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Continuing Medical Education

Hidradenitis Suppurativa: update and review of therapeutic modalities

Hidradenite supurativa: atualização e revisão de suas modalidades terapêuticas

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ABSTRACT

Hidradenitis suppurativa is a chronic inflammatory disease resulting from follicular obstruction. This recurrent condition leads to the formation of fistulas and scars, which affect a patient's quality of life. The literature offers multiple therapeutic modalities, such as topical and oral antibiotics, isotretinoin, dapsone, TNF-α inhibitors, finasteride, conventional surgical therapies, and lasers (CO_2, Nd:Yag). The present article provides a review of these treatments and their indications, according to the stages of Hurley, which provides the dermatologist with a greater command of different techniques, thus leading to a more adequate treatment of patients.

Keywords: hidradenitis suppurativa; therapeutic; laser therapy.

RESUMO

A hidradenite supurativa é doença inflamatória crônica resultante da obstrução folicular. O quadro recorrente leva à formação de fístulas e cicatrizes, que interferem na qualidade de vidas dos pacientes. A literatura mostra múltiplas modalidades terapêuticas, como antibióticos tópicos e orais, isotretinoína, dapsona, inibidores de TNF-α, finasterida e terapias cirúrgicas convencionais e lasers (CO_2, ND:Yag). O artigo traz uma revisão desses tratamentos e suas indicações seguindo os estágios de Hurley, o que permite ao dermatologista mais amplo domínio das diferentes técnicas, podendo, assim conduzir mais adequadamente os pacientes.

Palavras-chave: *hidradenite supurativa; terapêutica; terapia a laser.*

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INTRODUCTION

Hidradenitis suppurativa (HS), also known as acne inversa or Verneuil disease, is a chronic inflammatory condition, recurrent and debilitating, with a pathogenesis linked to the chronic obstruction of the follicular portions of the pilosebaceous units. It is estimated that its prevalence ranges from 1-4%. [1,2] Previously identified risk factors are: family history (40% of patients have a relative with this diagnosis); [3] obesity (prevalence is higher than that in the general population); [4] smoking habits (more prevalent in patients with HS, it is believed that nicotine exerts immunological effects, such as neutrophil chemotaxis and obstruction of hair follicles); [5,6] use of drugs (especially in females using oral and injectable contraceptives containing levonorgestrel acetate and medroxyprogesterone). [7]

CLINICAL PICTURE

Symptoms typically begin in the period after puberty and up to about 40 years of age, and is more common in women than in men (3.6:1), as described by a French retrospective observational study. [5,8] The clinical picture progresses with deep and inflammatory lesions at body sites that have apocrine glands, most commonly in the anorectal, axillary (Figures 1 and 2), inframammary (Figure 3), inguinal, and perineal regions. [9,10] These lesions begin as inflamed nodules, which can develop into fistulized and interconnected abscesses, with scarring, and pain, which is its main characteristic. [11] It is important to note that the pain picture, the foul odor of the secretions, and the scarring have a significant impact on patients' quality of life. The condition is prevalent in the population, and though therapeutic options are limited, the proper treatment of these patients is necessary due to the increased incidence of depression and sexual dysfunction in patients with HS. [12,13] Thus, due to its chronic nature and impact on patients' quality of life, proper handling of the condition is crucial.

TREATMENT - GENERAL MEASURES

The appropriate management of these patients is necessary due to the various psychological alterations that patients undergo 14 and the chronic nature of HS. Therefore, it is recommended that treatment addresses three fronts: reduction of the progression and extension of existing lesions and the prevention of new lesions; removal of bridges; and the reduction of scar formation.

The initial approach for these patients depends on their classification according to the Hurley's staging system (Chart 1) 15, which helps in choosing the treatment modalities that will be used. The Sartorious' staging system is also used (Chart 2) for the monitoring of patients during the treatment.

Patients should be encouraged to stop smoking given the importance of this factor in the pathogenesis of HS. [16] Patients must also be encouraged to adopt a healthy lifestyle, with regular physical exercise and a healthy diet in order to reduce weight. [17]

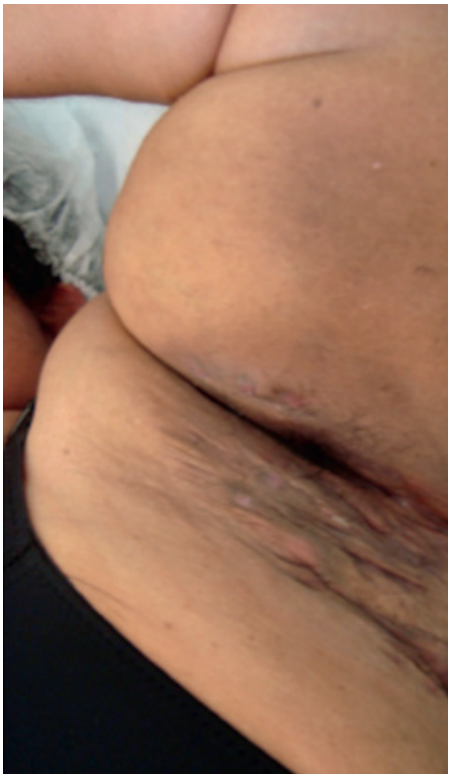

Figure 1: Axillary Hurley's III HS

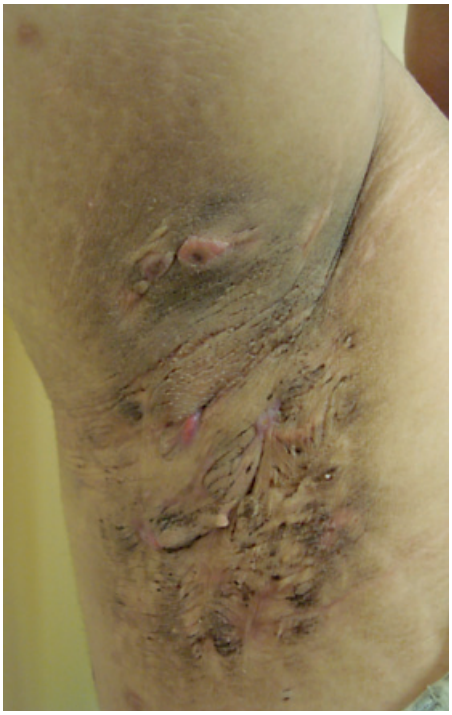

Figure 2: Axillary Hurley's III HS

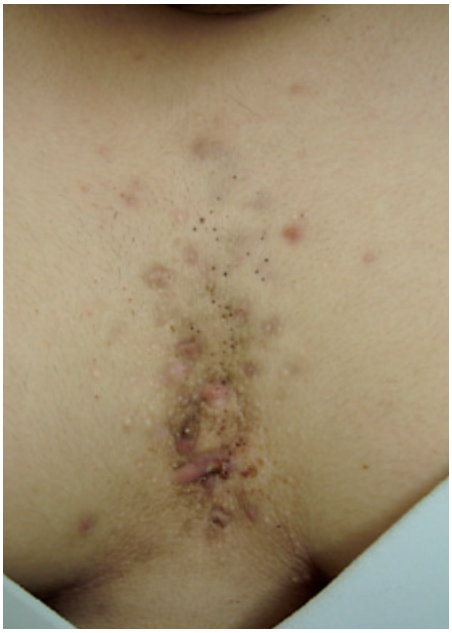

Figure 3: Hurley's III HS in anterior thoracic region

Chart 1: Hurley's Stages

Hurley's Stage	Clinical picture
I	Abscess(es) without fistulization or scars
II	Recurrent abscesses with the formation of bridges and scarring
III	Diffuse abscesses OR interconnected bridges and multiple abscesses

SPECIFIC TREATMENTS

Antibiotics

Due to its broad pathogenesis, there are currently three therapeutic modalities for the management of patients: topical, systemic, and surgical treatments – including lasers in the latter case.

The use of antibiotics is adopted as an initial therapy in cases of early diagnosis of HS, with the combination rifampicin-clindamycin being primarily used. The rationale behind this approach focuses on the fact that polymicrobial infections are associated with HS pictures, mainly due to their role of promoting inflammatory activity in the lesions 18 and to the formation of biofilm. [19] In a study carried out by Gener et al., 20 116 patients were treated with 300mg clindamycin and 300mg rifampicin twice daily, with 10 weeks of follow-up. It was possible to observe that there was a reduction in disease activity in the patients after the 10th week, with clinical improvement evidenced by a reduction in the patients' Sartorius staging system. Only 10 patients had adverse reactions to the treatment, with 6 of them choosing to withdraw due to intolerance to gastrointestinal symptoms (diarrhea, nausea, vomiting, and abdominal pain). In a retrospective study involving 34 patients, Zee et al. [21] studied different courses of rifampicin associated with clindamycin, and noted that the treatment's maximum effect takes place after 10 weeks. Of the 13 patients who had complete resolution of the condition, 8 reported recurrence of the clinical picture – these patients bore severe HS (Hurley'sStage III) at the beginning of the treatment.

Isotretinoin

Isotretinoin is a vitamin A derivative that is widely used for the treatment of acne vulgaris. Due to its inhibitory effects on sebum production, stimulation of keratinocytes differentiation, promotion of normalization of the cellular desquamation, 22 and excellent results in the treatment of this condition, some studies were carried out in order to determine the benefits of using this drug for HS.

In a retrospective study including 68 patients, Boers and Van Gemert 23 used isotretinoin as monotherapy, in 0.5 mg*day/kg doses during the first month, increasing to 1.0 mg*day/kg for at least 4 months. During the study's follow-up period (minimum of 4 and maximum of 6 months), the authors verified complete remission in 16 patients (23.5%), with 11 of those having maintained that response during an average follow-up period of 57 months.

Nevertheless, a retrospective study by Soria et al. 24 in which 88 patients used isotretinoin for treating HS showed that the treatment was ineffective. The patients used a variable daily dose of 23.0 mg/day to 65.0 mg/day for an average period of 7.8 months, and only 14 patients (16.1%) reported an improvement of symptoms, while 67 (77.0%) reported no change in symptoms, and 6 (6.9%) patients described worsening.

Dapsone

Dapsone is a competitive antagonist of para-aminobenzoic acid (Paba), which is used by bacteria in the synthesis of folic acid. Furthermore, it has anti-inflammatory properties that are not related to its antibacterial effect, and is thus used for the treatment of infectious and inflammatory dermatoses. Characteristically, conditions that respond well to this drug exhibit exuberant polymorphonuclear infiltrate in the affected tissue, with the neutrophils' products one of its main therapeutic targets. Due to the appearance of neutrophils in the later stages of HS lesions, its use was then investigated in this condition. [25]

Chart 2: Sartorius stages

Anatomical region involved (axilla, groin, gluteus, inframammary or other)	3 points per region involved
Number and stage of the lesions (abscess, nodules, fistulas, scars)	Scars: 1 point; Nodules: 2 points; Fistulas 4 points; Other: 1 point
Greater distance between two relevant lesions (or single lesion's size) in each affected region	<5cm: 2 points; <10cm: 4 points; >10 cm: 8 points
All lesions are separated by non-affected skin?	Yes: 0 points, No: 6 points

In a retrospective study by Yazdanyar et al. [26] 24 patients with HS in different stages were treated with a daily monotherapy of 50mg to 200mg of dapsone (the majority took 100mg daily, for an average of 4.3 months). After the treatment, 6 patients showed significant clinical improvement, and 3 showed little improvement, with none of these having been initially classified as HS Hurley's Stage III. Sixteen patients did not improve after the treatment.

TNF-αinhibitors

In a double-blind, randomized placebo-controlled study published by Grant et al., [27] it was demonstrated that infliximab yields good results for the treatment of HS. For 8 weeks, 15 patients received 5 mg/kg doses of infliximab, following the application program at weeks 0, 2, 6 (a program already used for other inflammatory conditions, such as Crohn's disease and rheumatoid arthritis).[28] The researchers found a significant reduction in the severity of HS in the study's patients, with reductions of up to 50% in the staging systems when compared to the beginning of treatment.

A systematic review by Alhusayen et al. 29 carried out in 2012, showed that this drug has enough evidence to be used in the treatment of HS. Nonetheless, due to its high cost and potential adverse effects, its use is recommended in patients with Hurley's Stages II or III, who have failed to achieve a significant improvement with the use of antibiotics and who have had a major impact on their quality of life. However, there is still a lack of large randomized studies to define the effectiveness of this approach in HS.

There are other drugs belonging in this class that are being studied, including adalimunab and etanercept. In the case of etanercept, a double-blind randomized placebo-controlled study was conducted by Adams et al., 30 where 20 patients were randomized to receive 50mg of etanercept or a placebo subcutaneously twice a week for 12 weeks. After that period, all patients received a new therapy course for 12 weeks. At the end of weeks 12 and 24, no significant improvement was seen in the patients. The adalimunab was evaluated in a phase 2 open study, in which 10 patients received 160mg adalimunab at week 0, followed by 80mg at week 1, with a weekly maintenance dose of 40mg for 12 weeks. Although the substance has been well tolerated and there have not been reports of serious adverse events, it was not possible to demonstrate a clinical improvement of patients. [31]

Finasteride

Finasteride is an antiandrogen drug that exerts its effects through competitive inhibition of 5 alpha-reductase type II, which is responsible for converting testosterone to dihydrotestosterone (DHT) – its active metabolic enzyme. [32] Due to the fact that it mainly inhibits 5 alpha-reductase type II, which is present only in hair follicles, it is believed that this drug acts by decreasing the inflammatory response at that location.

In a 2005 study, Joseph et al. [33] followed up on the use of finasteride in 7 patients who had not shown any improvement after treatment with antibiotics. The patients were followed up with for a period varying from 8 to 24 months, using 5mg of the drug, with 6 of them having important clinical improvement, and 3 achieving complete remission.

A study published in JAMA by Randhawa et al., [34] investigated the use of this drug in 3 children, obtaining interesting results in terms of treatment, with 3 showing significant improvement. Nevertheless, due to the fact that the drug has a high risk of causing feminization in male fetuses, it should be used with caution in women of childbearing age, as is the case with isotretinoin.

Surgical therapy and lasers

Surgical therapies and laser-based techniques are employed in situations where treating lesions with other modalities has failed. Initially, surgical excision was carried out, however this method proved ineffective for large lesions due to the limited feasibility of the procedure. As a result, laser-based treatments have emerged as an interesting option due to the possibility of their use in extensive lesions and the conservation of healthy tissue around the lesions, eliminating the necessity of using surgical grafts or flaps.

The use of carbon dioxide laser has been addressed by Lapins et al. [35] in a series of 24 patients with Hurley's stage II who had already undergone HS treatments without success. This technique induces the vaporization of the lesions, as it is able to reach the deep layers of the subcutaneous adipose tissue and muscle fascia, making it useful for treating infected lesions due to the bactericidal effects of heat. Of the 24 patients, only 2 had recurrences in the treated sites, and 4 showed new lesions (5-10cm away from the treated sites).

In a similar study, Hazen and Hazen 36 used the CO_2 laser technique in 61 patients with a total of 185 areas treated. Recurrence was observed in only 2 areas in the same patient during a follow-up period that ranged from 1 to 19 years.

Based on the role of hair follicles in the pathophysiology of HS, their selective ablation has emerged as an interesting option for controlling the disease. Among available treatments, 1,064nm Nd:YAG laser was evaluated by Tierney et al. 37 in a randomized controlled prospective study with 22 patients. Three monthly therapy sessions were carried out within half of each patient's body, and the results were compared with the other half, which had received topical treatment with antibiotics only. The results obtained showed significant improvement in all treated patients, with variations in the improvement in the Sartorius score (Chart 2), depending on the areas treated (73.4% for the inguinal region, 62.0% for the axilla, 53.1% for the inframammary region, resulting in an overall improvement of 65.3%).

Metformin

Metformin is an oral hypoglycemic drug that acts by reducing hepatic gluconeogenesis and insulin resistance. [38] It also presents antiplatelet and anti-inflammatory properties. [39] Given the association between polycystic ovary syndrome, HS and insulin resistance, there have been attempts to evaluate the drug's action in the treatment of this disease.

An open clinical trial was carried out with 25 patients, all bearers of HS (in all stages), who were initially treated with 500mg of metformin daily, with an increase in the dose to 1,000mg after one week and to 1,500mg after another week. After reaching the maximum dose of 1,500mg/day, patients used the medication continuously for 22 additional weeks and were evaluated at weeks 12 and 24 of the treatment. The degree of severity was reassessed at each consultation, and was initially calculated with the Sartorius system. The impact of the treatment was also assessed through the questionnaire Dermatology Life Quality Index.

Of the 25 patients, 18 (72%) had an average reduction of 12 points in the Sartorius system, with 7 of them having decreased by more than 50%. The 7 remaining patients (28%) had no response to the treatment. Regarding the quality of life questionnaire, [19] patients had improvement with a decrease in incidence rates of depression and absenteeism. However, further and more controlled clinical trials, with a greater number of patients, should be carried out in order to confirm the efficacy of metformin in HS, with its use being recommend in patients who have already tried other treatment modalities and do not wish to undergo surgical procedures.

DISCUSSION

Because it is a difficult to control disease, treatment for HS should be individualized. Initially, the patient must be closely examined in order to be rated according to the Hurley's staging system, and to have risk factors and associated conditions determined. It is important to bear in mind that this is a dynamic condition and treatments used in more advanced forms of HS can be recommended in the early stages, according to the dermatologist's evaluation.

Initially, Hurley's Stage I could be addressed with topical clindamycin, with the possibility of monthly 1,064nm Nd:YAG laser treatments being evaluated. [37]

Hurley's Stage II could be initially treated with 300mg clindamycin in combination with 300mg rifampicin twice daily for 10 weeks, 20,21 with 1,064nm Nd:YAG laser being performed for 3 or 4 months, with monthly sessions. [37] At this stage, in the event that the patient presents intolerance or refractory, it could be valuable to institute treatment using biologic agents, with infliximab being the first choice due to its encouraging results.[29] Finasteride, which is seldom used for HS, has only case reports, [33,34] however it seems to be an effective therapy – with or without association to the chosen antibiotic therapy – like metformin.

Hurley's Stage III can initially be addressed with the already mentioned therapies. However, excisional surgeries or CO_2 based excision must be considered.

Many dilemmas and difficulties are involved in the treatment of HS, since it is a chronic disease with a significant impact on the quality of life of patients who have a poor response to the more usual therapies. Most of the more effective treatments, such as the use of lasers or biological products, are difficult for much of the population to access. It is important for dermatologists to master the surgical and clinical options of the different treatment modalities in order to be able to change the course for individual bearers of HS.

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Questions for continuing medical education – CME

1) Below are risk factors for hidradenitis suppurativa, except for:
a) obesity
b) diabetes
c) smoking
d) positive family history
e) oral contraceptive use

2) About hidradenitis suppurativa, it can be stated:
a) it is more common in men
b) the onset usually occurs during childhood and adolescence
c) it is a disorder of the eccrine glands
d) it mainly affects the chest region and face
e) it is characterized by nodules, abscesses, and scars

3) Select the correct alternative:
a) most therapeutic options lead to the cure of hidradenitis
b) patients with Hurley Stage I already have small scars
c) the Sartorius score allows for the evaluation of the development and severity of hidradenitis
d) the Hurley's Staging System classifies hidradenitis in 5 stages
e) treatment of hidradenitis is independent of its clinical stage

4) The below are Sartorius score parameters, except for:
a) presence of purulent secretion
b) anatomical region involved
c) number and type of lesions
d) distance between the lesions
e) presence of normal skin between the lesions

5) Regarding the use of antibiotics in hidradenitis, it is correct to state:
a) it is never the first therapeutic option
b) the most frequently used scheme is monotherapy
c) the main combination described is clindamycin and rifampicin, at 600mg/day and 300mg/day respectively
d) it is aimed at treating associated infections and controlling inflammatory activity
e) control of the disease can already be observed in the first weeks with peak activity at 4 weeks

6) Select the incorrect alternative regarding the options for the treatment of hidradenitis:
a) Isotretinoin has an inhibitory effect on sebum production, on the stimulus of the differentiation of keratinocytes, and on the normalization of cell desquamation
b) The isotretinoin dose usually employed is 0.5 to 1 mg*day/kg
c) Isotretinoin has proved to be a scarcely effective method for treating hidradenitis
d) Dapsone is a competitive antagonist of para-aminobenzoic acid and has anti-inflammatory characteristics
e) A100 mg/day dose of dapsone is the gold standard in the treatment of hidradenitis

7) Regarding the use of biologicals in hidradenitis, it is correct to state:
a) 50mg etanercept twice daily can achieve an improvement of 50% in patients with hidradenitis
b) the use of infliximab did not achieve a significant reduction in the degree of severity of HS in patients
c) adalimumab is the biological of choice for the treatment of hidradenitis, for in addition to its good results, it is well tolerated by patients
d) the use of TNF-α inhibitors has already been allowed for hidradenitis, and should be indicated in the early stages of the disease
e) Infliximab can be an option for patients with Stage II and III Hurley's who have not had success with other treatments

8) Select the incorrect choice:
a) Finasteride is an anti-androgen and exerts its effects through the competitive inhibition of the enzyme 5 alpha-reductase type II
b) It is believed that the effect of finasteride is due to the decrease in the inflammatory response in hair follicles of patients with hidradenitis
c) The dose of finasteride used in hidradenitis is 5mg twice a day
d) Finasteride should be used with caution in women of childbearing age because of the risk of feminization of male fetuses
e) Despite the availability of just a few studies, the literature shows significant improvement in hidradenitis with oral finasteride

9) Regarding surgery and laser treatments in hidradenitis, it is incorrect to state:
a) they can be an option when there is failure in the treatment with other modalities
b) studies showed significant improvement of hidradenitis with 1,064nm Nd:YAG laser weekly sessions
c) Surgical excision is an efficient method, however it is difficult to implement in large areas
d) CO2 laser induces the vaporization of lesions and is capable of reaching the deep layers (subcutaneous tissue and muscle fascia)
e) 1,064-nm Nd:YAG laser allows selective ablation of hair follicles

10) Regarding the treatments for hidradenitis suppurativa, it is correct to say:
a) some reports on the use of metformin have shown an improvement in lesions and in patients' quality of life
b) the initial dose of metformin is 500mg/day, reaching a maximum dose of 2,500 mg/day
c) currently, the disease can be easily controlled with the treatment options available
d) 1,064-nm Nd:YAG laser can be employed only in Hurley's Stage III
e) Stage III should only be approached surgically

Key:
High-frequency ultrasound (22MHz) in the evaluation of malignant cutaneous neoplasms. 2014;6(2):1105-11.

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

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Original Articles

Cellulite grading assessment in women following three different diets

Avaliação do grau de celulite em mulheres em uso de três diferentes dietas

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ABSTRACT

Introduction: Although cellulite has been related to being overweight and having unhealthy eating habits, normal weight patients can also present with cellulite.

Objective: To assess the effects of three different diets in the reduction of cellulite grading in normal weight women.

Methods: Forty-three women were randomized into 3 groups: Group 1 followed a low-carbohydrate diet; Group 2, a high protein content diet; and Group 3, a control diet with standard amounts of macronutrients. Body weight for each patient was recorded and cellulite grading was assessed with the Cellulite Severity Scale.

Results: Patients in Group 2 had, on average, lower cellulite grading for the right and left gluteus compared to patients in Groups 1 and 3. Patients in Group 2 also saw a reduction in body weight and a reduction in cellulite grading on the thighs during the course of the study.

Conclusion: Patients in Group 2 had improvement in cellulite grading, possibly related to the reduction in body weight and the consequent reduction of adipose tissue. Larger studies are needed to support these data and establish the relationship between the composition of different diets and cellulite improvement.

Keywords: cellulitis; lipodystrophy, diet therapy.

RESUMO

Introdução: *Embora seja conhecida a positiva relação entre o agravamento da celulite pelo excesso de peso e hábitos alimentares incorretos, pacientes com peso normal também podem apresentar celulite.*

Objetivo: *Avaliar o efeito de três diferentes dietas na redução do grau de celulite em mulheres com peso normal.*

Métodos: *Quarenta e três mulheres foram randomizadas para três diferentes grupos: o grupo 1 seguiu dieta com teor de carboidratos reduzido; o grupo 2, dieta com alto teor de proteínas; e o grupo 3, dieta-controle com quantidades normais de macronutrientes. O peso das pacientes foi aferido, e o grau de celulite foi avaliado pela escala de gravidade de celulite.*

Resultados: *As pacientes do grupo 2 apresentaram grau de celulite mais baixo nos glúteos direito e esquerdo em relação às pacientes dos grupos 1 e 3. Ao longo do tempo, as pacientes do grupo 2 tiveram redução no grau de celulite nas coxas.*

Conclusão: *As pacientes do grupo 2 apresentaram melhora no grau de celulite, provavelmente relacionada à perda de peso e consequente redução do tecido adiposo. Estudos maiores e mais abrangentes serão necessários para corroborar esse dado e estabelecer a relação entre a composição de diferentes dietas e a melhora da celulite.*

Palavras-chave: *celulite; lipodistrofia; dietoterapia.*

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Conflict of interest: None

INTRODUCTION

Cellulite affects nearly all women. Its prevalence is estimated at around 80-90% and although it is not considered a pathological condition, it can cause emotional distress[1,2] and is a frequent complaint on the part of patients. It occurs more frequently in the obese population, however it also affects those who are lean. It is rare in men, and in women usually starts after puberty, mainly affecting the thighs, buttocks and abdomen. [3,4] Cellulite can arise with different clinical aspects, such as those referred to as "orange peel", "cottage cheese" or "mattress appearance".

Although cellulite's pathogenesis has not yet been fully elucidated, some scientific evidence links this condition to the peculiar anatomy of women. [5,6] Among the described etiologic factors are changes in the adipose tissue [7] and the configuration of the subcutaneous connective septa.[5,6] The literature also quotes hormone and genetic [7] influences, and changes in the microcirculation. [8,9]

Alterations in the skin's relief caused by cellulite include elevated and depressed lesions. Subcutaneous fibrous septa that connect the skin to the muscle fascia produce traction on the skin, resulting in depressed lesions. [5] Elevated lesions are caused by the accumulation of fat, which causes tension within the lobe, resulting in the herniation of fat through the dermis.[7] Those herniations protrude on the cutaneous surface, producing the different appearances of the elevated lesions (orange peel, cottage cheese and mattress appearance). Nevertheless, no differences in the adipose tissue of elevated areas is observed, compared to the other areas.[10] Furthermore, sagging skin is an important aggravating factor of cellulite, especially with increasing age, and is more visible in women over 40-years-old. [4,11]

Although there is a positive correlation between cellulite and being overweight,[10] its manifestation is also common in women of normal weight and even those that are lean. However, the correlation between specific dietary patterns and the presence or worsening of cellulite is not known. It is believed that treatments aimed at losing weight can have positive effects on the appearance of cellulite, however there is still controversy about what optimal composition of diet could help to reduce the degree of cellulite.[12] The present study was aimed at evaluating the effect of a diet low in carbohydrates on reducing the degree of cellulite in women with normal weight, compared to standard diets and those with a high-protein content.

METHODS

A prospective monocentric study was conducted at the Centro Brasileiro de Estudos em Dermatologia (*Brazilian Center for Studies in Dermatology*), in the southern city of Porto Alegre, Brazil, after having been approved by the Hospital Moinhos de Vento's Research Ethics Committee. In accordance with the applicable regulations and guidelines of good clinical practice, all patients were fully informed about the study, having signed a term of informed consent before participating in the study.

