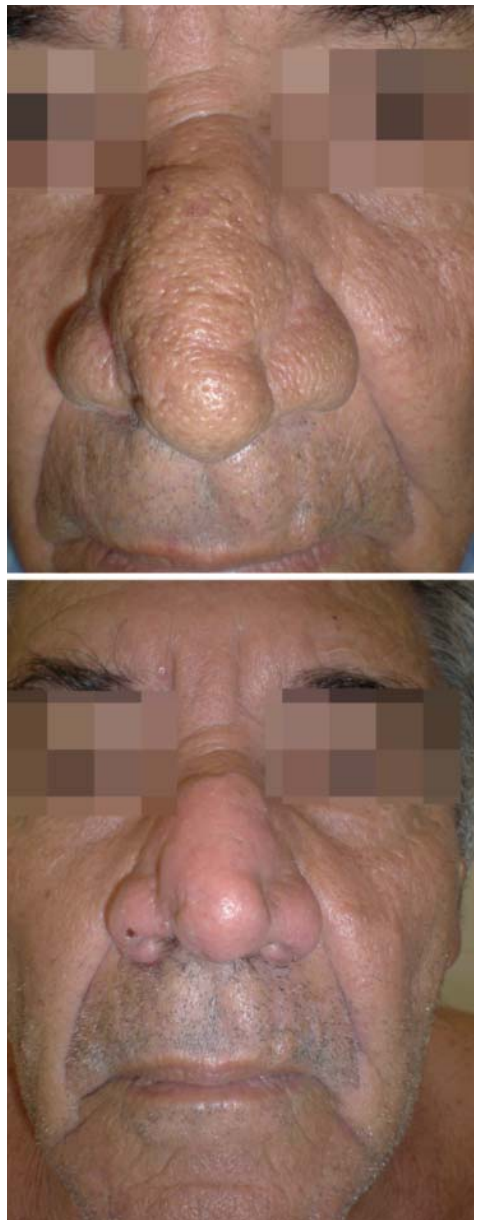

Figura 7: ATA 70% em rinofima localizado após duas semanas

RESULTADOS

A cicatrização ocorre de sete a dez dias, após o que o paciente deverá utilizar protetor solar na região.

A quase totalidade de nossos pacientes obteve resultado completo em apenas uma sessão de tratamento. Em nenhum dos pacientes por nós tratados houve qualquer efeito adverso, e a maioria retornou à consulta aparentando maior autoestima, revelada até por seus aspectos fisionômicos (Figura 7).

CONCLUSÃO

Trata-se de processo, simples, prático, não dispendioso e que não necessita de instrumental ou preparo especial do paciente ou do dermatologista. A restrição do procedimento aos casos "cicatriciais" se deve ao fato de que o ATA não tem efeito redutor para esse tipo de lesão. ●

REFERÊNCIAS

1. Wetzig T, Averbeck M, Simon JC, Kendler M. New rhinophyma severity index and mid-term results following shave excision of rhinophyma. Dermatology. 2013;227 (1):31-6.
2. Sarifakioglu N, Sarifakioglu E. Simple, easy, and still effective treatment option in severe rhinophyma: shave and paste. Dermatol Ther. 2013;26(2):168-9.
3. Husein-ElAhmed H, Armijo-Lozano R. Management of severe rhinophyma with sculpting surgical decortication. Aesthetic Plast Surg. 2013;37(3):572-5.
4. Selig HF, Lumenta DB, Kamolz LP. The surgical treatment of rhinophyma-Complete excision and single-step reconstruction by use of a collagen-elastin matrix and an autologous non-meshed split-thickness skin graft. Int J Surg Case Rep. 2013;4(2):200-3.
5. Lazzeri D, Larcher L, Huemer GM, Riml S, Grassetti L, Pantaloni M, Li Q, Zhang YX, Spinelli G, Agostini T. Surgical correction of rhinophyma: comparison of two methods in a 15-year-long experience. J Craniomaxillofac Surg. 2013;41(5):429-36.
6. Faris C, Manjaly JG, Ismail-Koch H, Caldera S. Rapid treatment of rhinophyma with powered microdebrider. Case Rep Otolaryngol. 2013;2013:621639.
7. Wheble GA, Ahmed F, Pandya AN. Electro-rhinosculpture for the surgical management of rhinophyma. Ann R Coll Surg Engl. 2014;96(1):81.
8. Prado R, Funke A, Bingham J, Brown M, Ramsey Mellette J. Treatment of severe rhinophyma using scalpel excision and wire loop tip electrosurgery. Dermatol Surg. 2013;39(5):807-10.
9. Madan V, Ferguson JE, August PJ. Carbon dioxide laser treatment of rhinophyma: a review of 124 patients. Br J Dermatol. 2009;161(4):814-8.
10. Serowka KL, Saedi N, Dover JS, Zachary CB. Fractionated ablative carbon dioxide laser for the treatment of rhinophyma. Lasers Surg Med. 2014;46(1):8-12.
11. Corradino B, Di Lorenzo S, Moschella F. "Downward steps technique" with CO2 ultrapulsed laser for the treatment of rhinophyma: our protocol. Acta Chir Plast. 2013;55(1):16-8.
12. Singh S, Peterson JD, Friedman PM. Management of mild to moderate rhinophyma using ablative fractional photothermolysis. Dermatol Surg. 2013;39(7):1110-3.
13. Madan V, Ferguson JE, August PJ. Carbon dioxide laser treatment of rhinophyma: a review of 124 patients. Br J Dermatol. 2009;161(4):814-8.

Relato de Caso

Polymethylmethacrylate (PMMA) filling in the lower limbs of a patient with lipodystrophy caused by antiretroviral drugs

Preenchimento com PMMA em membros inferiores em paciente com lipodistrofia por antirretrovirais

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ABSTRACT

The Highly Active Antiretroviral Therapy promoted a better quality of life for seropositive patients. However, metabolic changes in patients, such as HIV lipodystrophy syndrome, may occur with antiretroviral therapy. Thus, it is necessary to adopt strategies to prevent and treat lipodystrophy and other possible side effects of. We report the case of a female patient with prior antiretroviral therapy and decreased thickness of the lower limbs bilaterally, especially in knees and distal third of the legs. The sites with evidence of lipoatrophy were filled with polymethylmethacrylate, with satisfactory results and adherence by the patient.

Keywords: HIV-Associated Lipodystrophy Syndrome; Polymethyl Methacrylate; Acquired Immunodeficiency Syndrome.