Forty-three female patients aged between 18 and 40 years were included and randomized into one of three treatment groups receiving different dietary macronutrient content, with each diet having the same total caloric value. For the distribution of patients into the groups, a randomization list generated by a statistician external from the study was used. Table 1 summarizes the treatment groups according to the selected diet.

The main inclusion criteria were: body mass index (BMI) between 18.5 and 24.9 kg/m², use of effective contraception method, absence of signs of inflammatory or infectious process in the body sites studied by the evaluation, and a moderate to severe degree of cellulite in the buttocks according to the Cellulitis Severity Scale (CSS). [13]

Six follow-up visits were conducted during the study. At the screening visit, a dermatologist clinically assessed the patients and rated the degree of cellulite according to the CSS.[13] A dietitian was responsible for the nutritional assessment, as well as for the dietary guidance.

Assessed body circumferences included the waist (midpoint between the iliac crest and the lower costal margin), hip (point of maximum circumference over the buttocks) and arm (midpoint between the acromion and the olecranon), taken with a non-extensible tape measure, in centimeters and millimeters. The cutaneous folds measured were the triceps and subscapular folds. The cutoff point was parameterized using the 50th percentile, as described by Frisancho.[14] The patients' weight was measured using a scale (Welmy®, Brazil) without clothes and without shoes, while the height was measured using a wall stadiometer. The patients' diet was followed upon by the nutritionist, using the assessment tool of the standard food-questionnaire. The patients recorded their food intake for three days a week over five months – two working days (Tuesdays and Thursdays) and a weekend day (Sunday). This record served as the basis for calculating the percentage of the patients' adherence to the pro-

Table 1: Dietary treatment groups

Groups	Diet content
Diet 1 (reduced carbohydrates) 15% protein 45% fat	40% carbohydrates
Diet 2 (high in protein) 22% protein 33% fat	45% carbohydrates
Diet 2 (control: normal macronutrient standards) 15% protein 25% fat	60% carbohydrates

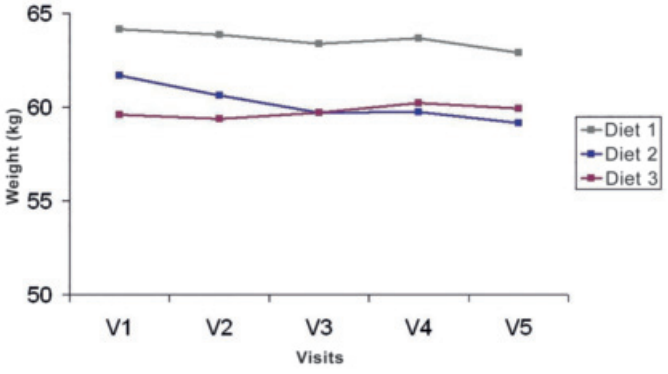
posed diet, taking into account the percentage of ingested macronutrients versus the percentage proposed in the diet.

RESULTS

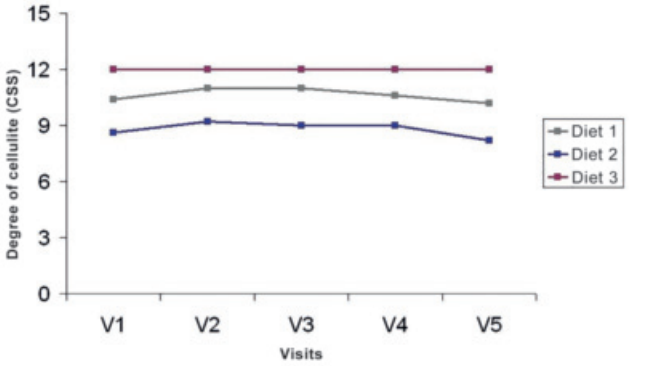
Nineteen of the 43 patients included (44.2%) completed the study: 5 in Group 1, 6 in Group 2, and 8 in Group 3. The demographics are described and stratified by diet in Table 2. The mean values for dietary adherence ranged between 85-89%, with no difference in adherence between groups. The average age of the patients who followed the diet with high-protein content (Diet 2) was higher when compared to that of those who followed the control diet (Diet 3) ($p = 0.04$). Other demographics were similar between diets, including weight and the degree of cellulite at baseline. Despite not being a significant aspect, the patients who followed the diet with high-protein content (Diet 2) had a lower degree of cellulite in the buttocks at baseline. That diet produced a significant decrease in weight over time ($p < 0.05$), which was not observed with the other two diets (Graph 1).

The patients who followed the diet with high-protein content (Diet 2) had lower average scores for the degree of cellulite (CSS) in the right and left buttocks, when compared to those who followed a low-carbohydrate diet (Diet 1) ($p = 0.005$ and $p = 0.051$, right and left buttocks, respectively) and the control diet (Diet 3) ($p < 0.001$ and $p = 0.007$, right and left buttocks respectively). The degree of cellulite in patients who followed Diets 1 and 2 did not differ significantly from each other in the left and right buttocks ($p = 0.080$ and $p = 0.142$, respectively). There was no improvement in the degree of cellulite in the right and left buttocks over the course of the study for any of the diet types (Graphs 2 and 3).

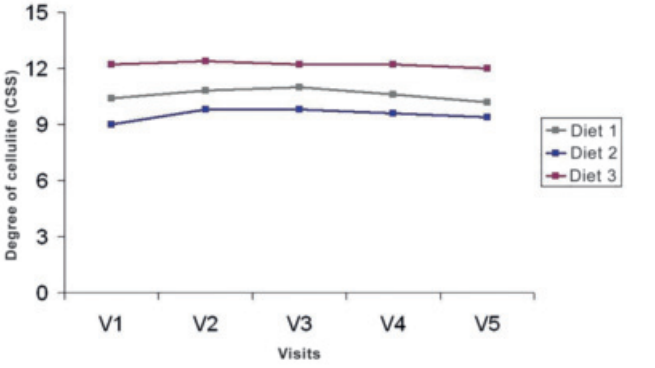
The patients who followed the diet with high-protein content (Diet 2) had a significantly lower degree of cellulite in the right thigh than those who followed a low-carbohydrate diet (Diet 1) in months 4 and 5, and than those who followed the control diet (Diet 3) in months 2, 4, and 5 (Graph 4). The patients who followed the diet low in carbohydrates (Diet 1) had a significantly lower degree of cellulite on the right and left thighs than those who followed the control diet (Diet 3): in month 2 for the right thigh and in months 2 and 5 for the left thigh. The group following the diet with high-protein content (Diet 2) showed an improved degree of cellulite on the right



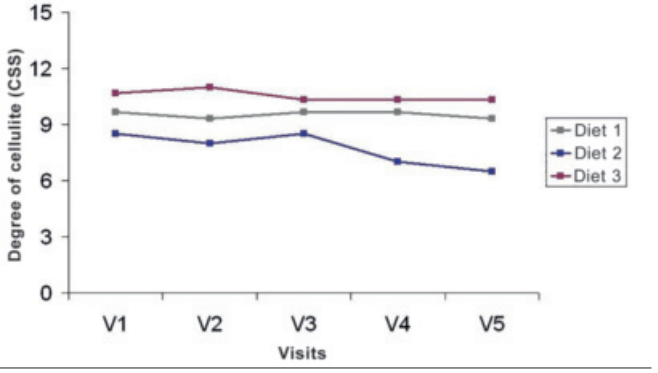
Graph 1: Average weight over time, diet described according to:



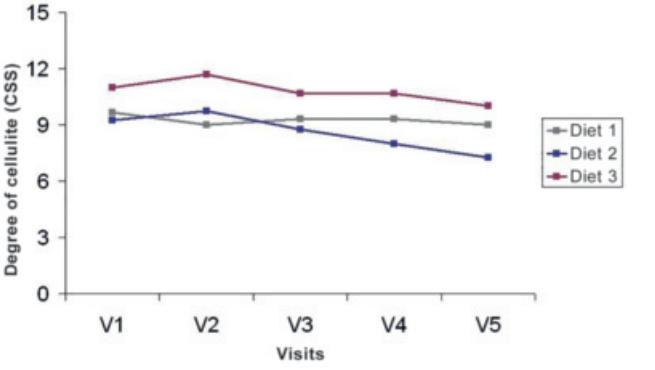
Graph 2: Degree of cellulite on the right gluteus over the course of the study



Graph 3: Degree of cellulite on the left gluteus over the course of the study



Graph 4: Degree of cellulite in the right thigh over the course of the study



Graph 5: Degree of cellulitis in the left thigh over the course of the study

Table 2: Demographic characteristics of patients by group

	Sample			Diet 1 (n = 5)		Diet 2 (n = 6)		Diet 3 (n = 8)	P
	n	%							
Age (years)				35a.b+8.06		39.3a+5.16		29b +7.39	0,043*
Adhesion (%)	19	(86.2)		85.9 + 9.58		87.3 + 7.94		85.4 + 4.35	0,893*
Weight (kg)	19	(61.4)		64.1 ± 8.2		61.7 ± 3.2		59.6 ± 4.7	0,364*
CSS right gluteus				10.40 ± 3.97		8.67 ± 2.52		10.7 ± 2.65	0,43
CSS left gluteus				10.40 ± 3.97		9 ± 3.16		11.13 ± 2.03	0,43
CSS right thigh				9.67 ± 1.53		8.50 ± 1.29		10.50 ± 2.07	0,26
CSS left thigh				9.67 ± 1.52		9.25 ± 2.50		10.67 ± 1.75	0,53
Marital status									0,198**
Unmarried	12	(63.2)	2	(40)	3	(50)	7	(87.5)	
Married	7	(36.8)	3	(60)	3	(50)	1	(12.5)	
Education level									0,580**
Secondary school	3	(15.8)	1	(20)	1	(16.7)	1	(12.5)	
Undergraduate	5	(26.3)	1	(20)	0	(-)	4	(50)	
Graduate	5	(26.3)	2	(40)	2	(33.3)	1	(12.5)	
Postgraduate	6	(31.6)	1	(20)	3	(50)	2	(25)	
Income									0,541**
<1 MW	1	(5.3)	0	(-)	0	(-)	1	(12.5)	
1 to 3 MW	3	(15.8)	1	(20)	1	(16.7)	1	(12,.5)	
3 to 5 MW	8	(42.1)	1	(20)	2	(33.3)	5	(62.5)	
5 to 7 MW	1	(5.3)	1	(20)	0	(-)	0	(-)	
> 7 MW	6	(31.6)	2	(40)	3	(50)	1	(1,5)	
Previous aesthetic treatment									0,509**
Yes	8	(42.1)	3	(60)	3	(50)	2	(25)	
Yes	11	(57.9)	2	(40)	3	(50)	6	(75)	
Allergy									0,432**
Yes	9	(47.4)	1	(20)	3	(50)	5	(62.5)	
Yes	10	(52.6)	4	(80)	3	(50)	3	(37.5)	
Use of medication									0,051**
Yes	8	(42.1)	4	(80)	3	(50)	1	(12.5)	
No	11	(57.9)	1	(20)	3	(50)	7	(87.5)	
Physical activity									0,509**
Yes	8	(42.1)	3	(60)	3	(50)	2	(25)	
No	11	(57.9)	2	(40)	3	(50)	6	(75)	
Children									0,265**
Yes	6	(31.6)	3	(60)	2	(33.3)	1	(12.5)	
No	13	(68.4)	2	(40)	4	(66.7)	7	(87.5)	
Smoker									
No	19	(100)	5	(100)	6	(100)	8	(100)	-
Oral contraceptive use									1**
Yes	7	(36.8)	2	(40)	2	(33.3)	3	(37.5)	
No	12	(63.2)	3	(60)	4	(66.7)	5	(62.5)	
Use of skin care products									0,434**
Yes	3	(15.8)	0	(-)	2	(33.3)	1	(12.5)	
No	16	(84.2)	5	(100)	4	(66.7)	7	(87.5)	

* Valor de p para teste Anova. As medias seguidas pela mesma letra não diferem pelo teste de significância estatística mínima. = * p-value for ANOVA. The means followed by the same letter do not differ on the minimal statistical significance test.

** Valor de p para teste exato de Fisher = ** p-value for Fisher's exact test.

thigh (p = 0.014) and left thigh (p = 0.013) throughout the entire study period (Graphs 4 and 5).

DISCUSSION

This was the first study to examine the effects of a low-carbohydrate content diet and high-protein content diet on the degree of cellulite.

The patients' adherence rate was low, considering that less than half of those who started the study (44.2%) participated up to the last proposed assessment follow-up visit. This fact demonstrates the difficulty these patients had in following a diet, regardless of the proposed diet, given that there was a high dropout rate in all groups throughout the study. In general, patients' poor adherence in studies evaluating the outcome of diets is a known fact. [15] Adherence rate is influenced by various factors, such as level of education, self-care conditions, concern with one's own quality of life, socioeconomic factors, and psychological conditions. [16,17]

The sample obtained was homogeneous regarding almost all demographics except for age, which differs between the diet Groups 2 and 3. Patients who received the diet with a high-protein content were older compared to those who received the control diet. That group's degree of cellulite, however, did not differ significantly from those of the other groups at baseline. Older patients can have a higher degree of cellulite than that of younger patients due to the sagging of skin, which tends to increase with age. [4,10,11]

It was possible to observe that patients who followed the high-protein diet showed the greatest reduction in weight when compared with those who followed other diets. In diets high in protein, 25% of the total energy intake is composed of proteins. These diets are considered effective in producing satiety due to increased dietary thermogenesis and a subsequent decrease in food intake, and can aid in weight reduction. [18]

Over time, a reduction was seen only in the degree of cellulite in the thigh, for patients who followed the diet with a high-protein content. Comparing the results of groups on each visit, it was possible to observe that these patients (Diet 2) had lower degrees of cellulite, particularly in the buttocks, when compared to patients who followed the other diets. The best effect of Diet 2 on the degree of cellulite can be related to the weight loss observed in this diet.

Lower levels of glucose, insulin, and glucagon production are attributed to the diet based on a reduced intake of carbohydrates. As a response, the body would produce oxidation of fatty acids with a corresponding result of the burning of fat stocks. [19] According to the literature, both diets low in carbohydrates and diets with reduced lipids promote weight loss. [20] Some studies [21,22] suggest that the storage of fats increases with higher concentrations of fat intake and decreases with diets low in lipid content. However, it is believed that a dietary plan low in carbohydrate content would be more effective in the long run than a diet with reduced lipid content. [20] It is possible that due to the lower thermal effect of fat and the higher energy expenditure required for the conversion of carbohydrates into fatty acids, fat is more easily stored than carbohydrates in adipose tissue.[19] Nonetheless, in the present study the diet low in carbohydrate content had no significant effect on the patients' weight or degree of cellulite.

The degree of cellulite was evaluated using the CSS, [13] a scale validated for the objective evaluation of the degree of cellulite. This scale considers the morphological components of cellulite, such as the number of visible depressed lesions, the depth of the depressed lesions, the clinical appearance of elevated lesions, sagging, and the old classification. Each of these five items is assessed with a grade scale ranging from zero to three. The sum of all items results in the final value of the degree of cellulite, which can be classified as mild (1 to 5 points), moderate (6 to 10), or severe (11 to 15 points).

The high dropout rate of patients reduced the sample considerably, affecting the power of the study. A limitation of the present study is that although the nutritional monitoring of patients has been carried out, no validated assessment tool was used to evaluate the patients' adherence to the proposed diets. The initial difference in the average age between the groups could be identified as a possible selection bias, nonetheless all inclusions were randomized.

Despite the limitations, the authors believe they have conducted an original study of a little studied topic: the different types of diet and their effect on the improvement of cellulite, a highly prevalent aesthetic condition among women. This subject deserves further analysis in light of the data from a previous study conducted in the authors' dermatological center, in which patients with nutritional bulimic behavior were found in the sample. [23]

CONCLUSION

Most of the patients studied had difficulty in following the proposed dietary regimen, regardless of the diet type. This was evidenced by the high dropout rate in the present study. The patients undergoing a diet high in protein content showed improvement in the degree of cellulite, probably related to weight loss and the resulting reduction in adipose tissue. Wider and more encompassing studies are necessary to establish the correlation between diet composition and the improvement of cellulite.

Although results are not relevant due to the small final sample, they allow for the suspicion that the reduction of body weight in patients with normal weight, independent of the specific diet type, may improve the degree of cellulite. ●

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Correction of facial asymmetries and dyskinesias with botulinum toxin type A

Correção de assimetrias e discinesias faciais com toxina botulínica tipo A

ABSTRACT

Introduction: *Facial paralysis triggers asymmetries and other functional and aesthetic facial changes, which lead to significant physical and psychological disorders. Botulinum toxin type A is a safe, effective, and well-tolerated therapy, making it a good option for treating those conditions.*

Objective: *To demonstrate the clinical improvement and the degree of satisfaction among patients bearing facial asymmetries and dyskinesias, who have been treated with botulinum toxin type A injections performed by dermatologists.*

Methods: *Patients with facial asymmetries and dyskinesias were selected between January 2011 and December 2013, to receive botulinum toxin injections aimed at reducing muscle activity on the normal side of the face (in cases of facial hemiparesis) or directly into the affected muscles in cases of dyskinesias. The clinical evaluations and photographic records in static and dynamic positions were carried out on the days of the first application (D0) and fifteen days after (D15). Each patient was rescheduled for a future session within120 days.*

Results: *There was clinical improvement with reduction of asymmetries and dyskinesias verified at the beginning of treatment following application of the toxin. A significant improvement in the patients' quality of life, with a positive impact in different areas of their personal lives, could be noticed.*

Conclusions: *Treatment with botulinum toxin type A, performed by dermatologists with previous experience in the management of this procedure in other conditions, proved to be an important alternative in the treatment of asymmetries and facial dyskinesias.*

Keywords: *facial asymmetry; facial paralysis; quality of life; botulinum toxins, type A.*

RESUMO

Introdução: A paralisia facial desencadeia assimetrias e outras modificações faciais funcionais e estéticas, que levam a desordens físicas e psicológicas significativas. A toxina botulínica tipo A, por ser terapêutica segura, eficaz e bem tolerada, torna-se boa opção no tratamento dessas condições.

Objetivo: Demonstrar a melhora clínica e o grau de satisfação de pacientes portadores de assimetrias e discinesias faciais, tratados com injeções de toxina botulínica tipo A realizadas por dermatologistas.

Métodos: Foram selecionados pacientes com assimetrias e discinesias faciais, no período entre janeiro de 2011 e dezembro de 2013, para receber injeções de toxina botulínica no lado normal da face, visando diminuir a atividade muscular nos casos de hemiparesia facial, ou diretamente nos músculos afetados, em casos de discinesia. As avaliações clínicas e os registros fotográficos nas posições estática e dinâmica foram feitos nos dias da primeira aplicação (D0) e 15 dias após (D15). Cada paciente foi reagendado para uma próxima sessão em até 120 dias.

Resultados: Após a aplicação da toxina houve melhora clínica, com suavização das assimetrias e discinesias apresentadas no início do tratamento. Notou-se importante melhora na qualidade de vida dos pacientes, com impacto positivo em diferentes âmbitos de sua vida pessoal.

Conclusões: A terapêutica com toxina botulínica tipo A, realizada por dermatologistas com experiência no manejo desse procedimento em outras condições, mostrou ser importante alternativa no tratamento das assimetrias e discinesias faciais.

Palavras-chave: assimetria facial; paralisia facial; qualidade de vida; toxinas botulínicas tipo A.

Original Articles

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INTRODUCTION

Craniofacial paralyses and dyskinesias trigger functional and aesthetic changes, which cause physical and psychological disorders. In the case of facial paralysis, there is excessive contraction of the contralateral side to the paralyzed side, due to the fact that there is no effective opponent musculature. The non-paralyzed side shows deviation of nasal, labial, and orbital regions, even when the muscles are at rest. Thus, rotation of the face towards the side not affected by paralysis takes place, causing shortening of that hemiface. The treatment of the resulting facial asymmetry aims at restoring muscle balance and regaining symmetry when in states of rest and motion. [1,2]

Surgical techniques are ineffective most of the time, and in addition present risk of complications.[2] Due to its safety, effectiveness and good tolerance levels, botulinum toxin type A therapy becomes a good option in the treatment of these pathological conditions, with the advantage of being made available by the Brazilian National Health System (*SUS*).[3,4] It has been used to treat synkinesis,[5] hyperlacrimation,[6] hyperkinesias,[7] and sequelae in the frontal and mandibular regions secondary to rhytidectomy.[8] The results have been so significant, that is has been considered by many to be the best treatment for the motor and autonomic effects caused by aberrant neural regeneration.[6] Based on the skill of the dermatologist – gained with the application of botulinum toxin in their daily practice for the treatment of various skin disorders such as facial aging –with this study the authors aim at demonstrating the safety and efficacy of this procedure when performed by an experienced professional, as well as the clinical improvement and degree of satisfaction of the patients who undergo it.

METHODS

A non-randomized parallel study, was carried out at the Dermatology Service of the Hospital Universitário da Universidade Federal de Juiz de Fora (UFJF), in the southern Brazilian State of Minas Gerais. It included 12 patients with facial asymmetries who were referred by the Dermatology Ambulatory or by other specialties, from January 2011 to December 2013.

Patients with significant facial asymmetries or dyskinesias, who had not undergone previous treatment, between the ages of 20 and 80 years, and not bearers of neuromuscular diseases, were selected.

The product used in the study (Botox®, Allergan Pharmaceuticals, Irvine, California, U.S. and Prosigne®, Lanzhou, Institute Biological Products, China) was supplied by the SUS. According to the needs of each patient, the toxin was applied in individualized doses in order to weaken the facial muscles in the hemiface not affected by the paralysis, and directly into the muscle responsible for the dyskinesia. Clinical assessments were carried out on the first day of the procedure (D0) and 15 days after (D15). The patients were photographed at each visit in static and dynamic standardized positions, using the same digital camera and ambient lighting (Figures 1 to 3). Each

Figure 1: Patient 1 in static position before the treatment, and after the 5thapplication.

Figure 2: Patient 1 in dynamic position before the treatment, and after the 5th application.

Figure 3: Patient 2
A) In static position before the treatment.
B) After the 5th application.
C) In dynamic position before the treatment.
D) After the 5th application.

patient was rescheduled for a future visit within 120 days of the last application. The study followed the ethical guidelines issued by the Helsinki Declaration of 2000, revised in 2008.

RESULTS

The 12 selected patients had a mean age of 56.4 years. Nine (75%) were females and 3 (25%) males. The etiology of asymmetries included tumors of the central nervous system, surgeries, Bell's palsy and indeterminate causes (Table 1). The total number of doses in each application varied according to individual needs (between 8.2 and 51 units per application). Patients were questioned about their overall degree of satisfaction after the treatment (Table 2) and were asked to rate their level of satisfaction with different aspects of their daily lives, using a scale varying from 1 to 5 (1 = mild improvement and 5 = great improvement). In the evaluation regarding the impact on professional life, the expression "not applicable (NA)"was used for patients already retired from their work activities (Table 3). A high level of patient satisfaction, as well as improvements in their personal relationships and social and professional lives, were observed after the correction of the asymmetries. Regarding complications, 2 cases of lagophthalmos and 1 of headache were verified. These symptoms were transient and did not cause inconvenience to patients.

DISCUSSION

Facial palsy and craniofacial dyskinesias trigger changes in speech, smile, swallowing, and chewing, and can cause serious damage to the patient's ability to express emotions and their own image.[1,3] In facial paralysis, the unaffected muscles become hyperkinetic, generating an imbalance based on the inaction of the opponents muscles.[1,2] Dyskinesias are defined as involuntary movements of the muscles of the face and neck, including blepharospasm, characterized by involuntary spasmodic bilateral closing of the eyelids[9] and hemifacial spasm, which consists of tonic-clonic unilateral contraction and of muscles innervated by the facial ipsilateral nerve. They are often accompanied by other sensory (visual or auditory disorders), motor (weakness of the facial muscles, trismus, bruxism, dysarthria) and/or autonomic (lacrimation and salivation) alterations. Muscle spasms start in the periocular region and progress to the perioral region and masticatory muscles.[10]

The main etiologies of facial asymmetry include strokes, surgical lesions, traumatic lesions, Bell's palsy, intracerebral tumors, and paralysis of undetermined etiology.[2] The treatment of facial paralysis aims at restoring the symmetry, in the static and dynamic state, that is seriously affected by progressive contralateral hyperkinesis.[1,2] A good treatment option is botulinum toxin type A due to the fact that it is safe, effective, and well tolerated. It is considered the treatment of choice for hemifacial spasm.[11] In the literature there are few reports by dermatologists on the treatment of facial asymmetry with the use of botulinum toxin, despite the fact it has been used since the 1970s to treat a number of conditions related to abnormal muscular contractions.[3,4] It works by blocking the release of acetylcholine at the neuromuscular junction, which prevents contraction of the muscle.[3,12] In hemifacial spasm, it is used directly in the affected muscle, blocking its involuntary action. It has been used for the treatment of facial hyperkinesia on the side not affected by paralysis, with the need for a higher total dose being described, however with a similar duration of action when used for other purposes.[3] In the present study, the number of units ranged between 8 and 51, with periodic reapplication after an interval of 90 to 120 days after the previous session.

Adverse events are rare with injections of the toxin to the face and are associated with the use of high doses.[12] In the present study there were no early complications, such as hematoma, infection, or allergy to the toxin, nor irreversible complications. Of all the patients who were evaluated, the

Table 1: Etiology of asymmetries

Etiology	Nº	(%)
CNS tumors	5	(41.6%)
Surgery	1	(8.3%)
Bell's palsy	2	(16.6%)
Undetermined causes	4	(33.3%)
Total	12	(100%)

Table 2: Degree of overall satisfaction after the treatment

Degree of satisfaction	Dissatisfied	Satisfied	Very Satisfied
Total Patients	0	2	10
% of patients	0%	16.66	83.33

Table 3: Different aspects of the improvement in quality of life

Improvement Index	Personal relationships	Professional life	Social life
Patient 1	5	NA	5
Patient 2	3	NA	3
Patient 3	5	NA	5
Patient 4	3	NA	3
Patient 5	5	5	5
Patient 6	5	5	5
Patient 7	5	5	5
Patient 8	5	5	5
Patient 9	5	5	5
Patient 10	5	5	5
Patient 11	5	5	5
Patient 12	5	5	5
Average	**4.66**	**5**	**4.66**

authors evidenced transient complications in 3 of them, with 2 presenting lagophthalmos and 1 headache. There was improvement in the mobility of the side affected by paralysis, as a secondary effect to the application of botulinum toxin in the uninvolved side. The various etiologies of facial asymmetries, the variety in the anatomy, and the strength of the musculature make it difficult to standardize the injection points and the amount of units to use in each of them, indicating that the experience of the professional carrying out the application is an important factor.[13] The use of botulinum toxin in the field of cosmiatry allowed the dermatologist to originally master its use. In line with the results obtained in the present study, the combination of this knowledge with the great aesthetic insight gained by dermatologists throughout his or her clinical practice reinforces the idea that such a professional is able to successfully treat such patients. The treatment of asymmetries is extremely rewarding, as it provides patients with reintegration and self-acceptance. The degree of patient satisfaction is high in contrast to the low rate of adverse effects. [1-3]

CONCLUSION

Botulinum toxin type A has proved to be an important alternative in the treatment of facial asymmetries. It contributes to improved self-image and self-expression, and leads to a positive social impact and improved quality of life for patients undergoing the treatment. Dermatologists are able to successfully treat such imperfections as evidenced by the clinical improvement, high degree of satisfaction of patients undergoing the procedure, and the few and limited adverse events. Nevertheless, more comprehensive studies, carried out by dermatologists, are necessary to consolidate the ability of such professionals to treat facial asymmetry with botulinum toxin. ●

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Original Articles

Evaluation of the effects of a cream containing liposome-encapsulated photolyase and SPF 100 sunscreen on facial actinic keratosis: clinical, dermoscopic, and confocal microscopy based analysis

Avaliação da ação de creme contendo fotolíase em lipossomas e filtro solar FPS 100 na queratose actínica da face: estudo clínico, dermatoscópico e por microscopia confocal

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Conflict of interest: Professor Francisco Macedo Paschoal is employed as a researcher at Laboratório ISDIN.