RESUMO

A terapia antirretroviral promoveu melhor qualidade de vida para pacientes portadores de HIV. Entretanto, alterações metabólicas nos pacientes, como a síndrome lipodistrófica do HIV, podem ocorrer com seu uso. Assim, é necessário adotar estratégias para prevenir e tratar a lipodistrofia e outros possíveis efeitos colaterais dessa terapêutica. Relata-se o caso de paciente do sexo feminino, com uso de terapia antirretroviral e diminuição do diâmetro dos membros inferiores bilateralmente, principalmente em joelhos e terço distal das pernas. Os locais com evidências de lipoatrofia foram preenchidos com polimetilmetacrilato, com resultado satisfatório e adesão da Tarv pela paciente.

Palavras-chave: *polimetil metacrilato; síndrome de imunodeficiência adquirida murina; síndrome de lipodistrofia associada ao HIV.*

INTRODUÇÃO

A síndrome da imunodeficiência adquirida (Aids) foi descrita nos Estados Unidos em 1981, e, mais de três décadas depois de seu descobrimento, estima-se que 33,4 milhões de pessoas apresentem o vírus HIV e que tenham ocorrido, aproximadamente, dois milhões de mortes associadas ao vírus.[1] O advento da *Highly Active Antiretroviral Therapy* (Haart), terapia que combina três drogas da classe dos inibidores da protease (IP), possibilitou importante e sustentada supressão na replicação viral, promovendo aumento significativo da sobrevida e da qualidade de vida dos pacientes soropositivos.[2]

No entanto, a terapia antirretroviral (Tarv) pode causar alterações metabólicas nos pacientes, como a síndrome lipodistrófica do HIV (SLHIV), caracterizada pelo aumento de colesterol e de triglicérides nos níveis séricos, resistência à insulina e mudança na distribuição da gordura corporal.[3] Os pacientes portadores dessa síndrome podem apresentar hipertrofia de teci-

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do adiposo com distribuição centrípeta, ocorrendo acúmulo de gordura no abdômen, na região peitoral e nas vísceras, surgimento de curvatura cervical denominada "corcova de búfalo" e perda de tecido adiposo na face, nas nádegas, nos membros inferiores e nos superiores.[4]

Essas mudanças corporais podem acarretar problemas psicossociais nos pacientes, uma vez que alguns portadores dessa síndrome a consideram marcador visível dos portadores do vírus HIV, percebida como a "face da Aids". O paciente, ao se sentir estigmatizado, pode apresentar problemas nas relações pessoais e familiares que, em alguns casos, engatilham distúrbios nas relações sociais, levando até ao total isolamento dos pacientes. O mais preocupante é que, a fim de evitar os efeitos psicossociais, os pacientes acabam desistindo do tratamento.[5,6]

Uma vez que, atualmente, não existe cura para a infecção pelo vírus HIV e que o tratamento com a Haart é essencial para a sobrevida do paciente infectado, é necessário adotar estratégias para prevenir e tratar a lipodistrofia e outros possíveis efeitos colaterais da terapia antirretroviral.[7] Dos tratamentos disponíveis, os preenchedores injetáveis são considerados, atualmente, ferramentas não invasivas importantes na terapêutica da lipoatrofia facial (LF) associada ao HIV/Aids. O preenchedor polimetilmetacrilato (PMMA) é disponibilizado pelo Ministério da Saúde para o tratamento da LF em pacientes do SUS portadores do HIV.[8] O PMMA apresenta excelente compatibilidade tissular, facilidade de manipulação nas cirurgias, resistência e radioluscência, baixa condutância térmica e elétrica, além de ser produto leve, quimicamente inerte, de fácil acesso e hipoalergênico.[9]

Diante do exposto, este trabalho tem como objetivo demonstrar a eficácia do uso de preenchimento com polimetilmetacrilato (PMMA) em membros inferiores de um paciente com lipodistrofia por antirretrovirais.

RELATO DO CASO

WBCG, do sexo feminino, 44 anos, solteira. Paciente portadora de HIV/Aids há sete anos, que faz uso de Tarv há cinco anos. Desde o início do tratamento, faz uso de Efavirenz, Lamivudina e Zidovudina. Refere há um ano diminuição da circunferência dos membros inferiores bilateralmente, sobretudo na região dos joelhos e do terço distal das pernas. Ao exame físico, apresentou lipoatrofia nos locais referidos (Figura 1). Optou-se pela realização de preenchimento com PMMA, tendo sendo injetados com cânula (40x0, 8mm) 2,5ml em cada um dos locais: terço distal de pernas e joelhos, bilateralmente. Após a aplicação, o resultado foi satisfatório (Figura 2).

DISCUSSÃO

Pacientes portadores do vírus HIV, em uso de Tarv, podem apresentar perda de tecido adiposo em face, nádegas, membros inferiores e superiores, caracterizando os sinais clínicos relacionados à lipodistrofia. Essas modificações corporais, além do desconforto físico, podem desencadear alterações psicossociais no paciente. Em trabalho revisado por Fernandes e colaboradores, em 2007,[10] diversas alterações, como as de humor, pro-

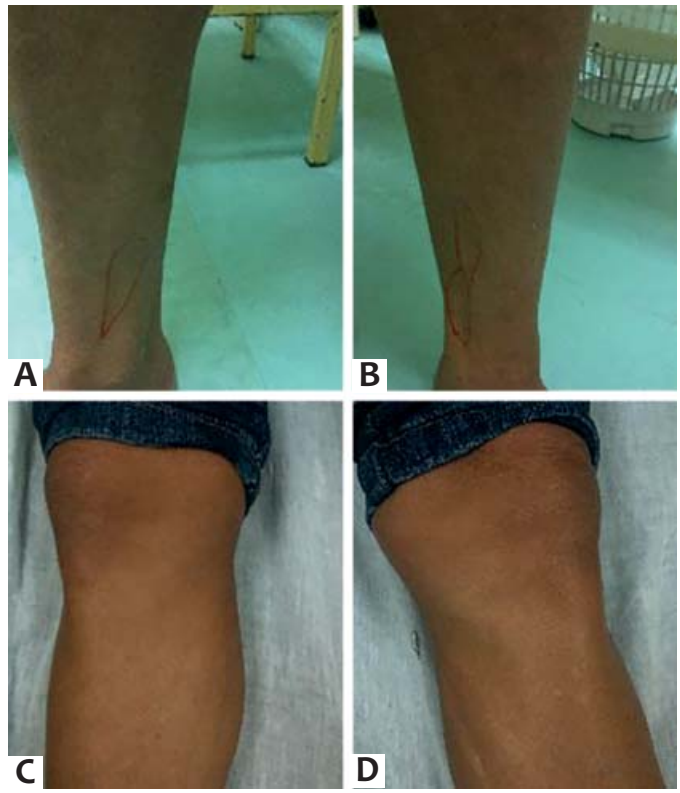

Figura 1: Lipoatrofia em membros inferiores **A:** terço distal da perna direita; **B:** terço distal da perna esquerda; **C:** joelho direito; **D:** joelho esquerdo

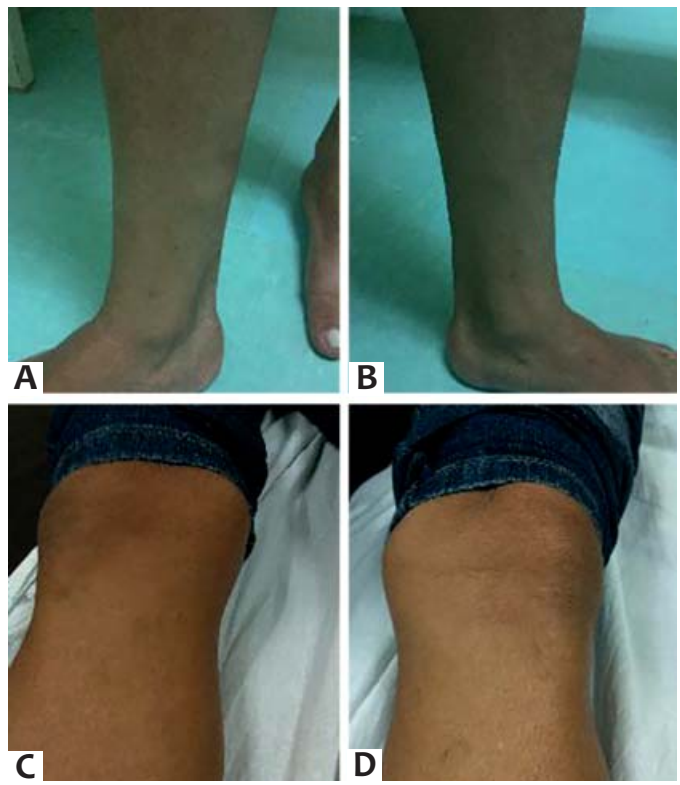

Figura 2: Uma semana depois do preenchimento com PMMA **A:** terço distal da perna direita; **B:** terço distal da perna esquerda; **C:** joelho direito; **D:** joelho esquerdo

blemas nas relações sexuais, redução da autoestima e depressão foram associadas com a lipodistrofia. Com o uso de técnicas de cirurgia dermatológica como o preenchimento com PMMA, podem-se minimizar esses efeitos adversos da medicação.

Neste trabalho, a paciente apresentava desejo de interromper o uso das medicações para diminuir a distribuição de gordura corpórea. Após ser realizado o preenchimento em membros inferiores com resultados satisfatórios, a paciente decidiu continuar o uso da Tarv. Esse dado é importante, pois os pacientes portadores da lipodistrofia tendem a interromper o tratamento antirretroviral a fim de evitar os efeitos psicossociais. Além disso, uma vez que, até o momento, o preenchimento com PMMA da região de joelhos e terço distal das pernas é inédito na literatura, acreditamos que este trabalho possa estimular o uso desses preenchedores nos pacientes portadores do vírus HIV com lipodistrofia.

REFERÊNCIAS

1. World Health Organization (WHO) [Internet]. Joint United Nations Programme on HIV/AIDS (UNAIDS). AIDS epidemic update. Geneva, 2009. [cited 2010 Sep 7]. Available from: http://data.unaids.org/pub/Repor t/2009/ JC1700_Epi_Update_2009_en.pdf
2. Palle Jr FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med. 1998;338(13):853-60.
3. Viraben R, Aquilina C. Indinavir-associated lipodystrophy. AIDS. 1998;12(6):F37-9.
4. Carr A, Samaras K, Chisholm DJ, Cooper DA. Abnormal fat distribution and use of protease inhibitors. Lancet. 1998;351(9117):1736.
5. Oette M, Juretzko P, Kroidl A, Sagir A, Wettstein M, Siegrist J, et al. Lypodystrophy syndrome and self-assessment of well-being and physical appearance in HIV-positive patients. AIDS Patient Care and STDs. 2002;16:413-7.
6. Power R, Tate HL, McGill SM, Taylor C. A qualitative study of the psychosocial implications of lipodystrophy syndrome on HIV positive individuals. Sexually Transmitted Infections. 2003;79:137-41.
7. Segatto AFM, Junior IFF, Santos VRS, Alves KCP, Barbosa DA, Filho AMP, et al. Lipodystrophy in HIV/AIDS patients with different levels of physical activity while on antiretroviral therapy. Rev Soc Bras Med Trop. 2011; 44(4):420-24.
8. Soares FMG, Costa IMC. HIV-Associated facial lipoatrophy: from the advent to current knowledge. An Bras Dermatol. 2011;86(5):843-64.
9. Frazer RQ, Byron RT, Osborne PB, West KP. PMMA: an Essential Material in Medicine and Dentistry. J Long Term Eff Med Implants. 2005;15:629-39.
10. Fernandes APM, Sanches RS, Mill J, Lucy D, Palha PF, Dalri MCB. Síndrome da lipodistrofia associada com a terapia anti-retroviral em portadores do HIV: considerações para os aspectos psicossociais. Rev Latino-am Enfermagem. 2007;15(5):1-5.

Subungual keratoacanthoma: a case report

Queratoacantoma subungueal: Relato de Caso

Relato de caso

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ABSTRACT

Keratoacanthoma is a malignant tumor that is rarely located in the subungual region, but which has a tendency to recur. Spontaneous regression of these lesions in the nail apparatus region almost never occurs, and a differential diagnosis with other neoplasias, particularly squamous cell carcinoma, is essential. The authors present the case of a man with a diagnosis of subungual keratoacanthoma, which responded well to surgical treatment and had a favorable development.

Keywords: nails; keratoacanthoma; finger falanges.

RESUMO

Queratoacantoma é tumoração maligna raramente localizada na região subungueal, apresentando tendência à recidiva. A regressão espontânea dessas lesões na região do aparelho ungueal praticamente não ocorre, e o diagnóstico diferencial com outras neoplasias, principalmente carcinoma espinocelular, é essencial. Apresentamos o caso de um homem com diagnóstico de queratoacantoma subungueal, com boa resposta ao tratamento cirúrgico e evolução favorável.