ABSTRACT

Introduction: *Chronic exposure to ultraviolet radiation is the primary cause of skin carcinomas. Actinic keratosis is considered a precursor lesion. Topical application of photolyase showed effectiveness with the removal of 40-45% of the dimers formed by ultraviolet radiation, contrasting with conventional photoprotection for its ability to repair already damaged cellular DNA. Confocal microscopy is used for the in vivo visualization of skin alterations.*

Objective: *To evaluate the effects of the cream containing photolyase and SPF 100 sunscreen on facial actinic damage and keratoses, using dermoscopy and confocal microscopy as evaluation parameters.*

Methods: *Observational longitudinal clinical trial in 17 actinic keratosis lesions. Dermatoscopy and confocal microscopy were carried out before applying the cream and 120 days after, with comparison of the images.*

Results: *Of the 14 Grade I actinic keratoses, nine showed clinical and dermoscopic improvement, three remained unchanged and one progressed to Grade II actinic keratosis. Confocal microscopy showed a reduction of scales and improvement in the epidermal architecture in the five Grade I actinic keratoses. The three Grade II actinic keratoses analyzed did not show improvement.*

Conclusions: *The application of photolyase in cream with sunscreen promotes photoprotection and DNA repair. Confocal microscopy is a useful tool for monitoring the treatment of actinic keratoses.*

Keywords: *keratosis, actinic; microscopy, confocal; dermoscopy.*

RESUMO

Introdução: A exposição crônica à radiação ultra-violeta é a causa primária de carcinomas de pele. A queratose actínica é considerada uma lesão precursora. A aplicação tópica da fotolíase mostrou eficiência com remoção de 40-45% dos dímeros formados pela radiação ultra-violeta, diferindo da fotoproteção convencional pela habilidade de reparar um dano já estabelecido ao DNA celular. A microscopia confocal é um recurso para visualização in vivo das alterações cutâneas.

Objetivo: Avaliar a ação da aplicação de creme contendo fotolíase associado ao filtro solar FPS 100 no dano actínico e queratoses actínicas na face utilizando a dermatoscopia e a microscopia confocal como parâmetros de avaliação.

Métodos: Ensaio clínico longitudinal observacional em 17 lesões de queratoses actínicas. Foi realizada dermatoscopia e microscopia confocal antes da aplicação do creme e após 120 dias. As imagens foram comparadas.

Resultados: Das 14 queratoses actínicas grau I, 9 apresentaram melhora clínica e dermatoscópica, 3 permaneceram inalteradas e 1 evoluiu para queratose actínica grau II. A microscopia confocal mostrou redução das escamas e melhora da arquitetura epidérmica nas 5 queratoses actínicas grau I. As 3 queratoses actínicas grau II documentadas não apresentaram melhora.

Conclusões: A aplicação da fotolíase em creme com filtro promove fotoproteção e reparo ao DNA. A microscopia confocal é uma arma útil no monitoramento do tratamento de queratoses actínicas.

Palavras-chave: ceratose actínica; microscopia confocal; dermatoscopia.

INTRODUCTION

Chronic exposure to ultraviolet radiation (UV) is the primary cause of skin carcinomas, and actinic keratoses (AKs) are considered a precursor lesion of squamous cell carcinoma (SCC). AK is one of the most common dermatological diagnoses and affects an estimated 58 million people in the United States.[1,2] In Australia it affects about 40-50% of individuals above 40 years of age due to the large proportion of individuals with phototype I and II skin in the population. [3] It is estimated that the relative risk of an individual carrying AK to develop SCC is 6-10%. [4]

Excessive exposure to UV radiation can cause gene mutations in the keratinocytes' deoxyribonucleic acid (DNA). The UV radiation energy absorption by the DNA of the epidermal cells results in the production of cyclobutane-pyrimidine dimers and pyrimidine-pyrimidone photoproducts, the initial event of the immunosuppression, mutation, and carcinogenesis process.[5] Topical application of photolyase –an enzyme present in virtually all living beings exposed to light with the exception of placental mammals – showed efficiency, with the removal of 40-45% of dimers from the DNA of human skin irradiated by UV. [6] Photolyase binds to cyclobutane-pyrimidine dimers (CPDs) and the exposure of the photolyase-dimer complex to radiation converts the dimerized pyrimidines to their original structure, fighting the carcinogenesis process. [5-8] When coupled with SPF 100 sunscreen, it enhances conventional photoprotection due to the potential for repairing the damage already established in the cellular DNA.

The classification of AK based on clinical and dermoscopic criteria results in Grade I and Grade II AKs (Table 1), with Grade II presenting the highest risk of progression into SCC. [9] In some patients it is possible to observe multiple AK lesions and in these cases, the concept of field cancerization can be used. It is a body area containing subclinical and multifocal pre-neoplastic abnormalities with genetic mutations that may constitute the origin of new primary tumors and local recurrence. [10-12]

In recent years, there has been increasing interest in the development of non-invasive diagnostic tests aimed at detecting not only clinically suspected AK lesions, but also detecting and defining sub-clinical lesions, which must also be treated. [10,13] The *in vivo* confocal microscopy is a resource for viewing cutaneous changes "*in vivo*" and can also be used to monitor treatment. The main diagnostic criteria of AK in confocal microscopy are: irregular hyperkeratosis, pleomorphism, an epidermal nuclear increase, and architectural derangement. [14-16]

The present study was aimed at evaluating the effect of applying a cream containing photolyase in liposomes, associated with SPF 100 sunscreen in patients with actinic damage and AK on the face, using dermoscopy and *in vivo* confocal microscopy (CM) as the evaluation parameter.

METHODS

A longitudinal, observational clinical trial was carried out at the Dermatology Department of the Faculdade de Medicina do ABC.

Fourteen patients (8 men and 6 women, aged 45-65 years), with AK Grade I and Grade II, and other cutaneous signs of chronic actinic damage on the face were prospectively studied.

Selected patients who agreed to participate in the study were volunteers from the outpatient dermatology clinic. After a detailed explanation of the study's objectives, and how they were expected to collaborate, in addition to the clarification of doubts, the patients signed a consent term for the research, which aligned with the ethical principles of good clinical practice.

The inclusion criteria were: age 45-85 years, ability to understand the method to be used, agreement to participate in the project, and the presence of AK Grade I or II (associated or not with other cutaneous signs of chronic actinic damage).

The exclusion criteria were: inability to understand the method to be used, pregnancy, lactation, neurological and psychiatric diseases, photosensitizing disease, bearers of collagenoses (such as lupus erythematosus), the use of photosensitizing or immunosuppressants drugs, clinical suspicion of skin cancer, and lesions on the face compatible with active infectious diseases.

After the selection of AK lesions per patient, the documentation was performed through clinical photography, optical dermoscopy with polarized light dermoscope (Derm Lite FOTO System, USA) and *in vivo* CM (Viva Scope 1500, Mavig Viva Scope Systems, Munich, Germany).

The area evaluated through CM was 8 mm^2, where half of the analyzed area presented the AK partially or fully, and the other half, the perilesional region.

The patients were instructed to perform daily application of the cream containing photolyase in liposomes and SPF 100 sunscreen (Eryfotona®-AK-NMSC, ISDIN Produtos Farmacêuticos LTDA, São Paulo, Brazil) and follow the recom-

Table 1: Classification of actinic keratosis

Grade 1 Actinic Keratosis	Grade 2 Actinic Keratosis
Flat, rough, pink lesions, in areas of photodamage.	Pink or erythematous papule or plaque, with scales and induration.
Red pigmentary pseudo-network (strawberry pattern).	Red star (starburst) pattern.
Lamellar scaling	Dotted or glomerular vessels.
	Opaque yellow desquamation.

Adaptado de Zalaudek e cols. [9]

mendations in an explanatory leaflet. Patients were followed up with every 30 days at dermatologic consultations. After 120 days, new clinical photographic, dermoscopic and *in vivo* CM documentation was carried out.

The images obtained before and 120 days after the beginning of the treatment were compared and the evaluation of the response to the treatment in the AKs was carried out based on the dermoscopic polarized light images and the *in vivo* CM.

Seventeen AK lesions (14 Grade I and 3 Grade II) were documented with clinical and dermoscopic photographs before and after 120 days' use of the cream containing photolyase in liposomes and SPF 100 sunscreen, with 8 of these lesions studied through *in vivo* CM.

RESULTS

From the 14 Grade I AK, 9 had clinical and dermoscopic improvement, with reduction of erythema and desquamation (Figure 1), 3 remained unchanged, and 1 lesion developed into Grade II AK.

All 3 of the Grade II AK did not improve clinically or dermoscopically after 120 days using the cream. (Figure 2)

In the CM examination of 8 lesions, 5 were Grade I AK and 3 Grade II AK. All patients with Grade I AK had a reduction in desquamation and improvement in the epidermal architectural pattern in the examinations. The 3 patients with Grade II AK did not present changes under the CM after 120 days' use of the medication. (Figures 1 and 2)

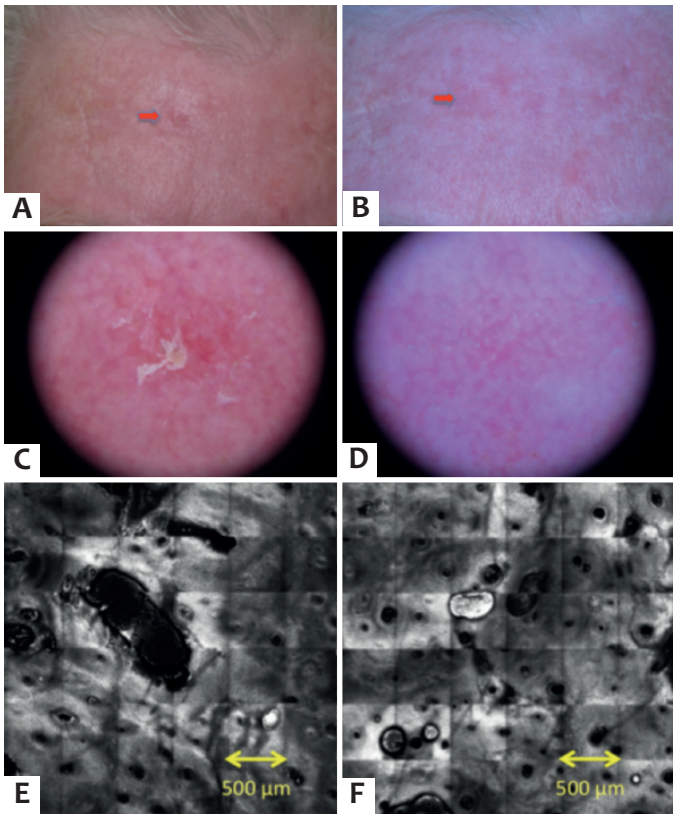

Figure 1: Clinical images (red arrows) of Grade 1 AK before and after 120 days' use of cream containing photolyase in liposomes and SPF 100 sunscreen **(A and B).** Dermoscopic comparison of the Grade 1 AK lesion: it is possible to observe an improvement of scales and erythema **(C and D).** Comparison under CM: it is possible to observe a reduction of scales and an improvement of epidermal architecture **(E and F).**

DISCUSSION

Risk factors that contribute to the development of non-melanoma skin cancers are well known and mainly include race, age, gender, chronic exposure to chemical and physical mutagenic agents. (UV radiation), in addition to genetic factors. Excessive exposure to UV radiation, especially type B ultraviolet (UVB), is associated with an increased risk for developing skin cancers, including basal cell carcinoma and SCC, as it can cause gene mutations in the DNA of the keratinocytes. Failure to repair these genetic alterations can lead to uncontrolled cell growth and cancer formation. Furthermore, the UV radiation has a significant effect on the cutaneous immune system, inducing a state of local immunosuppression that prevents the rejection of tumors in formation.

Mutations that occur in the gene that encodes p53 protein – an important tumor suppressor gene – are directly related to the development of skin cancer, with UV radiation being its primary cause. High levels of p53 (evidenced by immunohistochemistry) due to mutations and increased gene expression can be considered as biological markers of actinic damage and field cancerization. [10]

Photolyase is an enzyme belonging into the family of flavo-proteins and consists of 400 to 600 amino acids. It has an essentially globular structure. This enzyme is present in prokaryotic and certain eukaryotic organisms, including fish and marsupials, however it is absent in humans and placental mammals. These enzymes are produced by recombinant gene technology and/or extraction from bacteria and algae, and are then encapsulated in multilamellar liposomes. Photosomes® are liposomes containing biologically active photolyase, prepared from Anacystisnidulans (unicellular algae) cultures. The liposomal component comprises egg lipids, phosphatidylcholine, oleic acid, and cholesterol. [5,17]

The two main types of DNA damage are the formation of cyclobutane-pyrimidine dimers (CPDs) and pyrimidine-pyrimidone photoproducts (6-4PPs). These photoproducts interfere with the replication and cellular transcription processes, reducing the synthesis of RNA, decreasing the cell cycle's speed, and can result in apoptosis. The formation of dimers is of crucial importance in the carcinogenesis process: they promote mutations in tumor suppressor genes and contribute to cutaneous immunosuppression (allowing the disorganized growth of the transformed cells). [5-8]

Humans have a repair system (nucleotide excision repair - NER), which functions as a defensive process to prevent adverse events caused by UV radiation, protecting the genome and removing lesions from the DNA. In addition to the NER, some biological systems, except for those of placental mammals,

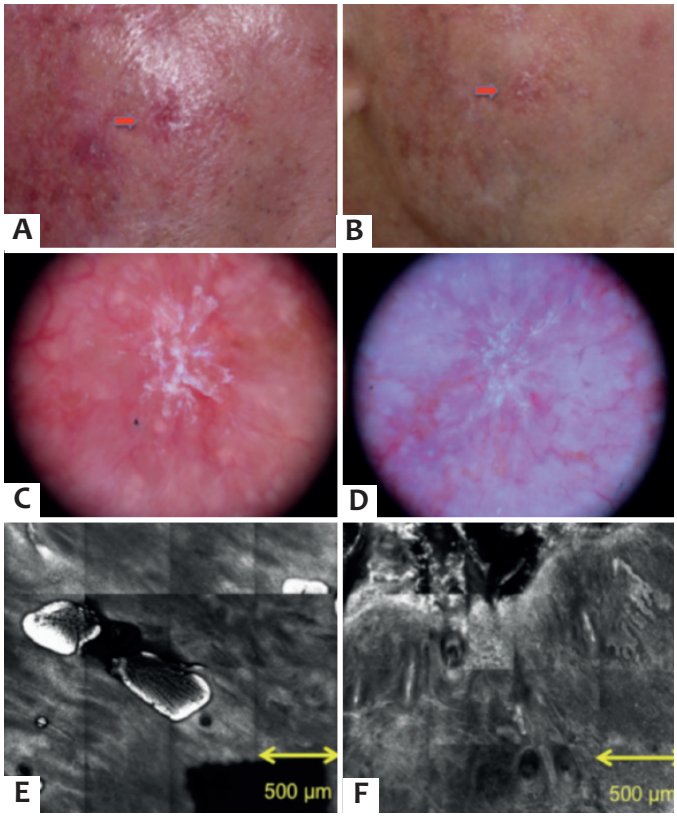

Figure 2: Clinical images (red arrows) of Grade 2 AK before and after 120 days' use of cream containing photolyase in liposomes and SPF 100 sunscreen **(A and B).** Dermoscopic comparison of Grade 2 AK lesion: unchanged red starry pattern (starburst) **(C and D).** Comparison under CM: permanence of scales and of the epidermal architectural derangement **(E and F).**

use photolyase to effectively remove the cyclobutane-pyrimidine dimers. Photolyase binds to cyclobutane-pyrimidine dimers (CPDs), creating a photolyase-dimer complex, whose exposure to radiation (300-500nm) converts the dimerized pyrimidines into their original structure (monomeric form). The process known as photoreactivation therefore involves two critical steps: the binding of the enzyme with the dimers (CPDs) – which is independent of light, and the catalysis process, which starts using a photon of blue light as the substrate, resulting in the repair of the CPDs. [5] Topical application of photolyase has proven very efficient, with the removal of 40-45% of the cyclobutane-pyrimidine dimers present in the UVB irradiated human skin, immediately after photoreactivation. Furthermore, it restored the expression of adhesion molecules (ICAM 1), which play a key role in maintaining the immune response of the skin following UVB radiation.

Another added benefit is that by reverting the CPDs, photolyase prevents the saturation of the natural repair systems and enhances the NER mechanism. [6]

The application of exogenous photolyase differs from the conventional photoprotection in its ability to repair an already established damage to the cellular DNA. It represents an innovative strategy that promotes conventional photoprotection and DNA repair in the same product. Patients in the current study had a significant improvement in the of AK Grade 1 lesions and in the photodamage after 120 days' use of the medication. The drug was proven to have worked directly in the field cancerization, which is currently the subject of many studies as it is a site that must be treated in order to prevent the formation of new AKs and non-melanoma skin cancer.

Actinic keratosis is currently considered an incipient *in situ* SCC that develops into a process that involves several steps, where UV radiation leads to the formation of field cancerization and AK, culminating with the onset of SCC. [1,18-20] Squamous Cell Carcinoma and AK are often contiguous lesions. In a study evaluating over 1,000 SCCs located in areas exposed to the sun, nearly 100% of the lesions had histological alterations consistent with AKs on their periphery. [21,22] Thus, in addition to being a precursor lesion of non-melanoma skin cancer, AK is also considered a marker of risk for the development of this group of neoplasias. Due to this fact, it is increasingly important to develop new technologies and products that also treat precancerous lesions and increase the awareness of the population regarding the use of sunscreen. The product in question has the advantage of associating an SPF 100 sunscreen to a drug that can inhibit some factors of carcinogenesis.

New non-invasive technologies that have aided in the diagnosis of these skin lesions are: dermoscopy examination and, more recently, the *in vivo* CM examination. These examinations are important not only to detect clinically suspicious lesions of AKs or SCCs, but also to detect and define subclinical field cancerization lesions and for following upon the proposed treatment.

Regarding the dermoscopy examination, there are few studies on the characteristics of this test in AK lesions. The more frequently described characteristic in the initial AK lesion is the red pigmentary pseudo-network pattern ("strawberry vascular pattern"). [23] As the lesion progresses into intraepithelial carcinoma, it develops a pattern called "red starburst", besides presenting diffuse yellow opaque scales. As the lesion gradually transforms into SCC, it increases neovascularization, developing grouped dotted or glomerular vessels, and finally linear and irregular vessels. In addition, the scales gradually become thicker and the presence of ulceration is common. [9] In the present study it was possible to analyze these patterns. The patients with a presence of a red pigmentary pseudo-network pattern and the presence of lamellar scaling showed an improvement in the dermoscopy examination after 120 days' use of medication. The patients with Grade 2 AK, with a "red starburst" pattern did not show such significant improvement in dermoscopy after taking the drug for only 120 days.

The *in vivo* CM emerged as a potential resource for studying epidermal cutaneous alterations, due to the fact that it allows the *in vivo* non-invasive visualization of the superficial layers of the skin, through images produced by different light reflection indices of the cutaneous structures, with a microscop-

ic resolution similar to that of conventional histology. [14,24,25] In this manner, CM can also be used for the diagnosis of AK with a sensitivity and specificity of 98%. [13] It can currently be considered a non-invasive method for the diagnosis and monitoring of AK and field cancerization. [13]

The CM findings of AK lesions include irregular hyperkeratosis with parakeratosis, architectural derangement, and enlargement of the nuclei of epidermal cells with pleomorphism. The architectural derangement pattern does not involve the total thickness of the epidermis in AK cases. The AK images can also have thick refractory bands in the dermis, corresponding to solar elastosis. [14, 15, 26–28]

The major limitation of CM is the limited depth that the wavelength of the device reaches in the skin, preventing the precise visualization of the dermoepidermal junction in hyperkeratotic lesions. Ulrich et al. [26] reported an estimated sensitivity of 97.7% of the examination after having studied 44 cases of AK through CM. Therefore, CM can be a useful diagnostic tool in the management and follow-up of patients with low skin phototypes and a history of intense exposure to the sun, allowing the early diagnosis of AK. [26] Its use was also described in the monitoring of the therapeutic response after photodynamic therapy, demonstrating progressive normalization of the epidermal architecture in the cases treated successfully, paving the way for its use in monitoring and evaluation of the therapeutic response of other treatment modalities for AK. [29] In the present study, the CM examination was proven to be an important complementary diagnostic test for monitoring AK lesions and perilesional areas of field cancerization.

CONCLUSION

The topical application of the cream containing photolyase in liposomes and SPF 100 sunscreen is an innovative strategy. It provides photoprotection and repair of DNA through a single product, leading to the improvement of Grade I AK and of field cancerization, from the clinical, dermoscopic, and CM perspectives.

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Original Articles

Hypertrophic scars and keloids: treatment with surgery and methotrexate injections: a pilot study

Cicatrizes hipertróficas e queloides: tratamento com cirurgia e infiltração de methotrexate – estudo-piloto

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ABSTRACT

Introduction: *Several therapeutic modalities have been used to treat keloids and hypertrophic scars.*
Objective: *Treatment of keloids and hypertrophic scars with excision and intralesional injection of methotrexate.*
Methods: *Therapeutic intervention open study with 11 patients. Laboratory tests and photographs were carried out before, during, and after the treatment. From the seventh day after the excision of the lesions, the suture was injected weekly with methotrexate for six months. The weekly dose was 2.5 mg / 10cm suture, with a maximum dose of 5mg per patient. The evaluation was carried out by the physician and the patient.*
Results: *Six months after the end of the treatment, there was no recurrence of the lesion in five cases, partial recurrence in six cases and an absence of cases with total recurrence. No alterations were observed in the laboratory tests.*
Conclusions: *The maximum weekly dose of 5mg methotrexate for six months used in this pilot study to treat keloids and hypertrophic scars is safe and hinders recurrence. Further studies are needed to complement the present paper.*
Keywords: *keloid; cicatrix, hypertrophic; therapeutics; skin.*

RESUMO

Introdução: Várias modalidades terapêuticas têm sido utilizadas para o tratamentos de queloides e cicatrizes hipertróficas.
Objetivo: Tratamento de queloides e cicatrizes hipertróficas com excisão e injeção intralesional de methotrexate.
Métodos: Neste estudo aberto de intervenção terapêutica 11 pacientes foram tratados. Exames laboratoriais e fotos foram realizados antes, durante e após tratamento. Após a excisão das lesões, a sutura foi infiltrada com methotrexate a partir do sétimo dia, semanalmente, durante seis meses. A dose semanal foi de 2,5mg/10cm de sutura, e a dose máxima de 5mg por indivíduo. A avaliação foi feita pelo médico e pelo paciente.
Resultados: Seis meses após o término do tratamento, não ocorreu recidiva da lesão em cinco casos, houve recidiva parcial em seis casos e nenhuma recidiva total. Não houve alteração dos exames laboratoriais.
Conclusões: A dose máxima semanal de 5mg de methotrexate durante seis meses utilizada neste estudo-piloto para tratamento de queloides e cicatrizes hipertróficas é segura e dificulta a recidiva. São necessários mais estudos para complementar este trabalho.
Palavras-chave: queloide; cicatriz hipertrófica; terapêutica; pele.

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INTRODUCTION

The first description of a treatment for keloids includes a mention of techniques dating back to 1,700 BC in Egypt. In 1806, Alibert used the term *keloid* to describe the lateral growth of tissue in injured skin. Such lesions result from the proliferation of dermal tissue after an injury of the skin [1] that extends beyond the borders of the original lesion – unlike hypertrophic scars, which are restricted to the limits of the trauma. [2] Keloids have a tendency to recur and generally do not spontaneously regress. [2-4]

The proliferated tissue is the result of an increase of collagen and glycosaminoglycans.[1] Its pathophysiology is poorly understood, and in addition to genetic and immunological factors.[3-5] includes alterations in growth factors, collagen turnover, and tension in the affected area.

The tissue repair occurs in four stages. The first phase is the *hemostasis*. Immediately after the trauma, vasoconstriction occurs and the formation of the primary hemostatic plug takes place with platelets and the activation of the coagulation cascade. The second is the *inflammatory phase*, which lasts from the 1st to the 3rd day, when there is an increase of vascular permeability, stimulation of RNA, and the formation of collagen and endothelial changes occur. Erythrocytes, platelets, and polymorphonuclear leukocytes migrate to the lesion, promoting phagocytosis and degradation of collagen. The third is the *proliferative phase*, in which the production of collagen occurs. During this phase, which lasts from the 3rd to 24th day, any deficiency in the precursor elements of the healing process leads to changes in the formation of granulation tissue and to fibroblasts and neovascular proliferation. In the fourth phase, the *remodeling phase*, which can last from months to years, the collagen undergoes remodeling and forms a mature scar.[6]

The incidence of keloid formation affects around 4-16% of the population, includes all population groups, and while it is rare in newborns and the elderly, an increase in occurrence is seen in individuals between 10 and 20 years old, and in people of Asian and African descent.[7]

The management of keloids can be difficult and frustrating. [5,7,8] Several therapeutic modalities have been indicated, including topical and intralesional corticosteroids, cryotherapy, surgery, laser procedures, silicone, radiotherapy, and other options on an experimental basis, such as: interferon, 5-fluorouracil, retinoids, verapamil, imiquimod, bleomycin, tamoxifen, tacrolimus, botulinum toxin and a promising therapy using transforming growth factor TGF-beta 3 and human recombinant interleukin-10, directed against the growth of collagen.

There is a trend towards individualization of treatment depending on the distribution, size, thickness, consistency of lesions, and presence of inflammation. [5,9] A combination of therapies seems to be the best option, [9] and, according to Leventhal et al. in a meta-analysis of multiple treatments, there was no statistically significant difference between them. [10]

One of the main rules for the treatment of keloids is prevention, which can be carried out with the use of compression therapy, reducing the tension in scarring, thus avoiding unnecessary procedures in patients predisposed to scarring aberrations.[1,3]

Excisional surgery used as an isolated therapy has a recurrence rate of 45-100%, and is generally used in combination with other modalities, such as radiation therapy, interferon, corticosteroids, and imiquimod.[1]

There are few reports in the literature on the use of methotrexate as an alternative therapy for keloids. In a study by Muzaffar et al. in 2004,[11] methotrexate was employed systemically in low doses for a short time after surgery for syndactyly. Also, a report by Onwukwe in 1980[12] discusses the systemic use of methotrexate associated with surgery.

The action of methotrexate takes place through competitive inhibition of the enzyme dihydrofolate reductase, which is responsible for the conversion of folic acid into tetrahydrofolate, with this cofactor being necessary for the transfer of carbon from many metabolic reactions, including the synthesis of purines bases and of thymidylate synthase. Cell proliferation is affected because it reduces the synthesis of thymidylate synthase and hence, of the nucleotide precursors that comprise DNA and RNA, affecting repair and replication of nucleic acids. Tissues with higher metabolic activity and increased cell growth are the most affected, which explains some pharmacological, secondary, and toxic effects. [11,12]

To calculate the weekly dose, the authors used the fundamentals of treatment for psoriasis, in which the minimum dose of 2.5-5.0mg is used for maintenance. [13]

OBJECTIVE

To treat keloids with excision and intralesional injection of methotrexate.

METHODS

An open study of therapeutic intervention was carried out with 15 selected patients with keloids or hypertrophic scars (5 men and 10 women), who were treated at the ambulatory of the dermatology department of the Universidade Santo Amaro (Unisa), in São Paulo, Brazil. Four men and 6 women had keloids, and 1 man and 4 women bore hypertrophic scars. Eleven patients completed the study (9 women and 2 men). The body sites treated were: shoulder (Figure 1), periauricular (Figure 2), cervical, pre-sternal, abdominal, infraumbilical, suprapubic abdominal (Figure 3), lateral dorsal, and lumbar regions, and the popliteal fossa. The study was conducted according to standards established by the institution's Ethics Committee.

The following examinations were performed in advance: blood count, AST, ALT, total bilirubin and fractions, urea, creatinine, CEA, Papanicolau test (in women), PSA (in men) and chest radiography. The examinations were carried out before the treatment, and 3 and 6 months after.

The lesion was completely excised in ellipse, with subcutaneous stitches combined with a continuous suture of the skin, having been removed after 4 weeks. The suture line was injected intralesionally with methotrexate from the 7th day after surgery, weekly for 6 months. The weekly dose was 2.5mg dilut-

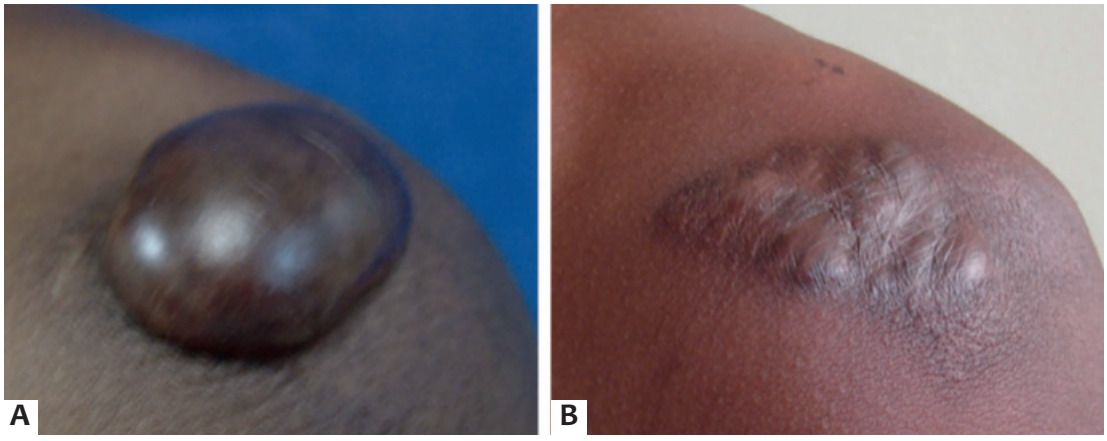

Figure 1: A. Pre-surgery in keloid on the shoulder; **B.** Moderate recurrence 6 months after the end of methotrexate applications.

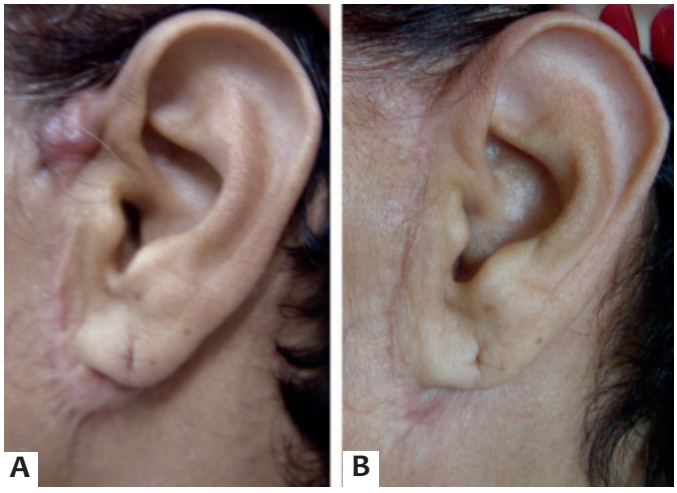

Figure 2: A. Pre-surgery in hypertrophic scar resulting from rhytidectomy; B. Six months after the end of the methotrexate applications

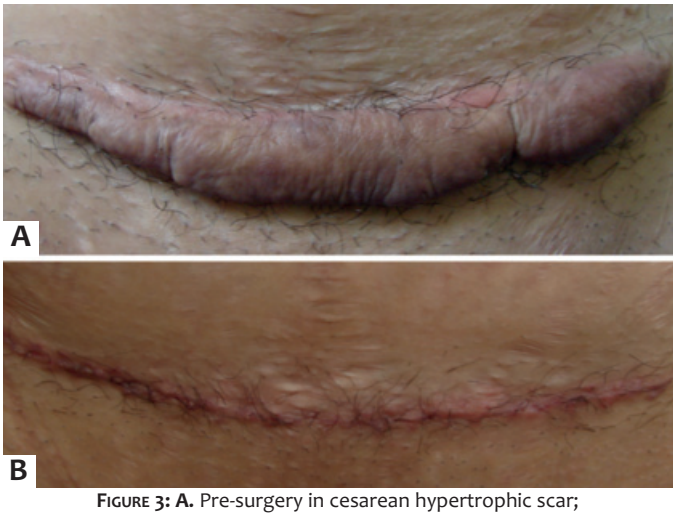

Figure 3: A. Pre-surgery in cesarean hypertrophic scar; B. Six months after the end of the methotrexate applications

ed in saline, in sutures of up to 10.0cm. No application with doses greater than 5.0mg/20cm was carried out. Prior to application, the skin was injected with 2% lidocaine to reduce the burning sensation caused by the drug.

In one of the cases, the authors have chosen 4 keloid lesions of similar size in the same area to undergo surgical exeresis, with suturing of three lesions, leaving the fourth as a control (no surgery and injections). Of the 3 excised keloids, one received methotrexate, the other received intralesional corticosteroids (5.0mg triamcinolone), while the remaining was left without associated injections.

The analysis was performed with photographs being taken before, during, and after 6 and 12 months (Figure 4). Some cases returned up to 24 months after the completion of the treatment. The lesion was examined by the physician and the patient regarding the final aesthetic result.

RESULTS

Of the 15 selected cases, 4 patients withdrew from the study (1 woman and 3 men). Among the 11 treated cases there was a partial recurrence in 6, and no recurrence in 5 (2 keloids and 3 hypertrophic scars). None had a full recurrence. Partial recurrences were classified as minimal and moderate. The minimal recurrences took place in 2 cases (1 keloid and 1 hypertrophic scar), and the moderate recurrences totaled 4 (3 keloids and 1 hypertrophic scar –1 shoulder, 1 lateral dorsal, 2 pre-sternal).

Regarding the final aesthetical results, all cases showed an enlarged suture, even when leaving the external stitches for 4 weeks. An unsightly hyperpigmentation in the infiltrated area was observed in all cases, showing little whitening over six months of control.

Regarding the case that had 4 lesions treated with 3 different methods and 1 control (a - surgery plus methotrexate injection, b - surgery plus corticosteroids injection, c -isolated surgery, and d -no surgery or injections), the results were: a– stable progress without recurrence, but with widening and hyperpigmentation of the scar six months after the last methotrexate session; b - hypochromia and scar recurrence six months after the last session (Figure 5); c - keloid recurrence soon after surgery and coursing without recurrence up to six months after the

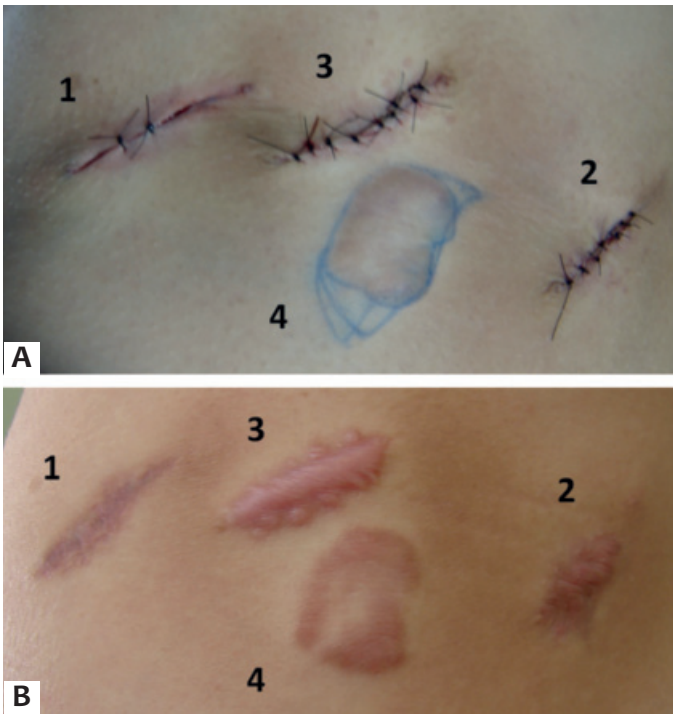

Figure 4: A and B. Immediate post-surgery: Number 1 --> infiltration with methotrexate, Number 2 --> infiltration with triamcinolone, Number 3 --> surgery without injections. Number 4 (control) --> no surgery or injections.

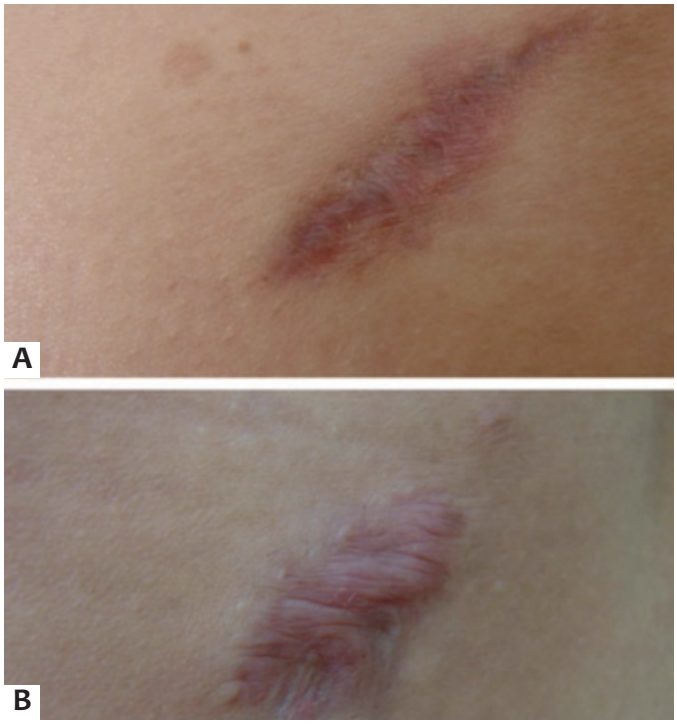

Figure 5: A. Comparison 6 months after the procedure, where methotrexate injections were associated with the absence of recurrence (figure above); B. Triamcinolone was associated with a moderate recurrence at 2two months after the end of the treatment (figure above)

procedure; d – unchanged progression.

None of the patients had alterations in the laboratory tests.

DISCUSSION

The present study is aimed at improving the aesthetics of hypertrophic scars and keloids. Occlusive silicones, injections of corticosteroids, cryosurgery, surgical excisions associated with beta therapy; and applications of CO2, Nd:YAG and dye lasers are the most common treatments in the daily practice to prevent aberrant scars, more or less effectively. [1]

The present study used methotrexate injections for 6 months after the surgical excision of the lesions with a six-month follow-up after the end of the injections.

A recent study by Smith[14] reports that there is still little information available about the natural history and prognosis of keloids formation. In its sample, the average number of years to achieve resolution of the keloids with treatment was. [11,4]

The long period of applications in the present study hampered patient compliance, especially among men. The removal of stitches four weeks after surgery was due to the risk of dehiscence, even though there was widening of the scar. The dose used is 2.5mg (injectable vials of methotrexate have 50mg/2ml), i.e. 0.1ml is diluted in 0.9ml saline.

This dose is enough for scars without tension and up to 10.0cm in length. Due to the fact that the injection is very painful, previous injection with 2% lidocaine with epinephrine is recommended along the surgical scar. In larger lesions or in areas of tension, a maximum dose of 5.0mg per week is used, with no laboratory abnormalities being observed during and after the application of methotrexate, demonstrating safety for that dose. The authors also noted that the location of the keloid is important. In the pre-sternal region and in areas of tensioning, such as in the shoulder and in lateral dorsal region, there was moderate recurrence. Therefore, the dose of 2.5mg/10cm scar may be insufficient. There was 1 case in the sternal region where a partial recurrence occurred before the end of the sessions. Due to the small number of cases, it is not possible to state whether there is any difference in outcomes between genders and between the two types of lesions approached. Leventhal [10] led a meta-analysis looking for the best treatment for keloids and hypertrophic scars, in a review of 70 studies from the literature available up to October 2005, concluding that 60% of cases result in improvement with treatment and that there is no statistically significant difference between them. It also concluded that most treatments result in little probability of improvement and even patients who go through long periods of controlled clinical symptoms would be far from cured.

In the case where the progression of keloids treated with steroids was compared with controls, the authors noted that methotrexate presented better stability of the scar as compared

with those treated with corticosteroids after the end of the applications. The scar injected with corticosteroids developed with mild atrophy and hypochromia until the last session, however the recurrence began 2 months after the end of the treatment, completing at 6 months. This case was followed up with for 2 years after the completion of the treatment, with the results remaining unchanged. Other resources can be employed using comparative treatments with a greater number of cases.

CONCLUSION

The application of 2.5mg methotrexate for every 10cm of scar after surgical excision of keloids or hypertrophic scars in 11 treated cases, resulted in an absence of recurrence in 5 cases; partial recurrence in 6 (minimal in 2 and moderate in 4 cases). No full recurrence was observed. The cases were followed up with for 6 months after the end of the applications. The maximum dose of 5.0mg was proved to be safe up until 6 months after the end of the treatment, with no alterations in laboratory tests. Further studies are necessary to complement this analysis.

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Ácido chiquímico para esfoliação cutânea

Shikimic acid: a potential active principle for skin exfoliation

RESUMO

Introdução: Ácidos orgânicos são amplamente utilizados na área dermocosmética, pois apresentam efeitos relacionados à esfoliação e à renovação celular. Deles, pode-se citar o derivado do anis-estrelado, conhecido como ácido chiquímico.

Objetivos: Avaliar a atividade antioxidante do ácido chiquímico e a eficácia clínica de preparações dermocosméticas acrescidas de 3% desse ativo.

Métodos: A atividade antioxidante foi avaliada por um método in vitro. Sequencialmente, foram elaboradas preparações de gel, gel creme e solução a 3% do ácido, as quais foram submetidas a estudos preliminares de estabilidade e análise sensorial. O estudo clínico foi realizado por técnicas não invasivas de biofísica e imagem da pele.

Resultados: O ácido chiquímico apresentou potencial antioxidante. Todas as preparações foram consideradas estáveis, e a adição do ácido chiquímico melhorou o sensorial do gel e do gel creme. No estudo clínico, o gel e a solução mostraram alterações significativas no microrrelevo e nos parâmetros relacionados à esfoliação da pele. Entretanto, a formulação gel creme não proporcionou tal efeito, mostrando a importância do veículo para a eficácia de cosméticos.

Conclusões: O ácido chiquímico pode ser considerado potencial ativo para aplicação em formulações dermocosméticas para esfoliação e melhora do microrrelevo da pele.

Palavras-chave: abrasão química; antioxidantes; cosméticos; eficácia; ácido chiquímico.

ABSTRACT

Introduction: *Organic acids are widely used in cosmeceutic-based skincare due to their exfoliation and cell renewal related effects. A star anise derivative known as shikimic acid is an example.*

Objectives: *To evaluate the antioxidant activity of shikimic acid and the clinical efficacy of dermocosmetic preparations containing 3% of this active principle.*

Methods: *The antioxidant activity was assessed through an in vitro method. Formulations of gel, gel cream, and a 3% solution of the acid were sequentially dispensed and preliminarily subjected to stability and sensory analysis. The clinical study was performed through non-invasive biophysical and skin imaging techniques.*

Results: *The shikimic acid showed antioxidant potential. All formulations were found to be stable and the addition of shikimic acid improved the sensory analysis of the gel and gel cream. In the clinical assessment, the gel and the solution showed significant alterations in microrelief and in the parameters linked to skin exfoliation. However, the gel cream formulation did not show such an effect, suggesting the importance of the vehicle for the effectiveness of the cosmeceutics.*

Conclusions: *Shikimic acid can be considered an active principle with good potential for application in dermocosmetic formulations aimed at exfoliation and improvement of the skin's microrelief.*

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

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INTRODUCTION

The dermo-cosmetics industry has turned its focus to the use of plant-based compounds, resulting in a significant level of acceptance by consumers, who have taken into account the pleasant fragrances, beneficial properties, and the understanding that these formulations are safer than their synthetic derivatives-based analogues.[1,2]

Among natural compounds, organic acids – which are commonly found in many types of fruits and have been widely used for many decades – stand out. Their effects on the skin are mainly linked to cellular exfoliation and renewal, and are thus indicated for the treatment of photoaging, acne, and cutaneous hyperpigmentation.[3,4]

As chemical exfoliating agents, organic acids have been employed over time for the treatment of various skin diseases, as well as for aesthetic purposes. The depth in the skin's layers at which the action of acids occurs may result in cell renewal, skin whitening, collagen synthesis, and epidermal thickening, among other effects.

The choice of the acid depends on the desired results, i.e., it depends on the depth of the action required.[5,6]

The chemical exfoliation process based on an organic acid can result from the reduction of the cohesion force between the cells of the stratum corneum, promoting desquamation and, therefore, a more flexible and compact layer.[7] In addition to these benefits, deodorant, antimicrobial, and antioxidant actions are also among the properties of an organic acid obtained from star anise (*Illicium verum*): the shikimic acid. This active principle is a multifunctional component capable of protecting the skin and helping it maintain its essential functionality. Recent studies report that shikimic acid can inhibit the activity of the lipase enzyme, blocking the production of fatty acids, thus also acting as an odor control agent. Moreover, it has an inhibitory effect on the microbial growth of a causative agent of seborrheic dermatitis of the scalp.[8,9]

When developing cosmetic formulations with organic acids, the concentration of the acid, the pH of the formulation, the amount of free acid present, the acid type, the vehicle, the duration of exposure, and the consumer's skin type among other factors, should be taken into account.[4] Interference in these conditions can lead to the ineffectiveness of the final product.

Next to development, a primary stability assessment is crucial for predicting the behavior of the active principle – as well as that of the formulation –as compared to the actual use and storage conditions. To this end, the organoleptic characteristics, pH behavior, and phase separation are analyzed.

In addition, *in vitro* methods for assessing the antioxidant action have been widely used as they provide valuable information on the potential of the substance to be used in the cosmetic product. Among them, the HRP-luminol-H2O2 based chemiluminescence method has currently been one of the most used because it is fast, reliable, and effective in determining the ability of some antioxidants to neutralize free radicals.[10]

Regarding the antioxidant effects of polyphenols, the characterization of shikimic acid's antioxidant activity is very important since it has a chemical structure capable of neutralizing free radicals and becoming stable, avoiding uncontrolled reactions with the skin's biomolecules.

Before having its clinical efficacy checked, the finished cosmetic product should be assessed for its sensory characteristics, which can decisively influence the consumers' choice for the product, and cause the user to change the form of application, frequency of use, and amount of product applied, depending on the greater or lesser acceptance of its sensory properties, which influences its effectiveness.[11]

Whereas the sensory evaluation – as well as clinical observations –are strictly qualitative, the quantitative assessment of the formulation's efficacy under actual conditions of use (i.e. in human skin through biophysical and image analysis techniques, which have been the choice in studies of safety and efficacy and have been recommended by regulatory agencies such as ANVISA, FDA and Colipa), is also crucial.

The biophysical and imaging techniques for analyzing the skin comprise the study of some variables such as the water content of the stratum corneum, transepidermal water loss (TEWL), and the skin's microrelief, among others.[12]

The measurement of the water content of the stratum corneum has been largely carried out using the capacitance method, with the assistance of a corneometer device.[12]

The *tewameter* measures the TEWL by analyzing the water pressure gradient adjacent to the skin's surface. Thus, the lower the gauged value, the better the skin barrier's function.[12]

For investigating the skin's surface Visioscan® VC 98 equipment (Courage & Kazaka Electronic GmbH, Cologne, Germany) can be used. This device allows qualitative and quantitative assessment of the skin's surface under physiological conditions through the optical profilometry technique.[13]

Finally, based on the properties of shikimic acid described above, it was introduced as an active ingredient for use in cosmetic formulations, which lent it great importance in studies aimed at proving the proposed benefits.

OBJECTIVES

The present study was aimed at evaluating the *in vitro* antioxidant activity of star anise derived shikimic acid, as well as the development and the clinical efficacy of dermo-cosmetic preparations containing this natural origin component.

METHODS

Research and development of cosmetic preparations

The pH stability, the concentration, sensory characteristics, and the interaction between the raw materials used were considered in the preparation of the formulations.

Three vehicles were developed: a gel cream, a gel, and an aqueous solution, to which shikimic acid was added (Table 1).

The developed gel, gel cream, and solution underwent centrifugation-assisted preliminary stability studies and pH

determination 24 hours after preparation, as well as weekly assessments (for 30 days) of their organoleptic properties, being kept in the environment and subjected to thermal stress (37°C and 45°C) in thermostated greenhouses (Eletrolab, model 111FC), with controlled humidity and photoperiod.

Preliminary stability studies

For the centrifugation test, a 3 g sample of each was centrifuged in Falcon plastic tubes for three 30-minute cycles at 3,000 rpm in an Excelsa Baby II centrifuge (model R-206, 0.0440 potency, Fanem). The measurement of pH was carried out with a DM 20 pH meter (Digimed), using aqueous solutions of the formulations at a concentration of 10%. [14]

Changes in color, phase separation and homogeneity were considered in the organoleptic evaluation.

Sensory evaluation

This evaluation was conducted as one of the stages of the development of the studied gel and gel cream formulations; 12 female volunteers applied a standardized amount (50ml) of the formulations in different regions of the lower middle portion of the forearms.

The analysis was carried out by comparing the formulations of the original vehicles with analogues, which were added to the active principle studied.

Finally, the volunteers received a sensory evaluation questionnaire and were asked to assign grades according to the quality parameters provided, [15] as shown in Chart 1.

The sensory evaluation was carried out in two steps, with the results being presented in a box type plot graph.

This graph type has a central box representing 50% of the core values of the scores assigned by the volunteers; a horizontal line inside the box represents the median of the scores, while the maximum and minimum scores are represented by lines running from the central box's upper and lower ends, respectively.

Antioxidant activity evaluation

The luminol-dependent chemiluminescence method was chosen to assess the studied compound's antioxidant potential. The method's principle is based on the detection of photons emitted by the luminol when it is oxidized by hydrogen peroxide in the presence of a catalyst, the HRP enzyme (horseradish peroxidase). As a result, an intermediate reactive is formed (free radical), and when this agitated product returns to the fundamental state it emits photons, which are captured by the device. [16]

Therefore, the stronger the signal captured by the device, the greater the production of free radicals. When an antioxidant substance is added, a partial neutralization of the free radicals takes place, leading to a lower emission of photons and hence, a weaker signal is detected by the device. [10]

Various dilutions of the active principle were prepared in a 0.1M (pH 7.4) phosphate buffer. Subsequently, 10µl aliquots of these solutions and of a control solution containing only the buffer, were added with 400µl of 0.1M (pH 7.4) phosphate buffer, 100µl H2O2, and 10µl luminol solution (5mg/ml). The reaction was then initiated by the addition of 500µl HRP solution (0.2UI/ml), with the chemiluminescence being quantified using a luminometer (Autolumat, LB953, EG&G Berthold). [10,17,18]

Three measurements were carried out for each sample and the results were expressed as a geometric area below the curve (AUC), which corresponds to the total amount of free radicals produced in 10 minutes at 30°C. In this manner, it was possible to calculate the inhibition percentage for each concentration of the compound according to the following equation:

Inhibition rate (%) = 100 - (100 x AUC_{sample} / $AUC_{control}$) where:

AUC_{sample}= area below the sample's curve

$AUC_{control}$= area under the control's curve [19]

Clinical efficacy evaluation

Case series

This phase of the study was carried out after approval by the Research Involving Humans Ethics Committee of the Faculdade de Ciências Farmacêuticas de Ribeirão Preto (Universidade de São Paulo – USP), Ribeirão Preto, São Paulo, Brazil, under the protocol N. 143 – CEP/FCFRP.

The volunteers were then informed and instructed about the objectives and methods of the research, having signed a free and informed term of consent, prepared according to the Declaration of Helsinki and approved by the Research Ethics Committee.

Table 1: Composition of the cosmetic preparations

Raw materials (% per part)	F1	F2	F3
Modified starch polymer	3	7	-
Non-ionic self-emulsifying cetostearyl alcohol wax and cetostearyl alcohol 20 EO	3	-	-
Methyldibromo glutaronitrile	0.2	0.2	0.2
Propylene glycol	2.5	2.5	-
Glycerin	2,5	2.5	-
Amino nitropropanol 95% (10%)	1	-	-
Water qs	100	100	100
Shikimic acid	3	3	3

Chart 1: Sensory evaluation form

Raw materials (% per part)	F1	F2	F3
Modified starch polymer	3	7	-
Non-ionic self-emulsifying cetostearyl alcohol wax and cetostearyl alcohol 20 EO	3	-	-
Methyldibromo glutaronitrile	0,2	0,2	0,2
Propylene glycol	2,5	2,5	-
Glycerin	2,5	2,5	-
Amino nitropropanol 95% (10%)	1	-	-
Water qs	100	100	100
Shikimic acid	3	3	3

Ten volunteers were selected (skin phototypes II and III, aged between 20 and 35 years). The following exclusion criteria were considered in this selection: pregnancy or lactation, previous history of adverse reactions with the use of cosmetic products, use of drugs likely to produce abnormal cutaneous response, localized or generalized skin conditions, and excessive hair growth in the areas of study.

Analysis of clinical efficacy through biophysical and skin imaging analysis techniques

Prior to the measurements, the volunteers were acclimatized for 10 minutes at room temperature (20°C to 22°C) and at a controlled relative humidity (45% to 55%) level.

The cosmetic preparations underwent the clinical study with the aim of comparing the used vehicles regarding the effectiveness of the shikimic acid.

The solutions, along with the other formulations considered stable in the preliminary stability studies, underwent the clinical study with a view to having their effectiveness determined.

The clinical study was carried out in two steps: firstly, the F1 preparation was evaluated, with analysis of the F2 and F3 preparations. Ten selected volunteers had the lower middle region of their forearms divided into 2 squares, each with 25cm^2. These regions were randomized and one of them was designated as a control-region. In the second step, the lower middle region of the forearm was divided into 3 squares, each with 25cm^2. These regions were randomized and one was designated as a control-region. Once acclimatized, the volunteers underwent baseline measurements for the assessment of the skin's microrelief, the water content of the stratum corneum, and the TEWL.

The application of the gel cream (F1) and gel (F2) was made with the help of an automatic pipette for viscous samples, while the application of the solution (F3) was carried out with an automatic pipette for fluid samples. Similar volumes of each formulation (50 ml or 2ml/cm^2) were applied in the delimited regions.

Two hours after the application of the cosmetic preparations, the volunteers returned and underwent another round of acclimatization, followed by a second round of measurements to evaluate the immediate effects being performed.