Palavras-chave: *unhas; ceratoacantoma; falanges dos dedos da mão.*

INTRODUÇÃO

O queratoacantoma localizado na unidade ungueal é variante incomum e destrutiva dessa neoplasia, que pode desenvolver-se no leito ungueal ou na dobra ungueal proximal. Em contraste com outros queratoacantomas, a regressão espontânea é incomum. A presença desse tipo de tumor na região do aparato ungueal é problemática, em função da localização, da escolha terapêutica e pela possibilidade de recorrências após excisão local.[1] Nessa topografia, esse tumor pode apresentar variações quando comparado aos de outras localizações, classicamente representados por lesão nodular, dolorosa, endoexofítica, com área crateriforme preenchida por queratina, sendo, necessária a confirmação histopatológica do caso. A terapêutica deve basear-se na correlação clínica, radiológica e histopatológica.[2]

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RELATO DE CASO

Trata-se de paciente do sexo masculino, branco, 60 anos. Referia que há dois anos iniciou alteração ungueal do primeiro quirodáctilo da mão direita, tratado como onicomicose sem resultado e crescimento da lesão. Ao exame clínico, apresentava distrofia ungueal, com destruição da placa e exposição de lesão do leito (Figura 1), com áreas de textura cérea à palpação, circundadas por tecidos queratinizados endurecidos e edema do quirodáctilo. As impressões diagnósticas iniciais incluíram carcinoma epidermoide, queratoacantoma, e melanoma amelanótico. O raio-X do dedo afetado mostrou tumefação de partes moles, porém não revelou alterações osteoarticulares, o que sugeriu tratar-se de provável lesão superficial não compressiva (Figura 2). Exames micológicos direto e cultural foram negativos. Optou-se então pela biópsia em cunha para remoção de um espécime representativo da lesão. O exame anatomopatológico confirmou o diagnóstico de queratoacantoma (Figura 3). Diante desse resultado, decidiu-se pela excisão cirúrgica com avulsão total da placa ungueal e remoção do tumor que englobava o leito e dobra ungueal proximal, até o plano justaósseo e cicatrização por segunda intenção. O anatomopatológico desse espécime confirmou tratar-se de queratoacantoma, com margens livres, recomendando a retirada total do tumor. Durante acompanhamento após extirpação da lesão, não se evidenciou recrudescência no pós-operatório tardio.

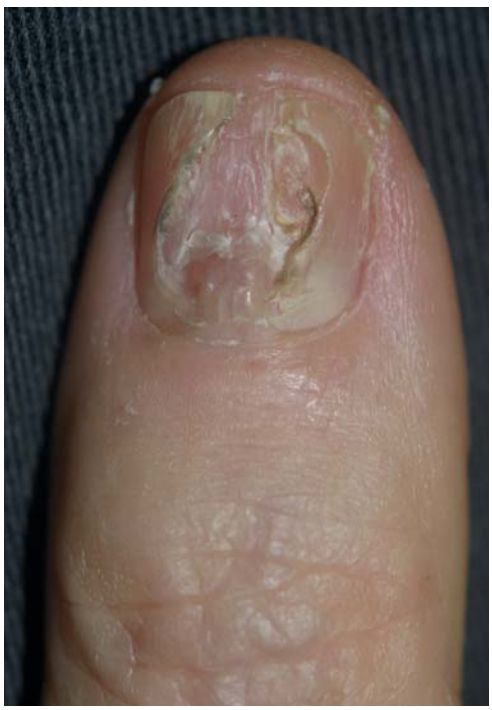

Figura 1: Distrofia ungueal severa, com destruição da lâmina ungueal devido à protusão tumoral do leito

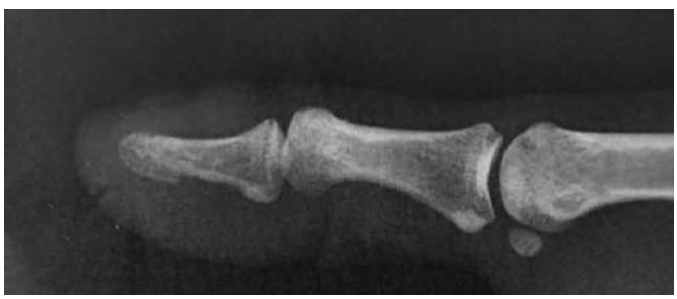

Figura 2: Raio-X do primeiro quirodáctilo direito pré-cirúrgico: peças ósseas radiografadas com estruturas íntegras e relações articulares preservadas

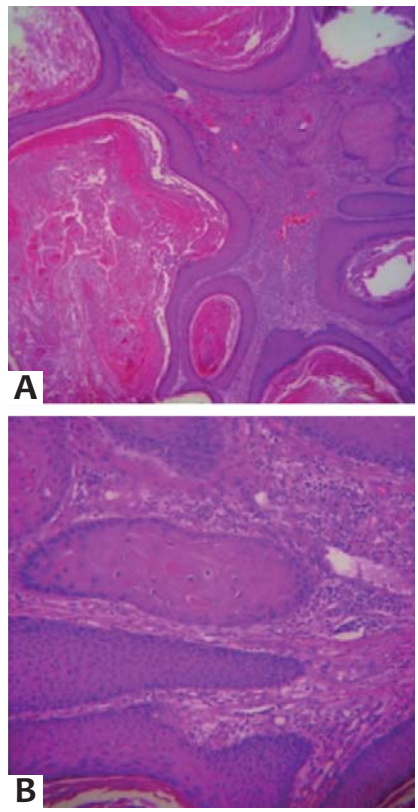

Figura 3: A) HE 40X Proliferação escamosa com centro crateriforme preenchido por queratina B) HE 100X. Grupamentos escamosos na base da lesão sem atipias, exibindo citoplama eosinofílico e amplo

DISCUSSÃO

O queratoacantoma envolvendo o tecido ungueal e periungueal é neoplasia de queratinócitos raramente encontrada nesses sítios, apresentando evolução destrutiva e, às vezes, afetando estruturas ósseas subjacentes por compressão tumoral. É variante rara e agressiva do queratoacantoma clássico, com tendência a aparecer nos primeiros três dedos das mãos, particularmente no primeiro quirodáctilo, podendo também ocorrer nos pododáctilos. O tumor geralmente ocorre em homens caucasianos de meia-idade. Pode ser solitário, múltiplo, eruptivo ou familiar.[1,2,3] O quadro clínico difere do queratoacantoma tradicional, pois na forma subungueal geralmente há dor, crescimento rápido e precoce compressão óssea subjacente. Ao exame apresenta-se como um nódulo verrucoso ou hiperceratótico no leito ungueal, junto da borda distal da unha, frequentemente em associação com onicólise parcial. Na porção do tecido subun-