Determination of the water content of the stratum corneum

The water content measurements of the stratum corneum were taken using a CM 825 Corneometer device (Courage & Kazaka Electronic GmbH, Cologne, Germany), which indirectly measured the hydration level of the stratum corneum by gauging the skin's electrical capacitance.

The results were quantified in arbitrary units (AU) –the device determines that 1AU corresponds to a range of 0.2mg to 0.9mg of water per gram of stratum corneum. [12,20]

The determination of the TEWL aimed at evaluating the barrier function of the skin was carried out with the TM 210 Tewameter device (Courage & Kazaka, Electronic GmbH, Cologne, Germany). The device measures the evaporation of water from the skin's surface, based on the Fick's laws of diffusion. [20,21]

Determination of skin microrelief

The Visioscan® VC 98 device was used for the assessment of the skin's surface, providing a qualitative and quantitative assessment of the cutaneous surface under physiological conditions through the optical profilometry technique.

The software provides a histogram showing the distribution of different hues of gray, quantifying the dark spots – which correspond to the roughness –and light spots – which correspond to plateaus in the skin's microrelief. The parameters related to the skin's surface were evaluated through this method (Chart 2). [13]

The experimental data obtained in the evaluation of clinical efficacy were subjected to statistical analysis, in which preliminary tests of distribution normality and homogeneity of variances involved in the experiment were performed.

Statistical analysis

The above statistical tests were performed using the GMC statistical software, developed by Maia Campos (1999), [22] and the Minitab statistical software. [16]

Chart 2: Skin surface related parameters measured with the Visioscan® VC 98 device.

Parameters	Definitions
SeR Aspereza	Roughness
SeW Rugas	Wrinkles
SeSM Suavidade	Smoothness
SeSC Descamação	Scaling
RT Rugosidade	Rugosity

RESULTS

Development of formulations

Preliminary stability analysis

The cosmetic preparations remained stable during the 30 days of the study

Sensory evaluation

The sensory evaluation results for formulation F1 as compared to its vehicle are in Graph 1. The results for F2 and its respective vehicle are in Graph 2.

Antioxidant activity evaluation

Graph 3 shows the results of the antioxidant activity evaluation through the percentage of inhibition of free radicals formed as a function of the concentration of the shikimic acid.

Clinical efficacy evaluation

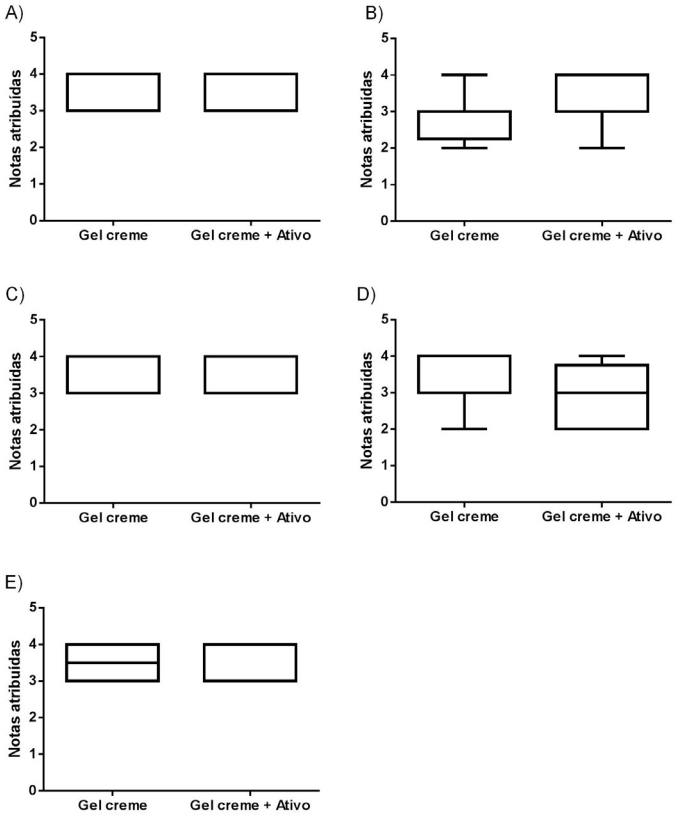
In this clinical study, measurements of the water content of the stratum corneum (Graph 4), TEWL (Graph 5), and cutaneous microrelief (Graph 6) were performed at baseline and 2 hours after the single application of the studied formulations in the volunteers' forearms. The values obtained were subjected to statistical analysis.

Statistical analysis of the results obtained

The experimental results of the assessment of the immediate effects of the preparation F1 after a single application in the forearms consisted of 40 numeric values corresponding to the factors *variation*, *time,* and *studied formulation*. These values are the result of the crossing of two areas of application of the formulation F1 and the control, at two different time points (before and 2 hours after the application of the formulations) x 10 repetitions, yielding the factorial product 2 x 2 x 10 = 40.

The experimental results of the assessment of preparations F2 and F3's immediate effects after a single application in the forearms consisted of 60 numeric values, corresponding to the factors *variation*, *time,* and *studied formulations*. These values are the result of the intersection of three areas of application of the preparations that are the object of study (F2 and F3) and the control at two different times (before and two hours after application of the formulations) x 10 reps, giving the product 3 factorial x 2 x 10 = 60.

The preliminary tests were performed in order to verify the normality and homogeneity of the sample's distribution, allowing for the decision as to whether to use parametric or nonparametric tests.



Graph 1: Sensory evaluation. Gel cream (**F1**) combined with or not (vehicle) with shikimic acid (active principle), regarding the parameters: **A)** feeling to the touch; **B)** spreadability; **C)** hydration; **D)** smoothness; **E)** skin feel after 5 minutes

The results of these preliminary tests indicated that the tested samples were homogeneous and the distribution of frequencies was close to that of the mathematically normal curve.

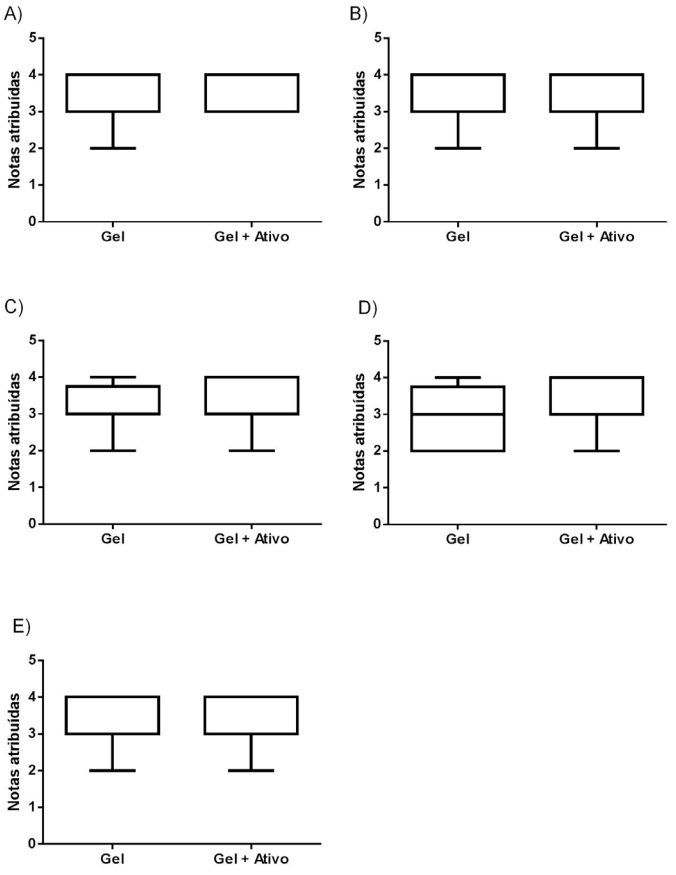
As a result, the parametric test that best fitted the experimental model was the variance analysis, followed by the Tukey's test for comparison of mean values.

DISCUSSION

Based on the preliminary stability analysis, the cosmetic preparations were evaluated. It was possible to verify that during the 30-day storage period, it remained stable. Regarding the visual assessment, it was possible to verify the absence of phase separation and changes in color and consistency.

All formulations remained at the initial pH range and when subjected to physical centrifugation stress, they remained homogeneous – i.e. without separation of phases.

According to the described protocol, formulations F1 and F2 underwent sensory evaluation. Initially, formulation F1 (gel cream) was evaluated as compared to its vehicle. As a result, both formulations showed adequate sensory characteristics, with the formulation containing the active principle deemed better in the following parameters: *sensation to the touch*, with varying



Graph 2: Sensory evaluation. Gel cream (**F1**) combined with or not (vehicle) with shikimic acid (active principle), regarding the parameters: **A)** feeling to the touch; **B)** spreadability; **C)** hydration; **D)** smoothness; E) skin feel after 5 minutes

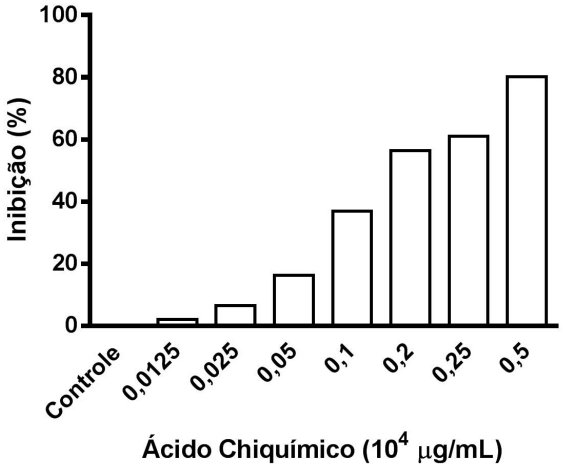
ratings ranging from 3 to 4; *spreadability*, with ratings from 2 to 4; *skin feel five minutes after application*, with ratings ranging from 3 to 4.

The two formulations were considered similar regarding the parameter *hydration capacity*, with ratings mainly falling between 3 and 4. For the parameter *smoothness*, the vehicle obtained more homogeneous ratings, which mainly fell between 3 and 4, with a median of 3.

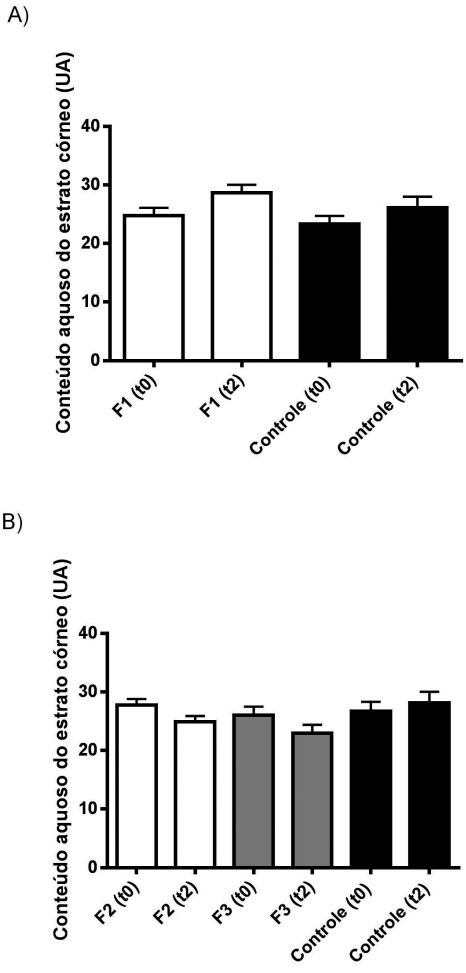
The second step occurred with the evaluation of formulation F2 (gel), and its respective vehicle. As a result, the formulations were deemed equal regarding the parameters: *spreadability* and *skin feel five minutes after application*, with ratings ranging from 2 to 4, with a median of 3.

The addition of the active principle earned formulation F2 a better final score than that of its vehicle regarding the other parameters: *sensation to the touch*, *hydration capacity,* and *smoothness*, with ratings falling mainly between 3 and 4.

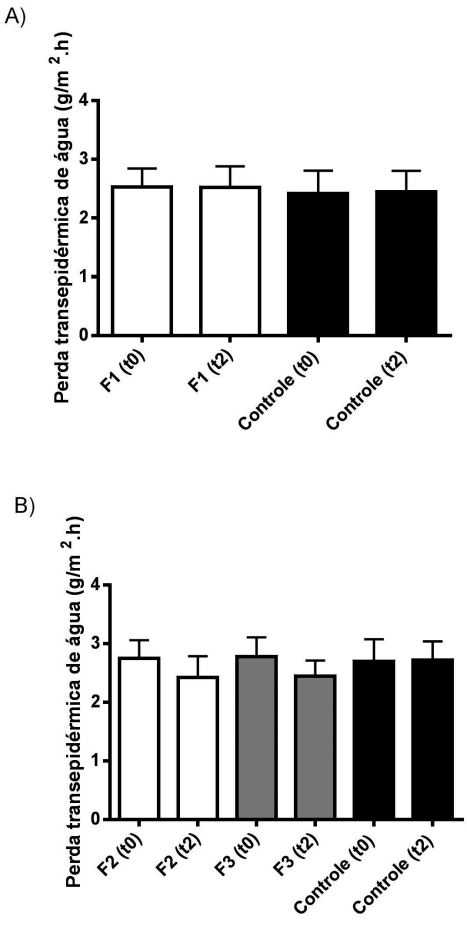
Analyzing the set of outcomes, it was possible to state that the formulation F1 (gel cream plus active principle) was deemed the best regarding the sensory parameters analyzed in the present study.



Graph 3: Inhibition of free radicals by shikimic acid through dependent HRP-luminol-H2O2 chemiluminescence trial.



Graph 4: A and B) Water content of stratum corneum with the application of preparations **F1** (cream gel), **F2** (gel), and **F3** (solution), at the baseline (t0) and after 2 hours (t2).



Graph 5: A and B) TEWL with the application of preparations **F1** (cream gel), **F2** (gel) and **F3** (solution), at the baseline (**t0**) and after 2 hours (**t2**).

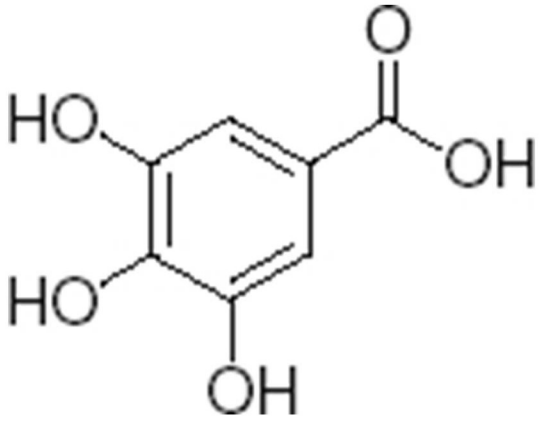


Figura 1: Ácido chiquímico

Once the sensory evaluation was complete, the active principle underwent evaluation for its antioxidant activity. With those results, it was possible to draw a graph for the inhibition percentage of free radicals formed due to the shikimic acid concentration.

The control was prepared in the absence of the active principle, thus representing 100% of the production of free radicals. It was possible to observe that an increase in the concentration of the active principle led to a reduction in the production of photons (i.e. increased neutralization of free radicals produced).

This inhibition of the radicals produced takes place as a result of the chemical structure of shikimic acid, which has a polyphenolic ring (Figure 1). According to past studies, the components that are mainly responsible for the antioxidant activity are the polyphenols. [18,22] This acid can thus stabilize the free radicals by donating electrons, therefore providing stability via an internal rearrangement. As a result, the stabilized free radicals become less reactive to biomolecules –the reaction of these free radicals with the skin's biomolecules (oxidative stress) contributes to aging.

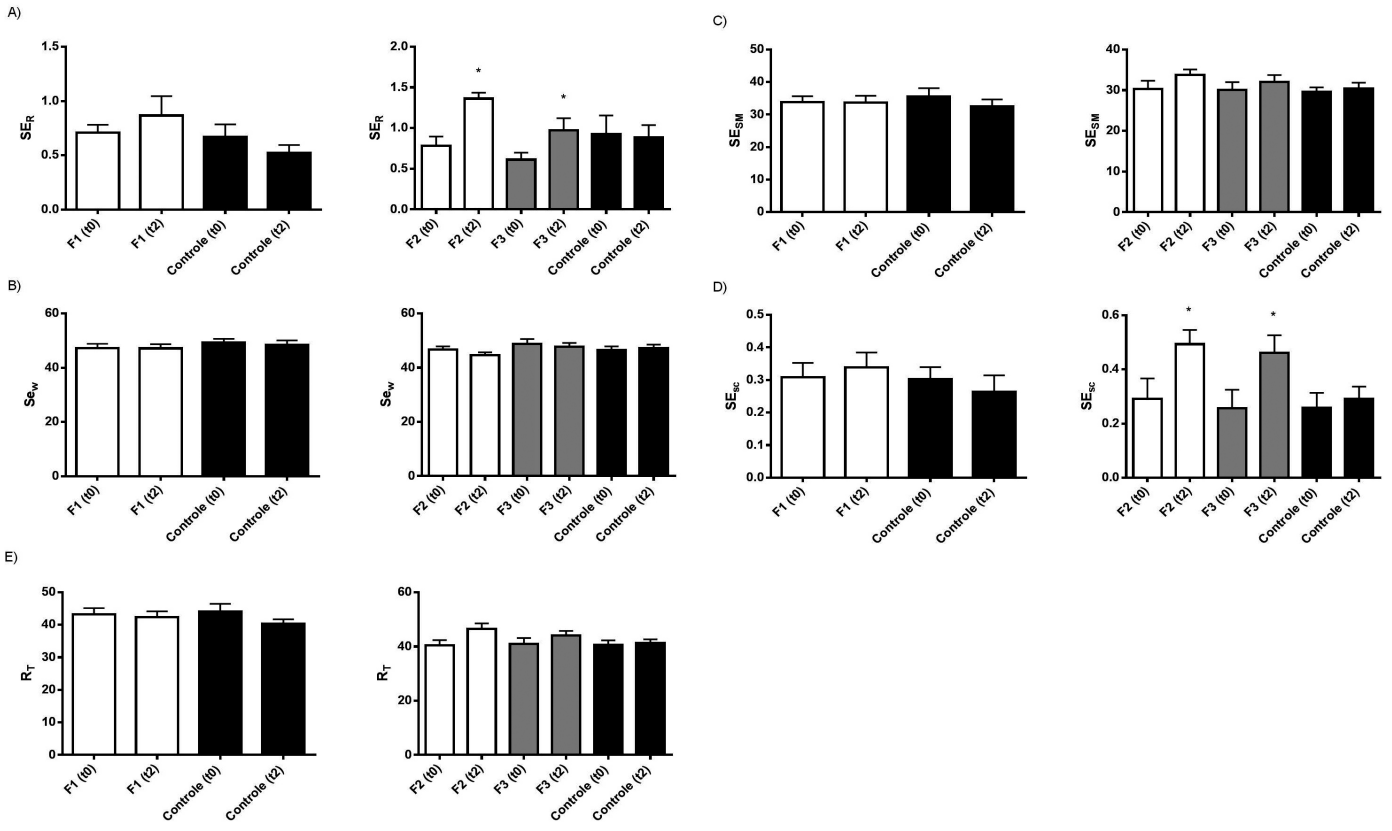
The chosen *in vitro* trial method HRP-luminol-H2O2 dependent chemiluminescence) has been widely used because it is highly sensitive, practical, and reproducible, thus allowing the analysis of many samples in a short period of time. [23]

Finally, the preparations underwent evaluation of their clinical efficacy. Based on the analysis of the present study's graphs, it was possible to verify that the preparations of gel cream (F1), gel (F2), and solution (F3), when combined with the studied compound did not result in statistically significant differences ($p>0.05$) for the water content of the stratum corneum (Graph 4) and TEWL (Graph 5), when compared with the baseline and control values. This outcome is very important in exfoliating products, for it can demonstrate that its mechanism of exfoliating action does not cause negative effects on the skin's hydration and barrier function (i.e.it does not affect the skin barrier, as some peeling agents do). [7,24]

For instance, an important feature for therapeutic applications in skin disorders such as atopic dermatitis is that they not disrupt the skin barrier, as the skin barrier's structure is chronically affected with these disorders. [7,24-26]

Regarding the microrelief of the skin, preparation F1 did not yield statistically significant differences ($p>0.05$). On the other hand, preparations F2 and F3 led to an increase in the SE_R parameter 2 hours after the application of the formulation, with a statistical significance of ($p <0.05$). However, this effect was more pronounced for preparation F2. The SE_{SC} parameter also increased 2 hours after the application of the two preparations, with a statistical significance of ($p <0.05$). The increase in the values of the roughness related parameter (SE_{SC}) is consistent with the properties of shikimic acid, since it can be related with the onset of the exfoliation process. In the long run, continuous treatment with shikimic acid could result in the cell renewal process, which makes it of interest as an application in dermo-cosmetic preparations with anti-aging properties.

According to the results obtained, the vehicle is of crucial importance in the development of a dermo-cosmetic prod-



Graph 6: Skin's microrelief with the application of preparations **F1** (cream gel), **F2** (gel), and **F3** (solution), at the baseline **(t0)** and after 2 hours (t2). Parameters: roughness **(A)**, texture **(B)**, smoothness **(C)**, scaling **(D)**, and rugosity **(E)**.

uct [27] since improper selection of the preparation's components may be related to the absence of significant outcomes regarding the expected effectiveness of the final product, rather than that of the active principle used. The vehicle should allow the incorporation of the active principle without destabilizing the formula, while being simultaneously capable of releasing it when applied on the skin in order for it to achieve its potential effect. In this manner, for the active principle in question, the best vehicles used in the present study were the gel and the solution, which probably allowed the release of the active principle and strengthened the effects in the improvement of the skin's microrelief.

CONCLUSION

Under the present study's experimental conditions, it was possible to conclude that:

the formulations assessed (gel, gel cream, and solution) were compatible with the active principle shikimic acid (i.e. they were stable in the preliminary stability studies);

the addition of shikimic acid to the gel cream and to the gel vehicles resulted in improved sensory parameters;

shikimic acid is a compound with antioxidant activity and is therefore indicated for use in cosmetic preparations with protective and anti-aging properties for the skin;

the immediate effects, two hours after the application of the preparations studied, were correlated to the alterations in the skin's microrelief parameters related to the roughness and squamation of the skin, which, taken together, suggest the onset of the exfoliation process;

in the present study, the gel and the solution were the most efficient cosmetic preparations in achieving the exfoliating effects attributed to the shikimic acid;

regarding the sensory and clinical effectiveness evaluations through objective methods, the gel preparation showed the most satisfactory results for the studied parameters;

according to the clinical efficacy evaluation results, shikimic acid can be considered an active principle with potential for use in cosmetics for exfoliation with an aim at improving the skin's microrelief. ●

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Reidratação injetável da pele: uma opção com resultados clínicos?

Could injectable rehydration of the skin be an option with clinical results?

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RESUMO

Introdução: Em dermatologia, vários medicamentos são injetados intralesionalmente com o objetivo de tratar doenças localmente. A microinjeção de ácido hialurônico não-reticulado na derme tem como objetivo restabelecer a hidratação da pele.

Objetivo: Determinar se houve melhora da hidratação da pele devida à injeção de ácido hialurônico não-reticulado puro nas rugas periorbitárias e na pele vizinha.

Métodos: Dez pacientes (entre 40 a 63 anos de idade) com rugas periorbitárias classificadas com graus entre 1 a 4 de uma escala de severidade de rugas (*Wrinkle Severity Rating Scale*) foram tratadas no ano de 2007 com microinjeções de ácido hialurônico não-reticulado nos dias 1, 15 e 30 do estudo. O médico pesquisador, o observador não-médico e os pacientes avaliaram a pele tratada no 45º dia do estudo de acordo com uma escala descritiva de resultados clínicos (ausentes, pobres, bons e muito bons). Durante 5 anos realizou-se follow-up para identificar possíveis complicações.

Resultados: Segundo a escala descritiva, os dados clínicos analisados indicaram os seguintes resultados: pacientes (pobres = 2, bons = 6, muito bons = 2); observadores não-médicos (pobres = 3 , bons = 4, muito bons = 3); pesquisador médico (pobres = 3, bons = 6, muito bons = 1). Houve ocorrência de equimoses e sangramento imediatamente após as aplicações.

Conclusão: A injeção de ácido hialurónico pode ser uma opção terapêutica para a hidratação da pele seca e danificada.

Palavras-chave: ácido Hialurônico; envelhecimento; processos fisiológicos de pele; mesoterapia

ABSTRACT

Introduction: *In dermatology, several medications are injected intralesionally to treat diseases locally and the microinjection of non-cross linked hyaluronic acid in the dermis is used for restoring skin hydration.*

Objective: *To determine whether there was improvement in skin hydration due to injection of pure non cross-linked hyaluronic acid in patients' periorbital wrinkles and surrounding skin.*

Methods: *Ten patients (between 40-63 years of age) with periorbital wrinkles rated between 1 and 4 according to the Wrinkle Severity Rating Scale were treated in the yeear of 2007 with microinjections of non cross-linked hyaluronic acid on the 1st, 15th and 30th days of the study. The medical researcher, the non-medical observer, and the patients assessed the skin at the treatment site on the 45th day of the study according to a descriptive scale of clinical outcomes (absent, poor, good, and very good). A followup evaluation was carried out during five years aimed at identifying potential complications.*

Results: *According to the descriptive scale, the analysis of the clinical outcomes data presented the following results, expressed in number of patients: patients' opinion (poor = 2, good = 6, very good = 2); non-medical observer's opinion (poor = 3, good = 4, very good = 3); medical researcher's opinion (poor = 3, good = 6, very good = 1). Echymoses and bleeding occurred immediately after the injections.*

Conclusion: *Injection of hyaluronic acid can be a therapeutic option for re-hydrating dry and damaged skin.*

Keywords: *hyaluronic acid; aging; skin phisiological processes; mesotherapy*

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INTRODUCTION

There are doubts about the validity of mesotherapy due to several factors: the fact that it combines multiple drugs, that there is lack of studies on those drugs, the interaction of mixtures of substances has an impact on the clinical outcomes, and safety issues. Specifically regarding skin rejuvenation, there is also the local response to the trauma caused by multiple perforations that characterize the Nappage technique – a fact that could explain any improvement in the aging skin. In certain countries, there is even an acceptance of mesotherapy based on the introduction of microscopic quantities of natural extracts, homeopathic agents, pharmaceuticals, and uncontrolled vitamins in the skin and/or subcutaneous tissue, as a dependable and reliable treatment modality for treating a variety of conditions. [1]

In dermatology, several drugs – such as corticosteroids for scarring, keloids, or other skin conditions – are injected intralesionally to treat diseases locally.[2] Microinjections of uncrosslinked hyaluronic acid in the dermis is theoretically intended to quickly and accurately fix the lack of hydration due to aging, directly on the area needing treatment, based on the principles of mesotherapy.

The introduction of uncrosslinked hyaluronic acid (HA) (14 mg/ml, Mesolis®, Anteis, Switzerland) for rehydrating the skin through micro-injections directly into the damaged skin has arisen as an interesting proposal. As it is intended to treat the problem locally, the techniques developed for the treatment of mesotherapy have been adapted and applied for the purpose of the present study.

OBJECTIVE

Patients were selected with the specific proposal of rehydrating periorbital wrinkles and the surrounding skin, with the injection of a pure, uncrosslinked HA. The goal of the authors was to determine whether there was clinical improvement of the skin after the treatment.

METHODS

A descriptive study of a group of 10 patients was carried out. A term of free and informed consent was signed by each participant, and the technique and indication for treatment were approved by the Clinical Research Committee of the institution. All patients were female, aged between 40 and 63 years, bearing periorbital wrinkles ("crow's feet") classified with grades 1 to 4 according to the Wrinkle Severity Rating Scale (WSRS). The "crow's feet" were treated (in 2007) with microinjections of 14mg/ml uncrosslinked HA on days 1, 15, and 30 of the study (Table 1).

The injections were administered on the surface (superficial/middle dermis) with a 30G needle throughout the length of the wrinkles, with punctures as close as possible to each other. The injected micro droplets had sufficient volume to fill the wrinkles. The applications were performed with slow and precise movements, with the needle bevel facing down. The volume of the papules ranged from 1 to 2 mm. The surrounding area of the periocular region was also injected through papules in an ordered layout, with spaces of 3 to 4mm between them. The mesotherapy technique of Nappage was used, consisting of multiple microinjections performed with very rapid upward movements of the needle, with the syringe moving gradually,

Table 1: Distribution of study patients by age, WRSR, injection volume, and evaluation of outcomes according to patients, a non-medical evaluator, and a researcher physician. Follow-up conducted from 2007 to 2012.

Patient	Age	WSRS	Volume mL (day 1)	Volume mL (day 15)	Volume mL (day 30)	Total volume	Self-evaluation by patients	Evaluation by non-medical evaluator	Evaluation by researcher physician	Follow-up
1	44	2	0.5	0.5	0.45	1.45	Poor	Poor	Poor	2007-2008
2	45	3	0.6	0.6	0.5	1.7	Good	Poor	Poor	Loss of follow up
3	63	4	0.8	0.8	0.8	2.4	Good	Good	Good	Underwent different treatment for "crow's feet" after 2007
4	40	1	0.5	0.45	0.45	1.4	Poor	Poor	Poor	2007-2011
5	63	4	0.8	0.8	0.8	2.4	Good	Good	Good	2007-2012
6	60	4	0.7	0.7	0.6	2	Good	Good	Good	2007-2012
7	63	4	0.8	0.8	0.8	2.4	Very good	Very good	Very good	2007-2011
8	48	3	0.6	0.6	0.5	1.7	Very good	Very good	Good	2007-2012
9	50	3	0.6	0.6	0.5	1.7	Good	Good	Good	2007-2012
10	49	3	0.6	0.6	0.5	1.7	Good	Muito bom	Good	2007-2011
Average	52,5	3,1	0.65	0.645	0.59	1.525				

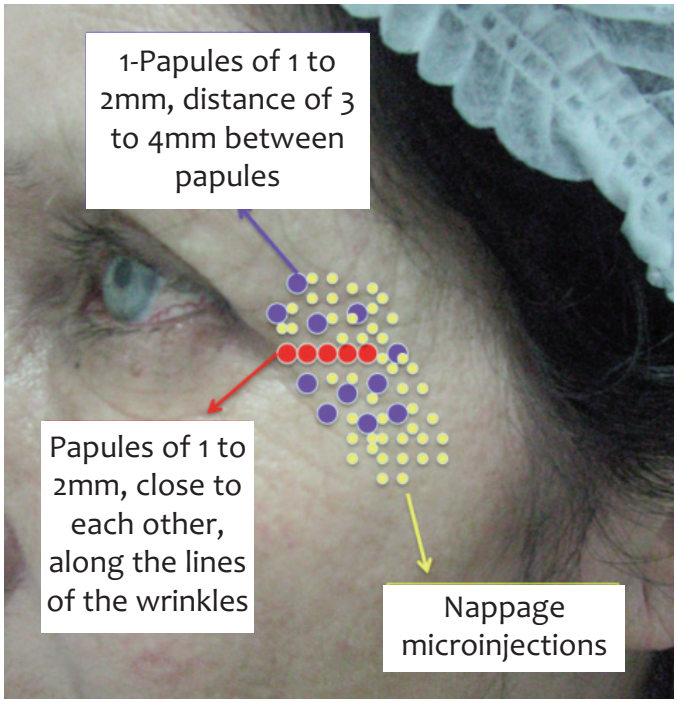

Figure 1: Patient 4, pre- and post-treatment (Table 1). The clinical outcome was deemed poor by the physician

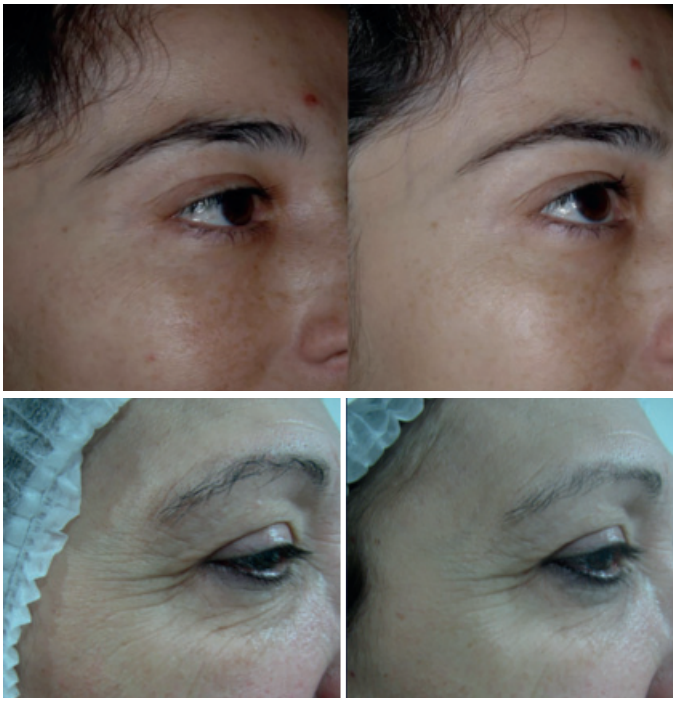

Figure 2: Patient 9, pre and post-treatment (Table 1). The clinical outcome was deemed good by the physician

covering the treated zone with very superficial injections in the epidermis and the superficial dermis. (Figure 1)

The amount of HA injected into each patient per session, as well as the total volume, were recorded. The result of the pretreatment was analyzed through pre- and post-application digital images recorded through the Canfield system, by a researcher physician, a non-medical evaluator, and the patients, on the 45th day of the study, according to the following scale: absence of improvement (no change), poor (improvement of around 25%), good (improvement of about 50%), and very good (improvement of about 75% or more). Follow-up with the patients was also carried out through annual interviews up until 2012, with an aim of verifying the occurrence of any complications or side effects.

RESULTS

The evaluation of the patients (mean age = 53 years) resulted in an average score of 3.1 according to the WSRS. The average volume for the first treatment was 0.650ml; for the second, 0.645ml; for the third 0.590ml. The total volume was 1.525ml. On the patients' self-assessment scale, the clinical results showed the following number of opinions per rate: poor = 2, good = 6, very good = 2. In the evaluation of the non-medical evaluator, the perception was as follows: poor = 3, good = 4, very good = 3. In the opinion of the researcher physician, the results were: poor = 3 (Figure 1), good = 6 (Figure 2), and very good = 1 (Figures 3 and 4). (Table 1)

There were immediate complications, such as ecchymosis (3 patients) and bleeding (4 patients), (Figure 5) while the injections were slightly painful on 3 patients. The patients devel-

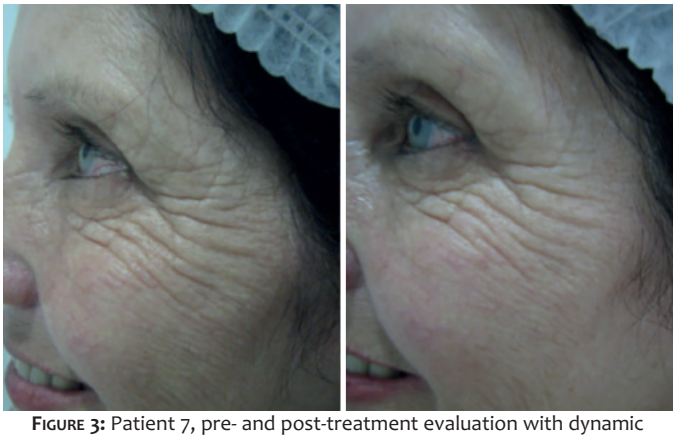

Figure 3: Patient 7, pre- and post-treatment evaluation with dynamic contraction of "crow's feet" (Table 1).

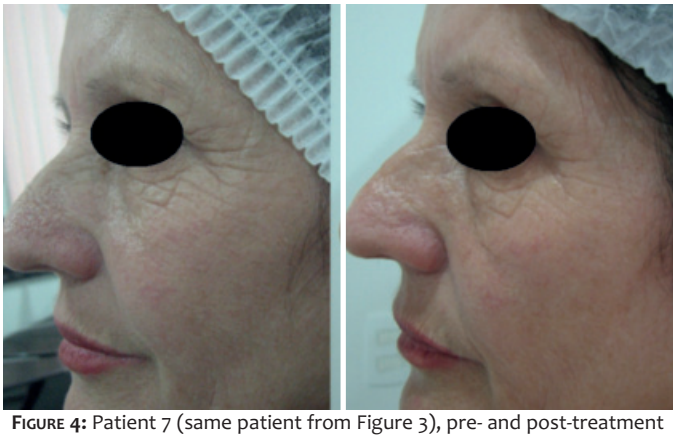

Figure 4: Patient 7 (same patient from Figure 3), pre- and post-treatment without contraction of "crow's feet". The clinical outcome was deemed very good by the physician.

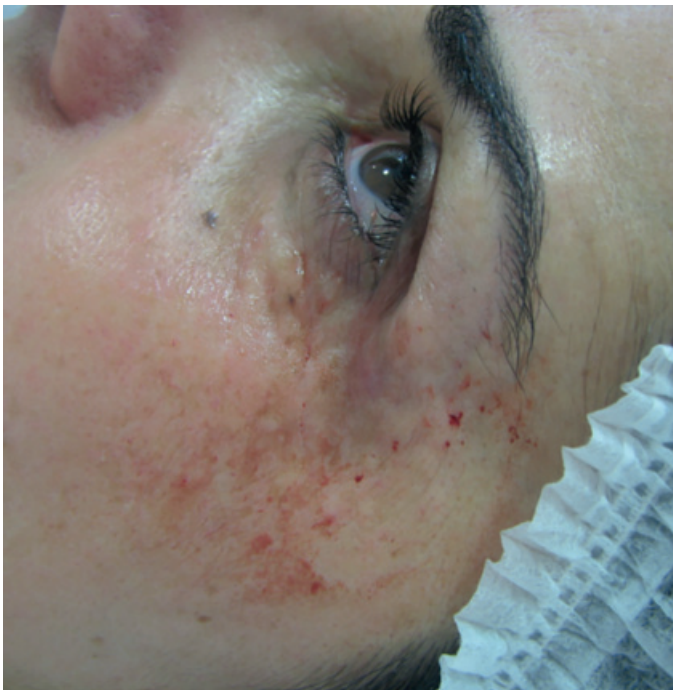

Figure 5: Ecchymosis, edema, erythema, and bleeding immediately after the injections.

oped mild erythema and edema immediately after the injections, however with the duration of only a few minutes to 2 hours. The papules resulting from the injections remained visible for 24 to 48 hours, disappearing more rapidly with the application of massage.

Four patients questioned the effect of the product regarding the filling effect that was obtained, receiving the explanation that the treatment was conducted only for the purpose of hydrating the skin and that the procedure was not aimed at providing the effects of cutaneous filling. Even though the HA had the effect of softening the wrinkles, it was necessary that the patients understood why the substance had not filled them. There were no complications or side effects when evaluated in the long run.

DISCUSSION

Visible aging comprises changes in the skin's appearance over time as a result of the degradation of its components, variations in texture, and color alterations. It is also known that there is an intrinsic physiological aging, which depends on genetics and time lapse, as well as a process of extrinsic aging caused by exposure to the sun, an unhealthy lifestyle, the effects of gravity, environmental pollutants, and chronic inflammation. In addition to analyzing the complexity of aging, the present study examines one of the effects occurring during this process: the drying and dehydration of the skin. [3-6]

When dryness and dehydration are discussed, it is understood that the reduction of natural moisturizing factors leads to an increased transepidermal water loss and to a delay in the desquamation, lending the corneum layer a compact, intensively scaly, and rough appearance, with the deceleration of the production of glycosaminoglycans (GAG). Due to extrinsic factors, an overproduction of hyaluronidase also takes place, reducing the HA levels and its interaction with collagen and elastin. As a result, there is a reduction of the bonds with water, contributing to the changes observed in the aging skin, including wrinkles, changes in the elasticity, reduction of turgor and a diminished capacity to provide support to the microvasculature. This picture can worsen due to the use of aggressive topical substances, cleaning products, and materials not suitable for hydration. [3-6]

HA is a glycosaminoglycan disaccharide consisting of repeatedly alternating units of D-glucuronic acid and N-acetyl-D-glucosamine. It has physiological pH, mainly exists as a sodium salt and is part of the extracellular matrix found in many human tissues, including the skin, the vitreous fluid of the eye, and the existing structure within the synovial fluid and joints. The largest amount of HA resides in the cutaneous tissue (7 to 8g per average adult human), corresponding to approximately 50% of the total HA existing in the body (~ 2.0 to 4.0 mg/ml in the epidermis and ~ 0.5 mg/ml in the dermis). As a polyanionic polymer with physiological pH, HA binds to water extensively. [6-8] Also a major component of GAGs, HA can bind to volumes of water corresponding to 1,000 times its weight, and may help the skin to retain and maintain water, and is therefore considered a natural free radicals scavenger. It is found in all connective tissues and is produced in the skin, mainly by fibroblasts and keratinocytes. HA is not only located in the dermis, but also in the intercellular spaces of the epidermis, especially in the middle stratum spinosum, however it is not found in the stratum corneum and stratum granulosum. [3,9-11]

Aging skin is characterized by reduced levels of HA, which decreases over the years and reaches about one third or less at 75 years of age, compared to the level that exists at 19 years of age. The function of HA in skin hydration is not clear, and this substance does not penetrate the skin via topical application. [12,13] In its natural state, HA has limited biomechanical properties as a cutaneous filler, nevertheless it has an excellent biocompatibility and affinity for water molecules, [13,14] which is the reason for using an uncrosslinked HA injected directly into the dermis with the aim of increasing the water content of the skin and compensating for the lack of endogenous HA. HA is also a soluble polymer that is quickly eliminated when injected into normal skin.

CONCLUSION

The patient series in the present study offered a sample of the effects of uncrosslinked HA when injected directly into the skin. Although HA in this form is eliminated in a few hours, it seems to be effective as a hydrating substance due to its affinity for water and the residual local hydration, which remains for a longer time than that provided by the skin's own HA. A greater mastery of the knowledge of pure uncrosslinked HA and its isolated, controlled, and safe injection, aimed at re-hydrating and restoring the brightness, vitality, and elasticity of dry and damaged skin, can constitute an additional tool in the usual armamentarium of treatment options for facial rejuvenation. ●

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Original Articles

Application of lactic acid peeling in patients with melasma: a comparative study

Aplicação de peeling de ácido lático em pacientes com melasma – um estudo comparativo

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ABSTRACT

Introduction: Melasma appears as a hyperpigmentation, which mainly affects body areas exposed to the sun, and is considered a common condition.

Objective: To evaluate the efficacy of 82% lactic acid peeling in the treatment of facial melasma through a prospective and comparative study.

Methods: Three fortnightly application sessions with 82% lactic acid peeling were carried out in 16 patients with facial melasma – eight of them were using the standard triple combination drugs for the treatment of hyperpigmentation while the others were untreated for 60 days. The Wilcoxon signed-rank test was applied in order to compare the two groups' values for the Melasma Area Severity Index.

Results: The lactic acid peeling improved the hyperpigmentation in all patients studied, with no permanent side effects, proving to be an effective treatment. The Wilcoxon signed-rank test showed a significant reduction (p = 0.0003) in the Melasma Area Severity Index, in all patients.

Conclusion: The 82% lactic acid peeling treatment can be an important tool in the improvement of resistant melasma.

Keywords: chemexfoliation; therapeutics; skin; lactic acid; hyperpigmentation.

RESUMO

Introdução: *O melasma se apresenta como hiperpigmentação que afeta principalmente áreas fotoexpostas, sendo um problema comum.*

Objetivo: *Avaliar a eficácia do peeling de ácido lático a 82% no tratamento do melasma facial mediante trabalho prospectivo e comparativo.*

Métodos: *Procedeu-se à aplicação quinzenal de três sessões de peeling de ácido lático a 82% em 16 pacientes com melasma facial, estando metade em uso da tríplice combinação e metade sem tratamento há 60 dias. O teste de Wilcoxon foi aplicado com objetivo de comparar os valores do índice de área e gravidade de melasma nesses dois grupos.*

Resultados: *O peeling de ácido lático melhorou a hiperpigmentação de todas as pacientes estudadas sem nenhum efeito colateral permanente, demonstrando-se tratamento eficaz. O teste de Wilcoxon mostrou redução significante (p = 0,0003) no índice de área e gravidade de melasma de todas as pacientes.*

Conclusão: *O peeling de ácido lático a 82% pode ser ferramenta importante na melhora do melasma resistente.*

Palavras-chave: *abrasão química; terapêutica; pele; ácido láctico; hiperpigmentação.*

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INTRODUCTION

Melasma is a common and usually symmetric pigmentation disorder, characterized by irregular and well-delimited hyperpigmented spots, affecting mainly the face in women, and which causes severe impairment in their quality of life. The natural history of melasma is characterized by a chronic clinical picture, recurrence despite treatment, and varying individual responsiveness to different therapies. [1-5]

The term *melasma* is derived from the Greek *melas*, which means 'darkened' and refers to its brownish clinical presentation. Despite being recognized since the time of Hippocrates (470-360 B.C.), its actual prevalence is unknown. In 2013, Handel et al. in a population study carried out with civil servants who worked at a university campus in the city of Botucatu (UNESP –São Paulo, Brazil), melasma was diagnosed in 34% of women. The authors of that study believe that 15-35% of adult Brazilian women are bearers of melasma. [6] It is estimated that 5 to 6 million people in the US are affected and that 40% of the Southeast Asian population has melasma (Sundara, 2014). [1,7-9]

Although it can occur in both genders and in any skin phototype, melasma is more common in women (9:1), prevailing in Fitzpatrick's phototypes III to V (and intermediate types), and is rare in extreme phototypes. It is believed that this is due to the inability of phototype I patients to induce pigmentation and those with phototype VI to produce pigment with maximum efficiency, thus characterizing stable phenotypes. [6]

In Brazil, the majority of cases in women develop between the ages of 20 and 35 years of age, with phototype II and III patients showing melasma earlier than those of higher phototypes – which is explained by the sun-blocking role of melanin in delaying the development of the disease. Genetic predisposition is suggested by reports of family history. In a Brazilian study carried out with 302 patients, family history was present in 56% of them. Patients with a family history of melasma are younger than those without a family history. [1,4,6-8,10-12]

Despite numerous studies on the subject, accurate causes of melasma are not fully understood. Most cases are associated with risk factors, such as ultraviolet radiation (UVR) and sex hormones, including combined oral contraceptive (COC) and pregnancy. Other factors include: anticonvulsant medications, phototoxic medications, ovaries and thyroid diseases, food, intestinal parasites, liver disease, hormone replacement therapy (HRT), cosmetics, photosensitizing drugs, skin inflammatory processes and events causing stress, suggesting that the etiology of melasma is multifactorial and depends on environmental and hormonal factors, in addition to the important role of genetics. [5-7,12,13]

Ultraviolet radiation is the most important factor in triggering the disease. The main melanogenesis inducing radiations are ultraviolet A (UVA) and ultraviolet B (UVB), while infrared radiation and visible light have a lower melanogenic potential. Various inflammatory mediators –in addition to inflammatory cells and vessels – are expressed in the skin with melasma in greater amounts than in healthy skin. It is also known that UV rays can lead to the production of multiple cytokines by keratinocytes, which stimulate melanogenesis. [6-11]

It is likely that the action of hyperfunctional melanocytes is involved in the physiopathogenesis of melasma, and in the increase in the amount of epidermal melanin, in the number of melanosomes, and in the intensity of dermal elastosis. Melanocytic activity, represented by larger cells with more prominent dendrites, is observed. In these cells, it is possible to verify a larger quantity of melanin being produced and stored in a great number of melanosomes, as well as a greater number of cytoplasmic organelles. Furthermore, electron microscopy demonstrates increased synthesis of tyrosinase in melasma lesions. [1,2,10,11,14]

The diagnosis of melasma is mainly clinical. It is a dermatosis characterized by asymptomatic, symmetrical hyperchromic brownish macules in varied hues that have clear and irregular borders, often occurring in geographical configurations. Its course is chronic, recurring, and is more frequent in photoexposed body sites, especially in the face and neck. [1,6,9,11]

There is no consensus on its clinical classification and, in practice, 3 main patterns of facial melasma are recognized: centrofacial type (affects the perioral, mentonian, and central region of the face); malar type (affects the zygomatic regions), and mandibular type (affects the mandible region).[8,11] The MASI (Melasma Area and Severity Index) is the most widely used assessment method in studies involving melasma. Described in 1994 by Kimbrough-Grenn, it is used to clinically quantify the severity of facial melasma. The calculation of the MASI is based on the subjective assessment of 3 factors: area of involvement, pigmentation, and homogeneity of the melasma. [4,6,9,13,15,16]

The treatment of melasma is a major clinical challenge whose main objective is the whitening of the lesions and the reduction of the affected area, with the fewest possible adverse effects. [6,10] Melasma has been traditionally treated with a combination of photoprotection, strategies to reduce melanin biosynthesis, and transport and transfer, in addition to therapies that reduce the amount of epidermal melanin, such as peelings. [6,12]

The worsening of hyperpigmentation can occur even immediately after an event of low exposure to UVA, since redistribution and oxidation of pre-existing melanin take place. It has been demonstrated that the use of broad-spectrum sunscreen reduces the disease's intensity by up to 50%, while its incidence in pregnancy decreases by 90%. For this reason, the regular use of sunscreen has been affective both in preventing melasma and in increasing the efficacy of other topical agents. [6,12]

Several treatment modalities are described that have as their aim to improve the appearance of melasma. However, none of these has emerged as resolutive, and cases of worsening are described mainly during summer. [17] Treatments with laser and intense pulsed light are popular yet still have questionable outcomes, with a great number of adverse effects and a paradoxical increase in pigmentation, especially in high skin phototypes. [5] Among the topical formulations are: hydroquinone, azelaic acid, arbutin ascorbic acid, retinoids, tranexamic acid, and others.[5,13,18]

Topical depigmenting agents are used with the aim of halting pigment production in melanocytes, and their main tar-

get is the tyrosinase. The inhibition of this enzyme reduces the conversion of DOPA into melanin. For over 50 years, hydroquinone has been used as a depigmentation agent through this mechanism.[8,18] Hydroquinone can still be combined with tretinoin and with corticosteroids, a treatment known as triple combination that increases its effectiveness and is considered superior to monotherapy. [3,5,12,18]

Superficial chemical peels have been used for years to treat melasma, especially refractory cases. [5] They inflict accelerated exfoliation or injury to the skin, induced by caustic agents that cause controlled damage to the basal layer.[19] Among the agents used in this type of chemical peel are: alpha-hydroxy acid (AHA) – which is derived from the fermentation of foods – retinoic acid, and others. Both show similar results in melasma treatment. [5,10,19] The benefits of AHAs have been long recognized. There are reports for instance that Cleopatra used whey (lactic acid) as a facial treatment. The more frequently cited AHAs for the treatment of pigmentation disorders are glycolic and lactic acids, which act by inhibiting the activity of the tyrosinase and decreasing the formation of melanin. Although lactic acid has emerged as promising for the treatment of resistant melasma, there are still few studies on the subject. [9,15,16,18]

OBJECTIVE

To evaluate the effectiveness of 82% lactic acid peel in treating facial melasma.

PATIENTS AND METHODS

A prospective comparative study was conducted at the Dermatology Department of the Faculdade de Medicina da Universidade de Santo Amaro (UNISA), in São Paulo. It was previously approved by the Committee for Research Ethics, and was carried out between September and November 2011. Sixteen women with facial melasma were treated with 3 sessions of 82% lactic acid gel peeling (dispensed by Center Formula® pharmacy – São Paulo, Brazil), applied at 15-day intervals.

The inclusion criteria were: female patients with a clinical diagnosis of moderate to severe facial melasma, who agreed to undergo the proposed treatment. All patients had high phototypes (III to V), had melasma for more than 1 year, and had already tried diverse treatments and clinical procedures. Pregnant and lactating women were excluded from the study.

Two groups of patients were randomly determined: one with patients who were previously using the triple combination (4% hydroquinone, 0.05% tretinoin, and 0.05% dexamethasone) for at least 2 weeks; the other with patients who had not been treating melasma for more than 60 days. A careful clinical evaluation was performed by the medical examiner. The average of the MASI severity index was individually estimated at time points before the treatment, 15 days after each session, and 15 days after the completion of the treatment. (Figures 1 to 4).