gueal proximal, o tumor pode manifestar-se como lesão similar à paroníquia. Em contraste com o queratoacantoma de outras localizações, a regressão espontânea é incomum. O diagnóstico diferencial de lesão dolorosa e nodular da falange distal inclui cisto dermoide, verruga comum, exostose subungueal, melanoma amelanótico, carcinoma espinocelular e queratoacantoma subungueal.[1,2] Devido a seu rápido crescimento, o queratoacantoma digital frequentemente causa erosão ou compressão óssea. O achado radiológico é o defeito em forma de taça da falange terminal. O dano ósseo usualmente se resolve após a excisão tumoral.[1,2] Queratoacantomas subungueais tendem a ter menos inflamação e maior invasão na profundidade, e podem estar presentes em casos de incontinência pigmentar, como na síndrome de Bloch-Sulzberger.[3,4] A histopatologia é similar à do queratoacantoma de outras áreas, revelando, tipicamente, paraqueratose e hiperqueratose epidérmica com centro preenchido por queratina.[1] Entretanto, características distintas do queratoacantoma digital incluem orientação vertical, presença de muitas células disceratóticas, escassos neutrófilos e eosinófilos no epitélio, e fibrose reduzida na base. É importante diferenciar o queratoacantoma do carcinoma espinocelular para melhor escolha terapêutica e para avaliação do prognóstico. Ambos podem apresentar-se clinicamente com dor, inflamação ou destruição da falange distal.[1,2,4,5] Radiologicamente, o queratoacantoma subungueal é quase indistinguível do carcinoma espinocelular subungueal. Entretanto, o queratoacantoma causa lesão na falange distal com borda bem definida, que se expande, mas não infiltra o osso; além disso, o queratoacantoma usualmente ocorre na quinta década de vida, enquanto o carcinoma espinocelular geralmente ocorre na sétima década de vida e tem crescimento mais lento.[1-3,5] Curetagem e excisão local são indicadas por muitos autores como tratamento inicial de escolha para queratoacantoma digita.[6] As recorrências, porém, são frequentes, provavelmente relacionadas a uma tendência do tumor à invasão profunda e conexão íntima com estruturas ósseas subjacentes. Pela habilidade em definir corretamente as margens tumorais, a cirurgia de Mohs pode ajudar na redução das recorrências e, consequentemente, preservar o envolvimento da ponta do dedo. Amputações têm sido relatadas nos casos de múltiplas recorrências, destruição óssea extensa ou quando a diferenciação do carcinoma espinocelular é difícil. Outros tratamentos com modalidades não cirúrgicas têm sido utilizados em casos peculiares com resultados variáveis.[1,2] Nosso relato apresentou aspectos que chamam atenção, como a falta de diagnóstico inicial e do tratamento como onicomicose, e a necessidade de biópsia frente a casos como esse de lesões tumorais do complexo ungueal. ●

REFERÊNCIAS

1. Cecchi R, Troiano M, Buralli L, Innocenti, S. Recurrent distal digital keratoacanthoma of the periungual region treated with Mohs micrographic surgery. Australas J Dermatol. 2012;53(1):e5-7.
2. González-Rodríguez AJ, Gutiérrez-Paredes EM, Montesinos-Villaescusa E, Burgués Gasión O, Jordá-Cuevas E. Queratoacantoma digital distal: importancia del diagnóstico diferencial con el carcinoma escamoso subungueal. Actas Dermosifiliogr. 2012;103(6):549-51.
3. Underhill T. Subungual keratoacanthoma: the importance of accurate diagnosis. J Hand Surg Eur Vol. 2010;35(7):599-600.
4. Connolly M, Narayan S, Oxley J, Berker DAR. Immunohistochemical staining for the differentiation of subungual keratoacanthoma from subungual squamous cell carcinoma. Clin Exp Dermatol. 2008;33(5):625-8.
5. André J, Richard B. Subungueal keratoacanthoma. Ann Dermatolol Venereol. 2012;139(1):68-72.
6. Pellegrini VD Jr, Tompkins A. Management of subungueal keratoacanthoma. J Hand Surg Am. 1986;11(5): 718-24.

Relato de caso

Reconstruction of the nasal dorsum with the Rieger flap following excision of nodular basal cell carcinoma

Reconstrução de dorso nasal com retalho de Rieger após excisão de carcinoma basocelular nodular

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ABSTRACT

Basal cell carcinoma is the most common skin cancer and can result in significant morbidity if not completely excised. The present article describes a case of nasal reconstruction using the Rieger flap, after the excision of a basal cell carcinoma, which yielded good aesthetic results. The authors have chosen this flap due to the fact that the donor area contains an abundant supply of tissue to cover surgical wounds, which is of a good color and texture for the upper region of the nose.

Keywords: carcinoma, basal cell; reconstructive surgical procedures; nose neoplasms; surgical flaps.

RESUMO

O carcinoma basocelular é o câncer de pele mais frequente e pode resultar em significativa morbidade se não for completamente excisado. Descreve-se caso de reconstrução nasal após exérese de carcinoma basocelular com retalho de Rieger com bom resultado estético. Os autores optaram por esse retalho, visto que a área doadora contém fonte abundante de tecido para a cobertura de feridas cirúrgicas, boa coloração e textura para a região superior do nariz.

Palavras-chave: *carcinoma basocelular; procedimentos cirúrgicos reconstrutivos; neoplasias nasais; retalhos cirúrgicos.*

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INTRODUÇÃO

O carcinoma basocelular (CBC) localiza-se principalmente em áreas fotoexpostas e é o câncer de pele mais frequente. Pode resultar em significativa morbidade se não for completamente excisado.[1] Por outro lado, os defeitos cutâneos nasais são um desafio à reconstrução, uma vez que irregularidades de cor, textura e espessura da pele são facilmente visíveis.[2,3] A integridade das subunidades estéticas do nariz (ponta, dorso, triângulo mole, columela e faces laterais) é fundamental para manutenção da harmonia das características faciais[4]. No dorso do nariz, estudos mostram bons resultados estéticos e funcionais com o emprego do retalho de Rieger.[4-6]

RELATO DO CASO

Apresentou-se à consulta paciente do sexo masculino de 71 anos de idade, fototipo I, eletricista aposentado, com história de exposição solar e excisão prévia de múltiplos CBCs. Ao exame clínico, observou-se nódulo de aproximadamente 2cm no de diâmetro, no dorso nasal, com cerca de dois anos de evolução (Figura 1).

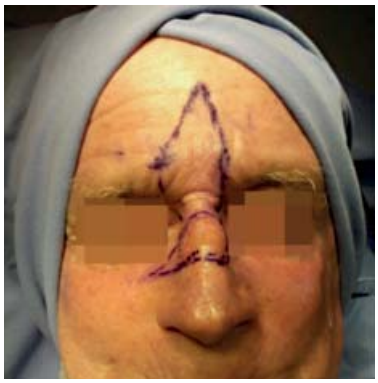

Figura 1: Marcação cirúrgica do retalho de Rieger

MÉTODO

À dermatoscopia, foram visualizadas telangiectasias arboriformes cruzando a lesão e ausência de pigmento. Realizou-se biópsia incisional cuja histopatologia revelou CBC nodular. Optou-se, então, por tratamento cirúrgico sob anestesia local, excisão da lesão com margem inicial de 4mm e controle intraoperatório de margens por patologista. Após avaliação de limites cirúrgicos livres de neoplasia, realizou-se a reconstrução do dorso nasal com retalho de Rieger (Figuras 2 a 4). Cuidados do pós-operatório incluíram: colocação de dreno, curativo compressivo e antibioticoterapia oral com cefalexina. No dia seguinte, procedemos à retirada do dreno, limpeza da ferida operatória e curativo com tiras de esparadrapo microporado estéril.