The calculation of the MASI is based on the subjective evaluation of 3 factors: the area of involvement, pigmentation, and homogeneity. Four areas of the face are evaluated in its calculation: frontal (FT), right malar (RM), left malar (LM), and mentonian (MT), respectively corresponding to 30%, 30%, 30%, and 10% of the total area of the face. Each area receives scores from zero to 6, according to its extension. The severity of melasma is measured by 2 factors: pigmentation (P) and homogeneity (H), in a scale ranging from 0 to 4. The mathematical formula is: MASI = 0.3 x (P x FT + H x FT) x AFT + 0.3 x (P x RM + H x RM) x ARM + 0.3 x (P x LM + H x LM) x ALM + 0.1 x (P x MT + H x MT) x AMT. Its output value ranges from 0 to 48. [4,13,15,16]

The 82% lactic acid peeling was applied to all patients. A gauze dampened with the product was used for the application only in areas affected by melasma. A local mild erythema was expected 5 minutes after the application. In the absence of this outcome a new layer was applied and 5 additional minutes added on. The product remained on the patient's skin for a max-

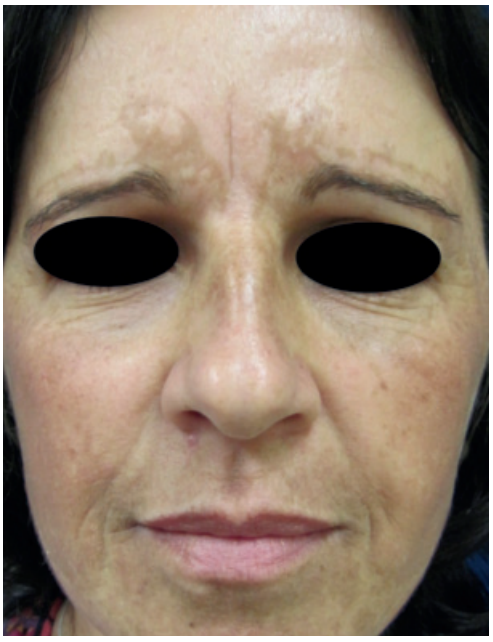


Figura 1: Paciente com melasma antes do tratamento

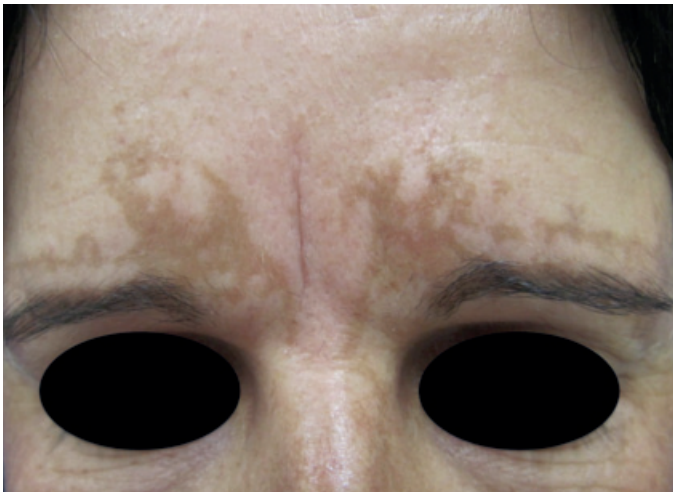


Figura 2: Paciente com melasma antes do tratamento

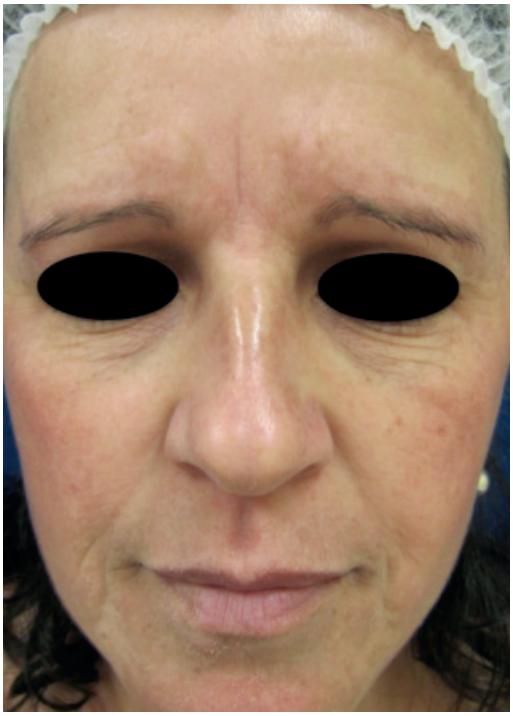


Figura 3: Paciente com melasma após o tratamento

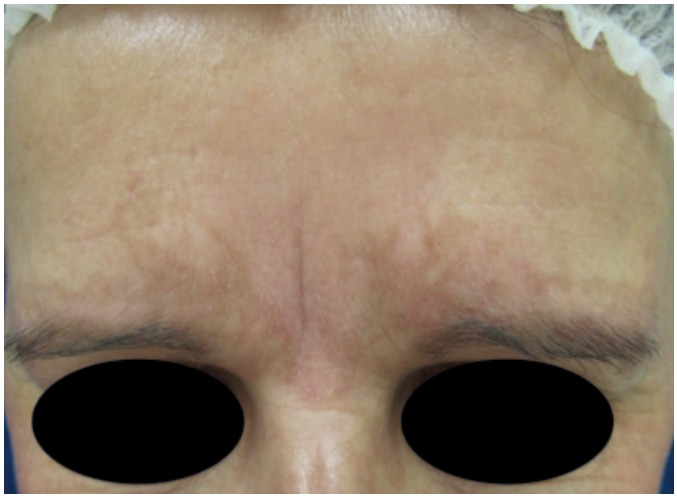


Figura 4: Paciente com melasma após o tratamento

imum of 10 minutes, and was then removed with saline solution.

The patients were instructed to apply 0.05% desonide cream at night during the first week after the procedure in order to avoid post-inflammatory hyperpigmentation. Those who were using the triple combination would resume it after this period. The adverse effects found were reported by the authors.

The Wilcoxon signed-rank test [20] was used in the analysis of the results in order to compare MASI values observed before and after the application of the product, for each group. The percentage differences were computed according to the following formula:

$\Delta\% = [(\text{post-value} - \text{pre-value}) / \text{pre-value}] \times 100$.

The Mann-Whitney test [20] was applied to compare values of $\Delta\%$ without the treatment and $\Delta\%$ with topical treatment. Significance levels were established at 0.05 (or 5%).

RESULTS

Sixteen patients were selected for the study, 1 patient did not return for the last evaluation after the third application, and was excluded from the study. The patients' ages ranged from 31 to 62 years (mean = 41 years).

Eight patients were previously using the triple combination, the remaining 7 were not using any topical medication. Most patients required 2 peel applications at each session in order to achieve the expected response (erythema). None of the patients complained of discomfort at the moment of application.

All patients saw their MASI values decrease (Table 1). In the group where patients were not using any topical agent for melasma, the average MASI was 13.7 before and 4.8 after the treatment. For the group that was using the triple combination, the initial average MASI was 18.5, falling to 5.7 after the completion of the treatment (Graph 1).

By comparing the MASI indices both pre- and post-application of acid lactic (82%), the Wilcoxon signed-rank test showed a significant reduction ($p = 0.0003$), with an initial MASI average of 17.3 as compared to a final MASI average of 5.3, with a 64% reduction (Table 1).

All patients showed the expected transient erythema immediately after applying the peel. Two had reversible complications after the first session – one of them with mild local desquamation and the other with exulceration – both in the malar region. All were treated with 0.05% desonide cream and had complete regression of these effects. From these patients, 1 belonged in the group that had been topically treated, with that treatment having been suspended for 30 days. All had improvement of lesions without formation of local post-inflammatory hyperpigmentation, and returned for other peeling sessions as planned. Regardless, 100% of patients were satisfied with the treatment that was performed.

DISCUSSION

Melasma is a common pigmentation disorder that affects a large portion of the population. According to a survey carried out by the Brazilian Society of Dermatology (SBD) in 2006, melasma corresponded to 8.4% of complaints in dermatology practices. [6] Due to the fact that it is an unaesthetic dermatosis located primarily on the face, it has a significant negative impact on affected individuals. Patients also report low self-esteem, withdrawal from social life, and have lower productivity levels. Although several treatments have been described for melasma, its therapeutic options remain a major challenge. [1,2,4,6,21]

Superficial chemical peels are relatively simple procedures that have been reported in the literature since 1962, hav-

Table 1: Wilcoxon signed-rank test comparing Melasma Area and Severity Index (MASI) values before and after the treatment of melasma with and without topical therapy.

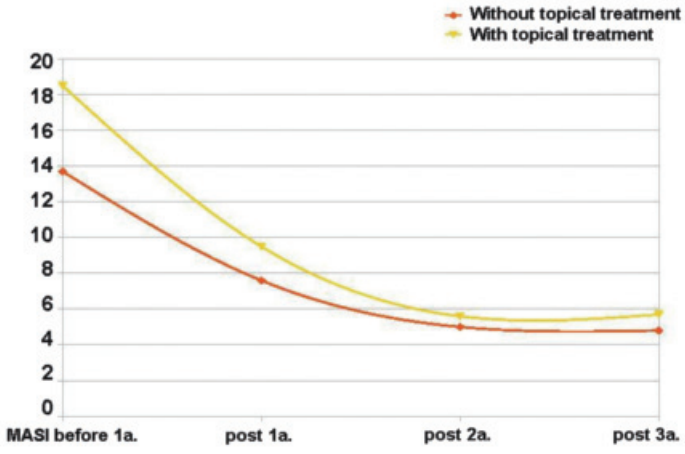
Without treatment				**Topical treatment**		
MASI pre		MASI post	Δ %	MASI pre	MASI post	Δ %
	15.0	6.9	- 54.0	3.6	1.5	-28.3
	13.5	5.4	- 60.0	7.2	3.0	-58.3
	26.1	10.2	- 60.7	18.0	9.0	- 50.0
	15.5	1.2	- 92.7	15.6	5.4	- 65.4
	9.6	4.8	- 50.0	16.5	7.7	- 53.3
	6.0	3.0	- 50.0	36.6	9.4	- 74.3
	10.5	1.8	- 82.9	29.9	4.5	- 84.7
				20.9	5.2	- 75.1
Average	13.7	4.8	- 64.3	18.5	5.3	- 64.9
Median	13.5	4.8	- 60.0	17.3	5.3	- 61.9

Wilcoxon signed-rank test
(pre x post)
z = 3,41
p = 0,0003

Without treatment
z = 2,37
p = 0,018

Topical treatment
z = 2,52
p = 0,012

Mann-Whitney test
D% without treatment x Δ% topical treatment
Z = 0,23
P = 0,8170



Graph 1: Evolution of MASI values after the 1st, 2nd, and 3rd lactic acid applications in patients who underwent topical treatment and in patients who did not undergo topical treatment

ing been consolidated by the dermatologic practice.[19] Chemical peels are indicated for the treatment of various dermatological conditions, and the most studied in the treatment of melasma are Jessner's solution and glycolic acid. [3,10] Side effects are possible after the use of peelings, with post-inflammatory hyperpigmentation being among them. It is suggested that prior preparation of the skin with topical products such as retinoic acid could reduce this complication. [3] This was not confirmed by the present study, as none of the patients had permanent side effects –nor by those who were not using any topical medication, with all patients having maintained the proposed treatment.

AHAs have been used effectively in the treatment of various dermatological conditions – among them glycolic acid, which is the main peeling agent used in the treatment of melasma.[9] The dominance of US literature on the subject may explain the great number of publications on glycolic acid, which seems to be the preferred agent for superficial peeling in that country. [19] Although lactic acid is safe and cost effective, there are few indexed studies on its use in peels for the treatment of melasma. [15,16] The majority of authors report the necessity of 2 to 5 peeling sessions to achieve some result. [9,15,16] Although those authors use higher concentrations of lactic acid (85% to 92%), the present study's patients underwent only 3 applications of 82% lactic acid peeling, with all achieving an improvement of melasma.

The population evaluated in the present study reflects the melasma patients' epidemiology (i.e. high phototype women).[1,6,7] In the studies describing the use of lactic acid, the patients had an initial MASI of 14.0 to 20.0, with a reduction of 57-80% after the application of lactic acid peel. [9,15,16] These data are aligned with the present study's findings, where the initial

average MASI was 17.0, with a reduction of 64% after treatment. The present study's data show that the improvement was more significant after the first peeling application, with the melasma continuing to regress later on, albeit to a lesser extent. None of the studies quoting lactic acid suggested such a response.

It is known that the triple combination is the first line treatment for melasma. [13,17,18] Although highly effective, there was no difference between the treated group and those who did not receive the formula, showing that the results of the present study were due to the application of lactic acid peeling.

Regular use of sunscreen is effective both in the prevention of melasma and in the improvement of other topical therapies. [6,18] In the present study, all patients adhered to the regular use of sunscreens, and the great improvement of MASI can be due not only to the application of lactic acid peels, but also to this fact.

In line with what is reported in the literature, no permanent complications were described during the treatment with lactic acid peeling, demonstrating that it is an effective and safe resource. Notwithstanding, there is still a necessity for further controlled studies.

CONCLUSION

Pigmentary disorders (including melasma) are generally resistant to several types of treatment, causing frustration for both the patient and the physician. [1,13,21] Although there are few studies on lactic acid peel for treating this disorder, the present analysis has shown that it can be an important tool for improving resistant melasma, especially in patients with high skin phototypes. ●

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Original Articles

Epidemiological delineation of cutaneous melanoma cases treated in a tertiary hospital in Campinas, São Paulo State, Brazil

Delineamento epidemiológico dos casos de melanoma cutâneo atendidos em um hospital terciário de Campinas, São Paulo, Brasil

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ABSTRACT

Introduction: Cutaneous melanoma has significant relevance among malignant skin tumors, for despite its low incidence (3-4%) it is associated with the highest mortality. In Brazil, estimates for the year 2014 correspond to 10% of all cancers, establishing this as an important public health issue.

Objectives: To present epidemiological data related to melanoma skin cancer in the midlands of the Brazilian State of São Paulo.

Methods: Descriptive retrospective cross-sectional analysis of data from a tertiary hospital's medical records. The analysis was subject to measurement and information bias. A descriptive analysis with frequency and percentage was carried out.

Results: There was a prevalence of cutaneous melanoma in women (71%), patients between 50 and 70 years of age (56%), Caucasians (78%), and individuals who identified their lesions through self-examination (42%), with predominant involvement of the trunk (35%). The most prevalent histological subtype was the superficial spreading (58%).

Conclusions: Understanding the epidemiology of cutaneous melanoma in a given geographic region enables and facilitates medical actions, allowing for the better establishment of strategies for primary and secondary prevention.

Keywords: melanoma, epidemiology, skin neoplasms.

RESUMO

Introdução: *O melanoma cutâneo apresenta significativa relevância entre os tumores malignos de pele, pois apesar de sua baixa incidência (3-4%) é o de maior mortalidade. No Brasil, as estimativas para o ano de 2014 correspondem a 10% de todas as neoplasias sendo portando um importante problema de saúde pública.*

Objetivos: *Apresentar dados epidemiológicos relacionados ao câncer de pele melanoma em uma região do interior do Estado de São Paulo.*

Métodos: *Estudo descritivo, retrospectivo e transversal através de análise de dados de prontuários médicos de um hospital terciário, sujeito a viés de aferição e informação. Realizouse análise descritiva com freqüência e porcentagem.*

Resultados: *A prevalência dos casos de melanoma cutâneo foi para o sexo feminino (71%), indivíduos entre 50 e 70 anos (56%), caucasianos (78%), que identificaram suas lesões através de auto-exame (42%), com predomínio de acometimento no tronco (35%). O tipo subtipo histológico mais prevalente foi o disseminativo superficial (58%).*

Conclusões: *Conhecer a epidemiologia do melanoma cutâneo em uma dada região permite e facilita ações médicas, a fim de serem estabelecidas melhores estratégias de prevenção primária e secundária.*

Palavras-chave: *melanoma; epidemiologia; neoplasias cutâneas.*

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INTRODUCTION

The incidence of skin cancer has increased worldwide in the last three decades. The propensity to develop skin cancer during one's lifetime is linked to both individual and environmental characteristics, including skin type and phenotype, family history of skin cancer, and level of exposure to ultraviolet radiation (UV), which is cumulative over a lifetime.[1] Cutaneous melanoma is of significant relevance among malignant skin tumors, for despite its low incidence (3-4%) it has the highest mortality rate.

On a global scale, cutaneous melanoma is estimated to be between the 12th and 15th most commonly diagnosed cancers. However, in some developed countries, it is the first or second most frequent tumor in young adults. A high prevalence is observed in Australia and regions where the population is predominantly Caucasian or light-skinned. Low to intermediate levels are seen in Latin America, and the lowest rates are found in regions with a high population of Asian or African individuals.[4] Between the years of 1998 and 2002, Sortino-Rachou (2011) found a total of 4,465 cases of melanoma reported in Latin America, corresponding to 1.2% of all cutaneous melanomas registered in CI5IX Data Base. The same author recorded the incidence of melanoma among inhabitants of Latin America as ranging from 1.1 and 6.5 cases/100,000 (4.6/100,000 inhabitants for females and 4.3/100,000 for females).[5]

In Brazil, estimates for the year 2014 are for 5,890 new melanoma cases (2,960 in men and 2,930 in women), totaling 10% of all neoplasias. For the Brazilian State of São Paulo, 830 new cases are estimated in male patients (incidence of 3.97 new cases/100,000) and 1,010 new cases in female patients (incidence of 4.59 cases/100,000), correlating to a serious public health problem.[6] The present study was aimed at presenting epidemiological data related to melanoma skin cancer in a region of the city of Campinas (São Paulo State, Brazil), since there are few studies describing population data for specific regions of the country.

METHODS

A cross-sectional, retrospective, descriptive study was carried out using secondary data from medical records of all patients diagnosed with melanoma, at the Dermatology Department of the Pontifícia Universidade de Campinas – PUC Campinas, São Paulo, Brazil.

The inclusion criterion was a diagnosis of melanoma with primary cutaneous neoplasia. Primary non-cutaneous melanoma was an exclusion criterion. Data were collected on age, gender, race, comorbidities, time since onset of the lesion, referral method, personal and family history, anatomic site of the primary lesion, histological type, Clark level, Breslow thickness, presence of mitosis, ulceration, and regression.

Descriptive analyses with study of frequency and percentage were carried out. For the quantitative variables, the measure of central tendency (mean) was calculated. Excel® was used to analyze the data. Due to the fact that the study is dependent on data obtained from patient records, it is subject to measurement and information bias. The study complied with the principles outlined in the Declaration of Helsinki.

RESULTS

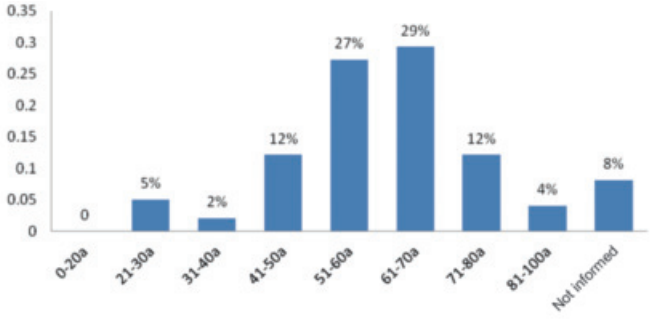
The service identified 99 cases of melanoma that were receiving follow-up. Of the total, 29% (29 cases) were male and 71% (70 cases) were female. According to skin color, 78% (77) of the patients were light-skinned, 9% (9) were mixed and only 1% was dark-skinned. Twelve percent (12) of the patients did not have their skin color mentioned in the initial anamnesis.

The mean age for the entire group was 61 years. The mean age by gender was 58 years for females and 59 for males. The distribution by age group shows a prevalence of cases in the 51 to 70 years group (56%), as shown in Graph 1.

When asked about the time of onset of the lesions, the patients either could not inform and/or this datum was not recorded (49% or 48 cases). Only 3 patients (3%) reported that the lesion was congenital, and once realizing a change in the pattern, were motivated to seek medical attention. Of the total, about 20% sought care within 1 year of identifying the lesion or perceiving a change in it. The lesion had been in place more than 3 years in 17% of cases and between 1 and 2 years in 11% of them.

In about 40% of recorded cases, there was no reference to how the patient had discovered the lesion (self-examination/spontaneous, referral by healthcare professional, or expert assessment). Thus, in the present study, 42% of patients noticed their lesions and sought medical attention. Only 4% were referred by a health professional that had noticed a suspicious lesion. In 14% of cases the exeresis of the lesion was recommended by a specialized professional, and in 49% of patients there was no information about the form of referral to the service.

Table 1 below presents the epidemiological data of personal and family history, and the presence of comorbidities in the melanoma cases reported. It was observed that 96% of patients had no personal history of melanoma and 82% had no family history. Of the 11% with a positive family history, 54% had a family history linked to parents and 36% had a family history linked to siblings. The most prevalent comorbidity was Systemic Arterial Hypertension, present in 35% of cases. Of the



Graph 1: Percentage of melanoma cases X age group affected

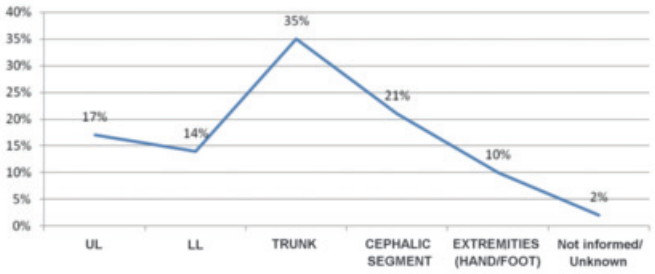
11% of patients who reported malignancy, breast cancer was the most prevalent, accounting for 50% of cases.

The prevalence of the primarily affected anatomical site is shown in Graph 2.

Regarding the histological type, the most prevalent in the dermatologic service in question was the superficial spreading melanoma (58%) as shown in Graph 3.

Table 1: Personal and family history, and comorbidities

	Nº ABSOLUTO	PORCENTAGEM
PERSONAL HISTORY OF MELANOMA		
YES	3	3%
NO	95	96%
NA	1	1%
TOTAL	**99**	**100%**
FAMILY HISTORY OF MELANOMA		
NO	81	82%
NA	7	7%
TOTAL	**99**	**100%**
FAMILY ANTECEDENT		
FATHER	3	27%
MOTHER	3	27%
SIBLING	4	36%
GRANDMOTHER / GRANDFATHER	1	9%
TOTAL	**11**	**100%**
COMORBIDITIES		
SAH	37	35%
DM2	7	7%
MALIGNANCY	**12**	**11%**
CARDIOPATHY	2	2%
NEPHROPATHY	1	1%
OTHER	10	9%
DENIES	38	36%
TOTAL	**107**	**100%**
MALIGN NEOPLASIAS		
BREAST CANCER	6	50%
BASAL CELL CARCINOMA	3	25%
LYMPHOMA	1	8%
PROSTATE CANCER	1	8%
BOWEL CANCER	1	8%
TOTAL	**12**	**100%**

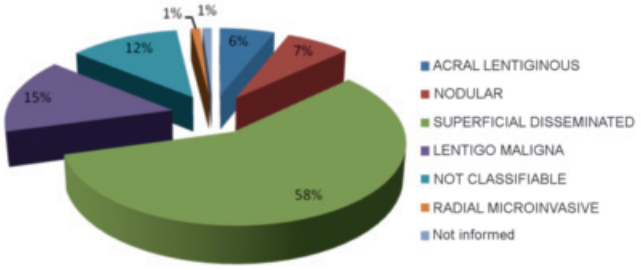


Graph 2: Prevalence of anatomic site of the primary lesion

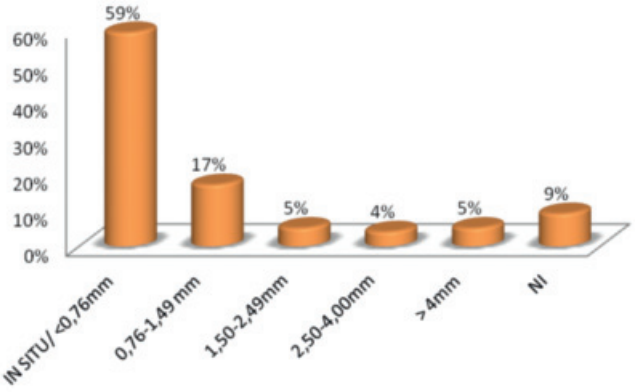
Graphs 4, 5, and 6 depict data on Breslow thickness, Clark level, and a presence/absence of mitosis, ulceration, and regression.

DISCUSSION

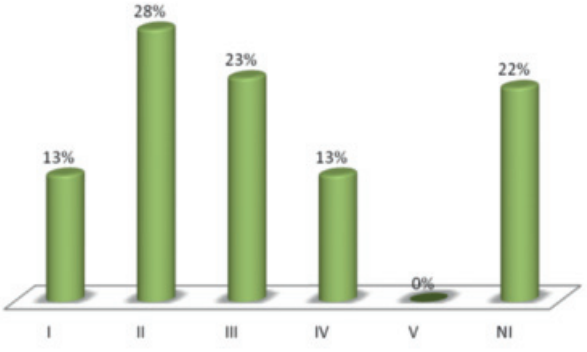
Melanoma is the cutaneous neoplasia with the worst prognosis, and therefore is a disease with a major impact on public health. It corresponds to approximately 5% of skin cancers and is responsible for roughly ¾ of deaths from that condition, a fact that makes its epidemiological knowledge of the utmost importance. [7]



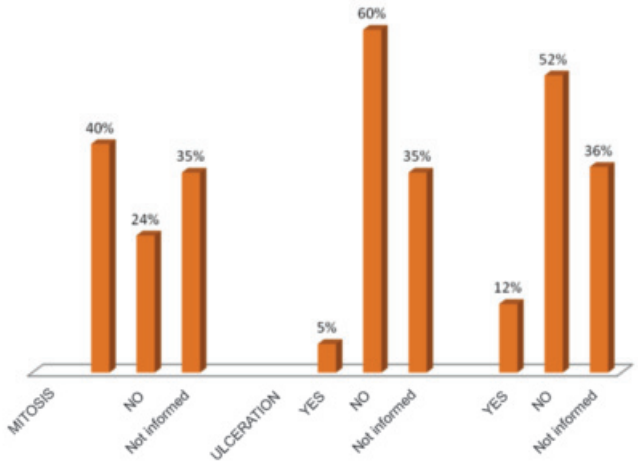
Graph 3: Prevalence of histologic type of melanoma



Graph 4: Percentage change in Breslow thickness



Graph 5: Percentage change in the Clark level



Graph 6: Percentage of mitosis, ulceration, and regression of the diagnosed melanomas

In the service in question, 29% of patients were male and 71% female. In a 30-year retrospective study carried out by Nasser (2011) in the city of Blumenau, in the southern Brazilian State of Santa Catarina, of the 1,002 cases of melanoma diagnosed, 44% were male and 56% female. [8] Another retrospective 20-year study conducted at a university hospital in Belo Horizonte, the capital of the southeastern Brazilian State of Minas Gerais, has shown that in a sample of 101 patients, 61% were female and 39% male. [9] As in the present analysis, those two studies also demonstrate a higher prevalence of the neoplasia in female patients – a trend that persists in most Brazilian studies. [10,11]

In the present study, the average age of the sample was 61 (58 years for females and 59 for males). The distribution by age group shows a prevalence of cases in patients between 51 and 70 years old (56%). Unlike other malignancies, melanoma affects younger individuals, with an average age below that found in other types of tumors, as described by Brandão et al., who reported an average patient age of 55 years. [9] The mean age found in the present study is similar to that found in most studies conducted in Brazil and abroad, again confirming the trend of melanoma affecting patients at a younger age. [10,12_16]

The predominant skin color on the present study was light-skinned (78%). Once again the present study was consistent with those carried out by Brandão et al., which revealed a prevalence of melanoma of 74% in light-skinned patients and 26% in darker-skinned patients. Another study by Pinheiro et al. also confirms a higher prevalence of melanoma in fair skin (87.5% versus 12.5% in darker skin). In the present study, the incidence found in non-Caucasian patients (10%) is higher than that found in the literature, [10,11,17,18] as evidenced by Purim et al. (2013), who found a prevalence of only 0.18% in dark-skinned patients. [19]

According to records, 96% of patients had no personal history of melanoma and 82% had no family history of melanoma. Of the 11% with a positive family history, 54% had parental history and 36% of cases had a history among siblings. In a study carried out at another university hospital in Brazil (Curitiba city, southern State of Paraná) 64.6% of patients had no history of skin cancer, however 24% of them described a family history of some type of skin cancer, not necessarily melanoma. [19]

In the present study, 42% of patients noticed their lesions on their own. Only 4% were referred by health professionals, for 14% of patients exeresis was recommended by a specialized professional, and in 49% of cases the form of referral to the service was not indicated. Almost half the cases are of patients who identified suspicious lesions on their own. This can be indicative of two scenarios: more well informed patients (awareness campaigns) or a lack of medical inspection of patients' skin. Maia & Basso (2006) reported that 54% of patients diagnosed with melanoma noticed the lesion themselves, while 24% were made aware by health professionals, and the remaining (22%) were made aware by spouses or others. [20] In Brazil it is not known who typically first discovers the melanoma cases. This knowledge could serve as a basis for education programs of the public and of health professionals.