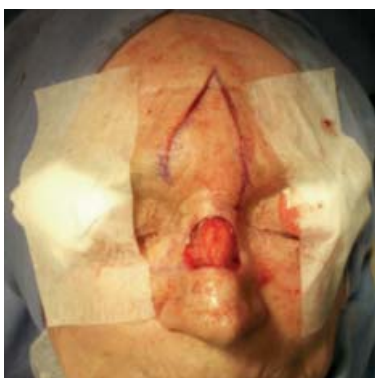

Figura 2: Excisão da lesão de carcinoma basocelular

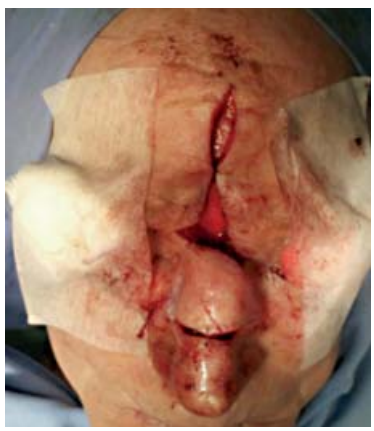

Figura 3: Posicionamento do retalho miocutâneo

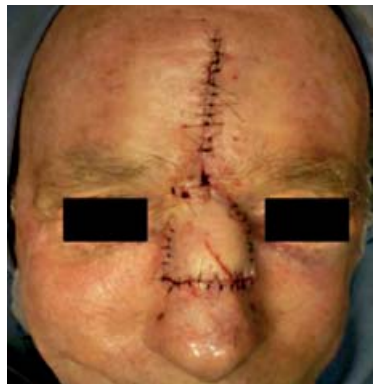

Figura 4: Resultado do pós-operatório imediato

RESULTADO

Após sete dias, os pontos começaram a ser retirados alternadamente, e em quinze dias todos os pontos haviam sido retirados. O paciente encontra-se em acompanhamento ambulatorial há 10 meses e, até o momento, não houve recorrência clínica ou dermatoscópica da lesão (Figuras 5 a 7). Além disso, foi obtido bom resultado estético.

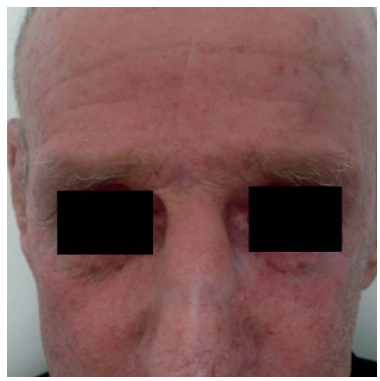

Figura 5: Resultado após seis meses

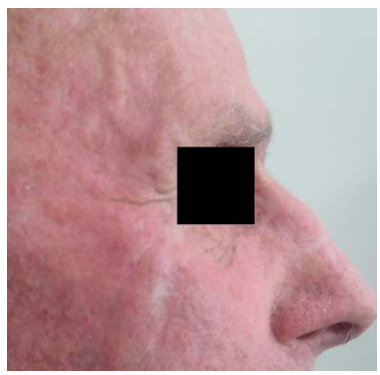

Figura 6: Resultado após seis meses

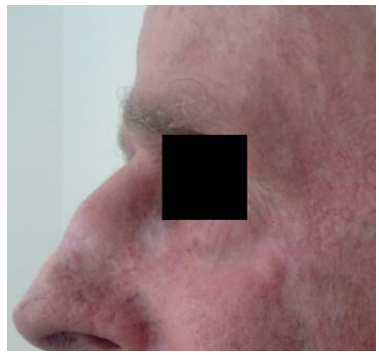

Figura 7: Resultado após seis meses

DISCUSSÃO

O CBC nodular pode atingir grandes dimensões e se aprofundar, causando considerável dano tecidual. O nariz é o traço mais característico da face e qualquer mudança em seu formato, cor ou pele torna-se óbvia. Desse modo, o cirurgião deve escolher o método de reconstrução que proporcione o melhor resultado estético possível.[4,6]

O retalho de Rieger foi descrito por seu epônimo, em 1967, como sendo boa opção para reconstrução de defeitos de até 2cm de diâmetro em ponta nasal.[4,5] Desde então, tem sido descrito na literatura com pequenas variações e múltiplas novas nomenclaturas como: retalho glabelar, retalho glabelar estendido e retalho nasal dorsal.[2,3] É um retalho de rotação/avançamento usado para defeitos do terço médio e inferior do nariz. Assemelha-se a um retalho romboidal que aproveita tanto o excesso cutâneo glabelar e por isso, é preferencialmente indicado para pacientes idosos.[5]

A pele é incisada desde a porção lateral do defeito, passando pelo sulco nasofacial, até atingir a região glabelar; em seguida, a incisão desce pelo lado contralateral até a região do supercílio. O retalho deve ser musculocutâneo. Após descolamento adequado, o retalho é rodado/avançado inferiormente, sendo o defeito glabelar suturado de maneira primária.[5]

Os autores optaram por esse retalho pelo fato de o paciente ser idoso e apresentar excesso de tecido na área doadora. Apesar da extensão e da localização do tumor, a utilização desse retalho permitiu a excisão de toda a lesão, com margem de segurança suficiente, além de manter a harmonia da unidade nasal.●

REFERÊNCIAS

1. Rigel DS, Cockerell CJ, Carucci J, Wharton J. Queratose actínica, Carcinoma Basocelular e Carcinoma Espinocelular. In: Bolognia JL, Jorizzo JL, Rapini RP. 2ª. Ed. Dermatologia. Rio de Janeiro: Elsevier, 2011. p. 1641-59.
2. Jackson IT. Reconstrução do Nariz. In: Retalhos Locais na Reconstrução de Cabeça e Pescoço. Rio de Janeiro: DiLivros; 2002.
3. Baker SR. Retalhos Locais em Reconstrução Facial. 2ª. ed. Rio de Janeiro: DiLivros; 2009.
4. Severo Jr LCV, Chambô F, Dibe MJA, Leal PRA. Retalho miocutâneo dorsoglabelar baseado na artéria nasal lateral para reconstrução de defeitos da ponta nasal. Arq Catarinenses de Med. 2007; 36(1): 124.
5. Valiati AA, Pereira Filho GA, Cunha TF, Minuzzi Filho ACS, E PB. Retalho de Rieger: resultados estéticos e satisfação dos pacientes. Rev Bras Cir Plást. 2011; 26(2): 250-3.
6. Laitano FF, Teixeira LF, Siqueira EJ, Alvarez GS, Martins PDE, Oliveira MP. Uso de retalho cutâneo para reconstrução nasal após ressecção neoplásica. Rev Bras Cir Plást. 2012; 27(2):217-22.

Relato de caso

Lichen planus pigmentosus: surgical treatment with dermabrasion

Líquen plano pigmentoso: tratamento cirúrgico com dermoabrasão

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ABSTRACT

Lichen planus pigmentosus is a rare variant of lichen planus and represents a therapeutic challenge. Dermabrasion was performed with a good clinical response in the treatment of this condition, on the face of a female patient who also bears frontal fibrosing alopecia.

Keywords: dermabrasion; lichenoid eruptions; alopecia.

RESUMO

O líquen plano pigmentoso é uma variante incomum de líquen plano e representa um desafio terapêutico. Foi realizada a dermoabrasão com boa resposta clínica para o tratamento dessa patologia na face em paciente do sexo feminino, portadora também de alopecia frontal fibrosante.

Palavras-chave: *Dermoabrasão; erupções liquenoides; alopecia.*

INTRODUÇÃO

Líquen plano pigmentoso (LPPig) é uma variante incomum de líquen plano (LP). É representado clinicamente por máculas acastanhadas reticulares, assintomáticas ou pruriginosas, geralmente encontradas em áreas expostas à luz solar e flexuras.[1]

Representa um desafio terapêutico, devido à pobre resposta a tratamentos tópicos e sistêmicos.[2]

RELATO DE CASO

Paciente do sexo feminino, de 38 anos, branca apresentando há quatro anos máculas eritematosas, que se tornaram acastanhadas, na região zigomática associada à rarefação dos supercílios (Figura 1). Foi tratada inicialmente com fórmula clareadora tríplice (hidroquinona 4%, tretinoína 0,05%, acetonido de fluocinolona 0,01%) e fotoproteção. Apesar do tratamento houve aumento na intensidade da coloração das lesões e uma biópsia foi indicada com hipóteses diagnósticas de melasma,

ocronose e líquen plano pigmentoso (LPPig). O exame anatomopatológico mostrou dermatite de interface com incontinência pigmentar (Figura 2), compatível com LPPig.[3] Devido à pouca resposta ao tratamento clínico e pelo impacto na qualidade de vida da paciente optamos pela dermoabrasão em pequena área de teste, com bom resultado. Realizamos então o tratamento de toda área afetada utilizando anestesia combinando bloqueio do nervo infraorbitário (lidocaína 2% sem vasoconstrictor) e infiltração de solução de lidocaína 0,5% nas áreas que mantinham sensibilidade. Para a dermoabrasão manual utilizamos lixas d'água com granulação 100 esterilizadas até formação de orvalho sangrante e remoção visual de todo o pigmento. Lixas com granulações de 400 e 600 também foram usadas para alcançar aspecto mais homogêneo e gradual nas bordas da lesão. A área abrasada foi ocluída com filme de poliuretano transparente estéril (Tegaderm®) durante cinco dias. Administrou-se profilaticamnete aciclovir oral durante dois dias antes e três dias após procedimento. Após a retirada do curativo (Figura 3) a paciente utilizou vaselina sólida até completa cicatrização, quando passou a utilizar clobetasol 0,05% creme ao longo de 30 dias, seguido por hidroquinona 4% creme durante três meses. Finalizando esse período introduzimos hidroxicloroquina 400mg/dia associado a tacrolimus 0,1% creme, após avaliação oftalmológica e de enzimas hepáticas.

O resultado cosmético satisfatório foi atingido e se manteve com leve eritema local aos seis e nove meses após procedimento (Figuras 4 e 5). Após 12 meses do procedimento, notamos recidiva em pequenas áreas, quando foi indicada nova dermoabrasão localizada; a paciente, entretanto, optou por continuar apenas com tratamento clínico por estar satisfeita com sua aparência (Figura 6).

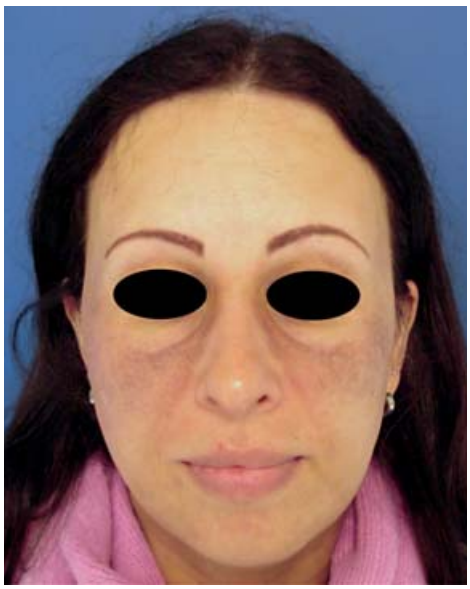

Figura 1: Antes do procedimento; máculas acastanhadas em região malar)

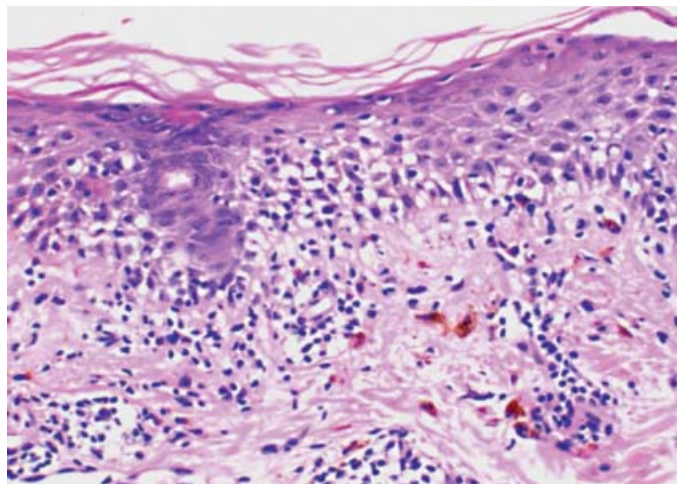

Figura 3: Aspecto imediatamente após dermoabrasão

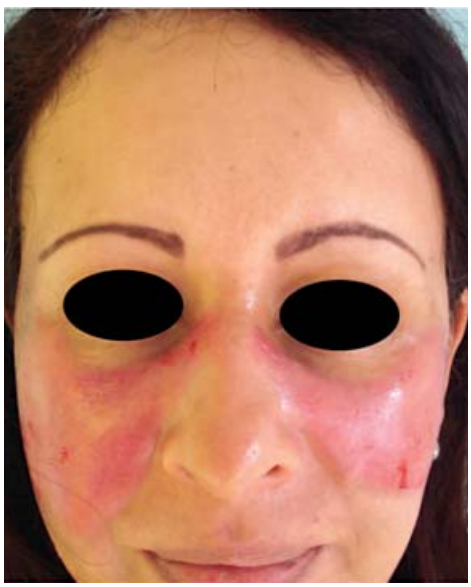

Figura 2: Biópsia da face; reação liquenoide de interface, degeneração vacuolar e incontinência pigmentar (H&E, 40X)

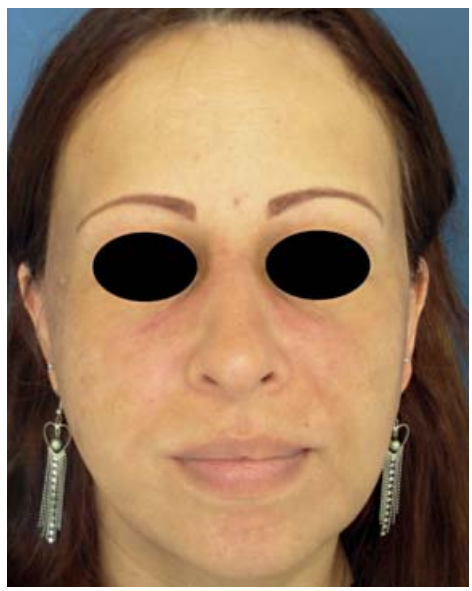

Figura 4: Seis meses após procedimento

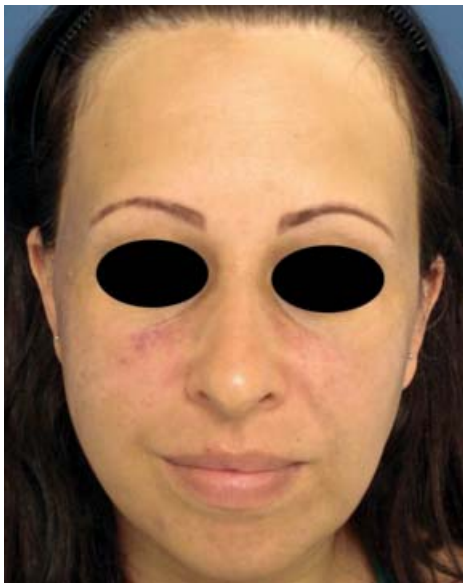

Figura 5:
Nove meses após procedimento

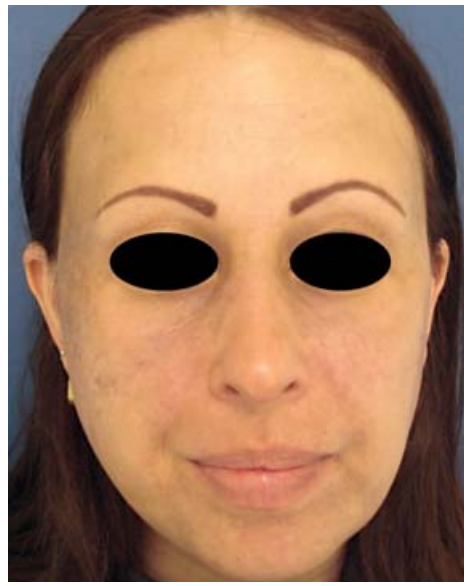

Figura 6:
Um ano após procedimento, repigmentação parcial do líquen plano pigmentoso

DISCUSSÃO

O tratamento do LPPig é difícil e com poucos dados na literatura, que mostram resistência a corticoides tópicos e inibidores de calcineurina.[4] Há relatos de resultados favoráveis com laser Nd:YAG,[5] luz intensa pulsada[6] e, apesar da controvérsia, com tacrolimus tópico.[7]

A dermoabrasão é descrita para o tratamento do LPPig e do melasma, patologias que compartilham a característica de ativação melanocítica e derrame pigmentar.[8] O mecanismo proposto é a remoção física do pigmento existente pela abrasão. Contudo faltam relatos de caso mostrando os resultados e seguimento de longo prazo desse procedimento.

Nossa paciente apresentou melhora quase completa do quadro mantendo resultados até um ano de seguimento quando notamos pequenas áreas de recidiva. Destacamos a melhora da qualidade de vida da paciente após uma sessão de dermoabrasão, encontrando-se satisfeita com aspecto estético até o momento, mantendo-se apenas tratamento clínico (hidroxicloroquina e tacrolimus).

O LPPig foi recentemente relacionada à alopecia frontal fibrosante (AFF), podendo anteceder seu aparecimento.[9] Isso pode sugerir acometimento sistêmico e necessidade de abordagem mais ampla da patologia. Nossa paciente foi diagnosticada com AFF pela perda de supercílios e recuo discreto de linha frontal capilar; a biópsia de couro cabeludo mostrou infiltrado liquenoide perifolicular, o que justifica nossa opção pelo uso concomitante da hidroxicloroquina .

Neste relato observamos que a dermoabrasão foi fundamental para remoção do pigmento facial associado ao LPPig. Apesar da boa evolução e satisfação da paciente com mínima recidiva no seguimento de 12 meses, entendemos serem necessários mais estudos para determinar o papel e as indicações da dermoabrasão no tratamento do LPpig. ●

REFERÊNCIAS

1. Namazi MR. Lichen planus pigmentosus presenting as diffuse facial melanosis. J Drugs Dermatol. 2004;3(4):436-7.
2. Khanna N, Rasool S. Facial melanoses: Indian perspective. Indian J Dermatol Venereol Leprol. 2011;77(5): 552-64.
3. Kanwar AJ, Dogra S, Handa S, Parsad D, Radotra BD. A study of 124 Indian patients with lichen planus pigmentosus. Clin Exp Dermatol. 2003; 28(5):481-5.
4. Kim BS, Aum JA, Kim HS, Kim SJ, Kim MB, Oh CK, et al. Coexistence of classic lichen planus and lichen planus pigmentosus-inversus: resistant to both tacrolimus and clobetasol propionate ointments. J Eur Acad Dermatol Venereol. 2008;22(1):106-7.
5. Kim J-E, Won C-H, Chang S, Lee MW, Jee-Ho, Choi JH, et al. Linear lichen planus pigmentosus of the forehead treated by neodymium:yttrium-aluminum-garnet laser and topical tacrolimus. J Dermatol. 2012;39(2): 189-91.
6. Parada MB, Yarak S, Michalany NS. Tratamento do liquen plano pigmentoso com luz intensa pulsada. Surg Cosmet Dermatol. 2009;1(4):193-5.
7. Al Mutairi N, El-Khalawany M. Clinicopathological characteristics of lichen planus pigmentosus and its response to tacrolimus ointment: an open label, non-randomized, prospective study. J Eur Acad Dermatol Venereol. 2010; 24(5): 535-40.
8. Kunachak S, Leelaudomlipi P, Wongwaisayawan S. Dermabrasion: A Curative Treatment for Melasma. Aesth Plast Surg. 2001; 25(2):114-7.
9. Dovla NC. Frontal fibrosing alopecia and lichen planus pigmentosus: Is there a link? Br J Dermatol. 2013;168(2):439-42.

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