The most prevalent anatomic site for primary lesions was the trunk (35% of cases), followed by the cephalic region (21%), upper limbs (17%), lower limbs (14%), and hands/feet (10%). In the study by Brandão et al., the main affected site was the head and neck (30.7%), followed by the trunk (21.1%), acral region (19.3%), upper limbs (15.1%) and lower limbs (9.6%). The most affected anatomical sites tend to vary according to the patient's histological type and gender. Most studies show a greater involvement of the trunk in men and of the legs in women. [12, 21-24]

The most prevalent histological type in the service in question was the superficial spreading melanoma (58%), followed by lentigo maligna (15%), non-classifiable tumors/radial microinvasive (13%), nodular (7%), acral lentiginous (6%), and uninformed (1%). International and Brazilian studies differ on the prevalence of histological type. There are reports of a prevalence of the extensive superficial type among Caucasians, [9, 25-27] and of the acral lentiginous type in non-Caucasians. [9,21,28] In the Brazilian literature, the authors also observed a variation in the histological type across different regions of the country, also with a predominance of the superficial spreading type where most of the population has fair skin. [9,29,30,31,32]

The majority of the studied patients (59%) had melanoma *in situ*, 17% had a Breslow thickness of 0.76-1.5 mm, 5% with a thickness of 1.5-2.49mm, 4% with a thickness of 2.5-4.0 mm, and 5% had lesions greater than 4.0 mm. The data of the present study are similar to those reported by Pinheiro et al. (2003), in which there is evidence of a higher prevalence of Breslow thicknesses of less than 0.75 (42.3%), which may trans-

late into specialists with a better ability to carry out early diagnoses, as this occurred in more developed countries. [29,30,33]

CONCLUSION

Having a knowledge of the epidemiology of patients with melanoma in a given geographical region provides a better understanding of the disease, with evaluation of the prevalence and associated risk factors. This facilitates medical actions, with better-established strategies for primary and secondary prevention. ●

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Review article

Botulinum toxin: a review of its applicability in diseases within the reach of dermatologists

Toxina botulínica: revisão de sua aplicabilidade em doenças ao alcance do dermatologista

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ABSTRACT

In dermatology, botulinum toxin stands out in the treatment of wrinkles and expression lines, mainly being used for aesthetic purposes. However, in recent years the use of botulinum toxin in the treatment of dermatological diseases has grown and shown good results. The present review is aimed at reporting the use of botulinum toxin in clinical conditions that may be treated by dermatologists, exploring its mechanism of action and long-term results, thus gathering practical information for specialist physicians.

Keywords: botulinum toxins; disease; dermatology; skin.

RESUMO

Em dermatologia, a toxina botulínica se destacou no tratamento de rugas e linhas de expressão, sendo utilizada principalmente com finalidade estética. Nos últimos anos, porém, o uso da toxina botulínica no tratamento de doenças dermatológicas tem crescido e apresentado ótimos resultados. O objetivo desta revisão é relatar o uso da toxina botulínica em doenças clínicas que possam ser tratadas pelos dermatologistas, explorando seu mecanismo de ação e resultados a longo prazo, reunindo, assim, informações práticas ao especialista.

Palavras-chave: *toxinas botulínicas; doença; dermatologia; pele.*

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INTRODUCTION

Botulinum toxin is a neurotoxin produced by the anaerobic bacterium called *Clostridium botulinum*.[1] This toxin causes botulism, a severe disease characterized by paralysis of facial muscles, limbs, and paralysis of the respiratory muscles in more aggressive cases, leading to death. The toxin's mechanism of action inhibits the release of acetylcholine in the presynaptic neuromuscular junction, causing flaccid paralysis.[2]

According to Paracelsus (1493-1541), the difference between medicine and poison lies only in the dose. Thus, despite botulinum toxin being considered one of nature's most toxic substances, its therapeutic potential has been explored over the years.[3] The initial application of botulinum toxin in medicine

was performed by Scott in 1970, with an aim at treating strabismus. [4] Since then it has been used for the treatment of neurological and ophthalmic diseases, as well as for cosmetic purposes. [3]

Botulinum toxin can be differentiated into eight serotypes called A, B, Cb, C2, D, E, F, and G. The type A and type B toxins are commercially available. [1] In dermatology, botulinum toxin type A has been widely used for the treatment of wrinkles and expression lines since its approval by the FDA in 2002.

In this manner, the main dermatological use of botulinum toxin is related to the aesthetics of the facial muscles. In recent years, however, botulinum toxin has been used for dermatologic conditions with great therapeutic results. The objective of the present review is to report the use of botulinum toxin in clinical diseases that can be treated by a dermatologist:

Hailey-Hailey disease

Hailey-Hailey disease – also known as benign familial chronic pemphigus – is an uncommon acantholytic dominant autosomal disorder characterized by flaccid blisters and erosions in the intertriginous regions, especially in the axillary and inguinal areas. Erosions associated with local factors such as heat, moisture, microbial colonization, and secondary infections induce the appearance of typical lesions in intertriginous areas. The treatment of Hailey-Hailey disease is traditionally carried out with corticosteroids, and topical and systemic antibiotics, with the use of topical corticosteroids being associated with the development of atrophy and striae, while the antibiotics can lead to bacterial resistance. [1,5]

Lapiere et al. reported the case of a 54-year-old patient diagnosed with Hailey-Hailey disease, who despite topical treatment with corticosteroids, and oral and topical treatment with antibiotics, had not had remission of the condition for three years. The patient underwent an injection of 25U of botulinum toxin A, administered at 20 points on the left axilla, with a 50% reduction in the affected surfaces after three weeks, while the right axilla remained unchanged. Six months after the first injection, the patient was treated with 50U of toxin in each axilla, experiencing complete remission of the disease in both armpits after three weeks. The other regions affected by the disease did not improve or worsen, indicating that there was no spontaneous remission of the disease, and the remission was due to the toxin. [6]

Bessa et al. described the use of botulinum toxin in two sisters, both bearers of Hailey-Hailey disease, who had experienced limited response to the classical treatment. The patients received 125U application of botulinum toxin A: one of them in the axilla and the other in the inguinal region (50 injection points at a distance 1cm from each other, with 2.5U toxin each). One month later, the patient that had the treated axillae showed complete remission of the lesions, and the patient treated in the inguinal region had mild residual erythema and minimal maceration. [7]

The authors linked the improvement in the condition to the decreased local sweating caused by botulinum toxin through the inhibition of acetylcholine in the sympathetic fibers of the sweat glands. The reduction of sweating probably leads to less local irritation (caused by friction) and reduced colonization by microorganisms involved in the exacerbation. Thus, they conclude that botulinum toxin A is a safe and easy to apply treatment option in Hailey-Hailey disease. [6,7]

Raynaud's phenomenon

Raynaud's phenomenon is a condition caused by the spasm of the digital arteries causing pain, numbness, ulceration, and even gangrene in some cases. Botulinum toxin has been shown to produce improvement in Raynaud's phenomenon in several recent studies, in addition to leading to improved digital perfusion that can be visualized on Doppler.

The use of botulinum toxin was first described in 2004 by Sycha et al., who observed improved pain and digital perfusion in two patients, both bearers of Raynaud's phenomenon who underwent treatment with 10U doses of botulinum toxin. [8] In 2009, in a more encompassing study of 19 patients who underwent palmar injection of 50U or 100U of botulinum toxin, it was possible to observe an improvement in pain immediately after the injection, with 84% of patients. Improvement of digital perfusion on Doppler was also observed, with all digital ulcers healing within 60 days. [9]

In a review study on the use of botulinum toxin in Raynaud's phenomenon, Iorio et al. concluded that botulinum toxin acts on vascular smooth muscles by blocking the transmission of norepinephrine and preventing vasoconstriction, as well blocking the alpha-adrenergic receptors[2] leading to the reduction of cold-induced vasoconstriction and pain. In that review, the authors report that different studies disagree regarding the dose, concentration, and distribution of injections, in addition to including Raynaud's phenomena of different etiologies, leaving the impression that a better standardization of the treatment is required. [10]

Notalgia paresthetica

Notalgia paresthetica is a chronic sensory neuropathy that affects the interscapular area, mainly T2-T6, and is characterized by local pruritus and for being a brownish area. Other symptoms are pain, paresthesia, hypoesthesia, hyperesthesia, and a burning sensation. [11] The usual treatments for this condition include local anesthesia, topical corticosteroids, and capsaicin – which do not have good results or long-term effectiveness. [12]

In 2007, Weinfeld proposed that botulinum toxin A would be an effective and safe treatment for notalgia paresthetica. The author conducted intradermal injections of 4U of botulinum toxin A in the affected area, with a distance of 2 cm between points, in two patients with notalgia paresthetica. Followed up with for 18 months, the patients showed significant long-term improvement in the pruritus, associated symptoms, and local hyperpigmentation. [12] It is known that botulinum toxin inhibits the presynaptic release of acetylcholine, and that the acetylcholine mediates the pruritus in atopic dermatitis. Furthermore, the toxin also inhibits Substance P and glutamate – both probably involved in the pruritus – and is capable of

reducing histamine release induced pruritus, thus making it a therapeutic option for pruritic conditions. [13] Wallengren and Bartosik also reported improvement of pruritus in four patients with notalgia paresthetica treated with botulinum toxin. [14]

On the other hand, when treating five patients with notalgia paresthetica, Pérez et al. observed that the improvement of pruritus varies by case, however none of the patients had resolution of the picture or improvement of the brownish stain.[11] Maari et al. also did not find improvement of pruritus or hyperpigmentation in notalgia paresthetica when comparing treatments with botulinum toxin A (10 patients) and placebo (10 patients). Therefore, botulinum toxin's benefits for this disease are still controversial. [15]

Postherpetic neuralgia

Postherpetic neuralgia is a complication of the infection caused by the *Varicella zoster* virus that causes pain and significant discomfort at the site, after the infection has been resolved. The neuralgia – complex mechanism for pain, often very severe –can be explained by an increase in the amount of nerve fibers P in the infection's site and a reduction in the number of wide nerve fibers, which are responsible for inhibiting the transmission of pain. Botulinum toxin exerts an analgesic role in neuralgia by inhibiting substances, such as glutamate, substance P, and the calcitonin-related peptide gene, all involved in the nociception. [16]

Emad et al. evaluated the effectiveness of botulinum toxin in 15 patients with neuralgia postherpetica through 15U injections per 10cm² of affected area, with an improvement of the pain in all patients – although the analgesic effect has decreased over the weeks. [16] Xiao et al. compared the use of botulinum toxin A to a placebo and obtained significant improvements in pain and sleep in patients treated with toxin. [17] In another study with 30 patients, the effectiveness of botulinum toxin was also proven in post-herpetic neuralgia, including tolerability and safety, when compared to a placebo. [18]

The application should be performed at points (with a distance of 1 cm from each other) within the area delimited by the patient, in amounts of 0.5U to 1U per point.

Rosacea

Rosacea is a chronic skin condition characterized by facial erythema, telangiectasia, papules, and inflammatory pustules, with periods of exacerbation and remission, affecting patients' quality of life. The main treatment currently includes topical medicaments such as metronidazole and azelaic acid, oral antibiotic therapy, and laser treatment with variable results.

Dayan et al. carried out a study with 13 patients, all bearers of rosacea, applying intradermal injection of botulinum toxin A totaling 8U to 12U per cheek. The outcome included a reduction of flushing, erythema, and inflammation within one week, persisting for up to three months, without side effects. The authors suggested that the mechanism of action involved is related to a neurogenic component associated to a vascular dysfunction, inflammation, and sebaceous activity. [19]

As described, botulinum toxin can be an innovative option in the treatment of rosacea. Because it is a difficult to control chronic condition that requires ongoing treatment due to periods of constant exacerbation, the toxin can represent a more durable treatment for this disease.

Lichen simplex chronicus

Lichen simplex chronicus, also known as neurodermatitis, is characterized by chronic pruritus that leads to areas of lichenification on the skin, resulting from excessive scratching. It is believed that this pathology is associated with psychological disorders, such as depression and anxiety.

Heckman et al. carried out a pilot study in five lichen simplex chronicus lesions in three patients who underwent intradermal injection of botulinum toxin A. The pruritus decreased within 3 to 7 days in all patients, and lesions completely disappeared between the 2nd and the 4th weeks after treatment, without recurrence during the four months of follow-up. The authors suggested that acetylcholine had mediating action in the pruritus, since it was blocked by the toxin. [20]

Pruritus is conveyed by nerve C fibers, which are sensitive to neurotransmitters, histamine, and other inflammatory mediators such as the substance P and calcitonin gene-related peptide. [21] In a recent study it was demonstrated that botulinum toxin is responsible for reducing histamine-induced pruritus, as well as vasomotor reactions and neurogenic inflammation. Other studies have demonstrated that botulinum toxin A reduces the release of glutamate, substance P, and calcitonin gene-related peptide. [22, 23]

Based on this evidence, botulinum toxin becomes an effective option in the treatment of lichen simplex chronicus, since pruritus is the hallmark of the disease. Furthermore, it emerges as an option for various diseases associated with chronic pruritus.

Parry-Romberg syndrome

Parry-Romberg syndrome is a rare condition characterized by sclerosis and hemifacial lipodystrophy – a form of localized scleroderma. It can be associated with a loss of local hair, retinal vasculopathy, and even headache in the affected side (secondary to trigeminal neuralgia).

Gary et al. described the case of a patient diagnosed with Parry-Romberg syndrome affecting the right-hand side of the forehead, eyebrow, and scalp, with loss of local hair and debilitating pain. At 53 years of age, the patient received 50U of botulinum toxin, distributed in six areas of local involvement, with significant improvement in the pain. Ten years later, the patient had severe facial atrophy, affecting the eyelid, orbit, and masticatory muscles, in addition to evidence of cerebral atrophy associated with low blood flow in the affected side, as visualized by MRI. The patient then underwent injections of botulinum toxin again, with relief of pain, decreased hair loss, and improved memory. [24]

It is believed that the pain relief achieved after intradermal botulinum toxin is caused by an increase in local perfusion, as botulinum toxin causes vasodilation by causing relaxation of

smooth muscles. Thus, if tissular perfusion can increase with repeated applications of botulinum toxin, it is possible that atrophies caused by vascular disease may have a new option of treatment with the use of botulinum toxin.

Erythromelalgia

Erythromelalgia is a neuropathy characterized by severe pain, heat, and erythema in the affected areas, and is known to be difficult to treat. The pain caused by the burning sensation worsens with heat and is relieved with cold. Lin et al. treated one patient with significant symptoms of the disease who had been refractory to multiple prior treatments (propranolol, escitalopram, alprazolam, gabapentin, aspirin, prednisone, amitriptyline, venlafaxine, duloxetine, or even combinations of these drugs) with botulinum toxin injections. A12.5U amount was injected subcutaneously on each cheek with an improvement of pain and redness within one week. The authors hypothesized that the pain present in erythromelalgia is neuropathic and that the erythema and heat are induced by an intense neurogenic inflammation. Having botulinum toxin A proven effective in neuropathic pain and also in diabetic neuropathy, it leads to good outcomes in erythromelalgia. The improvement in the erythema and redness can be explained by the inhibition of proinflammatory neurotransmitters, such as calcitonin gene-related peptide, the substance P and glutamate. [25]

Eccrine Angiomatous Hamartoma (EAH)

Eccrine Angiomatous Hamartoma (EAH) is a benign tumor composed of capillary channels and eccrine glands, that usually appears in childhood, in the distal part of the limbs, arising as a nodule or plaque, with red, blue, violet, brown, yellow, or skin colored pigment. It can be painful, hyperhidrotic, or cause excessive sweating. When associated with pain or hyperhidrosis, it can be treated with surgical excision or laser therapy.

Barco et al. reported a case of a 12-year-old patient with an EAH measuring roughly 6cm in the sacral region, with complaint of intense sweating in the region. Doses of 2.5U botulinum toxin A were injected at 14 points (distant 1.5cm from each other) in the region, resulting in an absence of sweating for five months. Through the blocking of acetylcholine, botulinum toxin reduces the activity of smooth striated muscles and of autonomic structures, reducing the secretion of eccrine glands – and is therefore widely used in hyperhidrosis. [26]

Based on this case report, it is possible to conclude that botulinum toxin A arises as a therapeutic option for symptomatic EAH, improving the quality of life in patients who prefer to avoid the surgical treatment of this pathology.

Multiple eccrine hidrocystomas

Eccrine hidrocystoma is a benign and asymptomatic tumor of the sweat glands that originates from the cystic dilatation of the gland's excretory duct. It is located in the centrofacial area, and is characterized by 2-6mm skin-colored, vesiculopapular lesions, usually multiple in number. [27,28] Although a single eccrine hidrocystoma can be easily treated with excision, surgical elimination of multiple lesions can be problematic depending on their amount and location.[29] Blugerman, Schavelzon and D'Angelo initially described the benefits of botulinum toxin A application in multiple eccrine hidrocystomas, highlighting the ease of application and lack of local scar. [29]

Correia et al. described two cases of multiple eccrine hidrocystomas treated with botulinum toxin A. The first patient had multiple hidrocystomas in the nose and nasolabial region that had been refractory to various treatments including CO_2 laser, cryosurgery, and oral isotretinoin. She underwent intradermal injections of botulinum toxin A totaling 50U (1 to 3U perilesionally, with a distance of 5mm). The patient had complete clinical resolution in five days, and there was no evidence of lesions for six months. Nevertheless recurrence was observed eight months after. The second patient had lesions distributed in the frontal and periorbital regions, and having undergone perilesional injections of botulinum toxin A (1U to 4U) presented a dramatic response in five days, and remained in complete clinical resolution for 11 months.[28] Woolery and Raipara also reported good results with the use of botulinum toxin A in eccrine hidrocystomas. [30]

Kontochristopoulos et al. recorded the treatment of a patient with multiple eccrine hidrocystomas in the centrofacial region who had been unresponsive to various previous treatments. She underwent 1U perilesional injections of botulinum toxin in the superficial dermis with a distance of 40mm between applications, totaling 60U. Improvement was observed in seven days, with complete resolution in 14 days, without recurrence for four months. As a side effect, the patient experienced difficulty with smiling in just the two days after the treatment, due to a compromise of perioral muscles, besides improvement in rhytids located near the lesions. [28]

The probable mechanism of action for botulinum toxin is involved in the treatment of eccrine hidrocystoma, consisting of the reduction of sweating due to the chemical blocking that takes place in the sweat glands. [29] Thus, botulinum toxin A emerges as a new treatment option for patients with multiple hidrocystomas resistant to other treatments, with the advantage of being simple, well-tolerated, producing excellent results and having no risk of scarring.

Inverse psoriasis

Inverse psoriasis is a form of psoriasis that affects flexural areas and is usually associated with chronic intertrigo, and is characterized by erythematous plaques with different degrees of infiltration, pruritus, and local burning sensation. The treatment of this disease can be difficult and requires a different approach as compared to that used to treat its common form, due to the skin's sensitivity in the affected areas.[31]

Botulinum toxin A can be a treatment option for inverse psoriasis due to its action of reducing both local sweat in the neuroglandular junction (and consequently, decreasing the maceration and infection), and inhibiting neuropeptides and other substances responsible for inflammation and pain transmission.[32]

Zanchi et al. demonstrated the first positive results with the use of botulinum toxin A in inverse psoriasis. They have carried out a study where 15 patients with inverse psoriasis were treated with 2.4U injections of botulinum toxin A (2.8cm between points), totaling 50U or 100U of toxin per patient, according to the lesion's size. There was improvement of the extent of the erythema and the intensity of infiltration in 87% of patients, an outcome that continued for 12 weeks after the treatment, which was well tolerated by patients, with an absence of side effects.[31] Saber, Brassard, and Brnohanian reported the case of a patient with inverse psoriasis and axillary hyperhidrosis, with significant improvement of the picture after one week of treatment with botulinum toxin A.[33]

Acting on the control of inflammation and of substances involved in the mechanism of inverse psoriasis, botulinum toxin can be considered a new treatment option.

Hyperhidrosis

Primary or idiopathic hyperhidrosis is a benign condition of unknown etiology characterized by excessive sweating in specific body sites, usually the palms, soles, axillae and, occasionally, the face and scalp. It is a common condition, affecting up to 3% of the global population and can even trigger psychological, social, and occupational problems. Until recently, treatment options were ineffective (e.g. aluminum salts or glutaraldehyde), complicated (e.g. iontophoresis) or extremely invasive (e.g. excision of axillary sweat glands). Other approaches have included the use of systemic drugs (sometimes with side effects), psychotherapy, and thoracic sympathectomy.

In 2004, the use of botulinum toxin was approved by the FDA for treatment of difficult to control axillary hyperhidrosis.[34] In the technique described by Del Boz et al., it is recommended that the axillary area to be treated be identified through a starch-iodine test. After defining the quadrants, antiseptic is applied, and topical or injectable anesthetic can be applied in order to minimize the discomfort. A 50U dose of toxin is applied in each axilla, intradermally in 0.1vml injections, observing a distance of 2cm between the points. Clinical improvement usually develops within one week after application, which can be repeated once a drop-off in clinical effect occurs.[35]

The effectiveness of botulinum toxin injections in axillary hyperhidrosis ranges from 2 to 24 months. Lecouflet et al. reported that the duration of the injection's effect increases with repeat treatments, allowing patients to reduce the frequency of injections over time. This can be explained by the action of botulinum toxin, which blocks synapses in the motor neurons, causing degeneration of the terminal axon, which in turn grows again, lending a transitory character to the effect of botulinum toxin. Due to the repeated injections of toxin, however, the terminal axon regeneration becomes slower, allowing a longer-lasting effect.[36]

Although the only approved indication for the treatment of hyperhidrosis with botulinum toxin is the persistent, severe primary axillary hyperhidrosis that is resistant to topical treatment, more recently other body sites have been successfully treated for hyperhidrosis with botulinum toxin.[35]

Facial hyperhidrosis can be safely and effectively treated with botulinum toxin, nevertheless in order to avoid side effects on facial muscles, very small amounts should be injected (0.3U), at distances of 1- 2cm. [37] In palmar hyperhidrosis, the result of the application of 100U of toxin on each palm lasts about 6 months, remarkably improving patients' quality of life. Injections in the palms of the hands can lead to transient weakness of the small muscles of the hands due to the diffusion of the toxin.[38] The treatment for plantar hyperhidrosis has also proven effective, with 100U in each sole remaining effective for 3 months. [39]

The anhidrotic effect of botulinum toxin can be noticed within 2-4 days after the application. Several studies have demonstrated its efficacy in 90% of patients. Despite the fact that the apocrine glands are innervated by adrenergic fibers, treatment with botulinum toxin also improves the unpleasant odor of sweat, with a mechanism that reduces sweating and therefore the environment conducive to bacterial growth. [38]

Botulinum toxin for treating focal hyperhidrosis has proven to be a very effective and safe option, which improves patients' quality of life – especially when other treatments are ineffective. [38]

Masseter muscle hypertrophy

Benign hypertrophy of the masseter muscle is an unusual clinical phenomenon of unknown etiology, characterized by swelling in the mandible's angle. It is occasionally associated with facial pain and can be important enough to compromise the aesthetics of the face. Several treatment options for hypertrophy of the masseter muscle have been reported, ranging from simple drug therapy to invasive surgical reduction. The application of botulinum toxin type A in the masseter muscle is considered a less invasive modality, able to sculpt the angles of the face. [40, 41]

The use of botulinum toxin for the treatment of the hypertrophic masseter muscle was initially described by Moore and Wood.[42] Kim, Park, and Park have evaluated 121 patients who received injections of 100 - 140U of botulinum toxin into the masseter, with a decrease in the muscle's thickness then observed through ultrasonography.[43] Aydilet al. conducted a retrospective study analyzing 28 patients with masseter hypertrophy, who underwent six toxin botulinum treatment courses in six-month intervals, concluding that the toxin was capable of reducing the thickness of the masseter muscle.[44]

In a review study on the efficacy and safety of botulinum toxin type A for the treatment of the masseter hypertrophy, Fedorowicz et al. did not identify any randomized controlled scientific study that confirmed the efficacy of botulinum toxin when injected in that muscle, for people bearing benign hypertrophy of the masseter. [40]

However, several studies have demonstrated that botulinum toxin A is a safe and effective treatment for masseter muscle hypertrophy, with significant long-term results and a positive correlation between the number of applications and the reduction of muscle volume. Its use has in some cases also been cor-

related with the decrease of associated pain. [45]

Dyshidrosis

Dyshidrosis – or dyshidrotic eczema – is characterized by the occurrence of vesicular lesions, usually in the palmar and/or plantar region, of a chronic and recurrent nature. Multiple etiopathogenetic factors are reported, including emotional factors, atopy, medications, and contact with substances.

Botulinum toxin has recently been used in the treatment of focal hyperhidrosis, which is often associated with dyshidrosis, for it acts as an aggravating factor in almost 40% of patients with dyshidrotic hand eczema. According to Swartling et al., botulinum toxin A is a valuable alternative for patients who are refractory to treatment of dyshidrotic eczema – especially those with associated hyperhidrosis or that which worsens during summer. It acts as a potent inhibitor of the release of acetylcholine, which induces the production and release of sweat. The halting of sweating leads to an improvement in outcomes and a reduction in the number of recurrences. [46] In addition to halting sweat production, there are reports of a possible antipruritic effect, suggesting that it not only interacts with the release of acetylcholine, but also with the substance P. [47]

In a prospective pilot study, Wollina et al. compared left and right hands in order to investigate whether the denervation of the sweat gland by botulinum toxin would be superior to a standard, topical corticosteroids-based therapy. The improvement of dyshidrosis was more significant with toxin than under topical therapy. Pruritus and the vesiculation were inhibited early when corticosteroids and botulinum toxin were used in combination. [47]

Botulinum toxin acts both on the reduction of perspiration – which aggravates dyshidrosis – and on the inhibition of the sensory system – with a direct effect on the ascending fibers through the inhibition of neurotransmitters – making it a therapeutic option in the treatment of dyshidrosis.

Hypertrophic scars

Hypertrophic scars occur due to excessive deposition of fibrosis and extracellular matrix, with unpleasant aesthetic and functional impacts. The etiology of their development has not been clearly determined; therefore its clinical management remains a problem. Many treatments are available, including surgical excision, injection of corticosteroids, radiation therapy, laser pressure, and therapy –though they do not always bring about good therapeutic results.

Recent studies have reported that botulinum toxin type A can inhibit the growth of hypertrophic scars and improve their appearance. Wang et al. created a model of hypertrophic scarring in the ears of rabbits, through which they discovered that botulinum toxin type A can inhibit the formation of scars and fibroblast activity. This can significantly reduce the expression and the proportion of collagen I and III in the hypertrophic scar.[48] Furthermore, there is evidence that botulinum toxin is involved in cell cycle regulation, reducing the TGF-α1 growth factor, which is expressed in the fibroblasts of hypertrophic scars.

An intralesional injection of botulinum toxin was performed in a recent study at doses of 70 - 140U per session, with the application being repeated every three months, for up to nine months. During the course of one year, 3 of the 12 patients had excellent results, 5 achieved good results, and 4 had reasonable results. The analysis of the lesions showed a reduction in their periphery in addition to flattening in all patients. There were no recurrences in the 1-year follow-up after the treatment.[49]

Notwithstanding, in another recent study the authors performed intralesional injections of 70 - 140U of botulinum toxin in keloids in four patients every two months, for six months, with an absence of clinical improvement. The assessment of the lesion's volume performed with 3D optical profilometry did not evidence changes after the treatment.[50]

In a recent review study on the treatment of keloids, Gauglitzet al. concluded that despite the fact that the reduction in tension strength caused by the intradermal injection of botulinum toxin corresponds to the ideal mechanism of action for the aesthetic treatment of scars, botulinum toxin's clinical efficacy in those lesions remains uncertain, requiring more in-depth comparative studies aimed at proving its action in scarring.[51]

Non-dermatological diseases having a therapeutic approach within the reach of dermatologists

Below are reported non-dermatological conditions that can nevertheless be successfully treated by a dermatologist, taking into consideration the comprehensive use of botulinum toxin by this expert and his or her experience with the toxin:

MIGRAINE

Migraine corresponds to the sensation of pain due to the activation of the afferent trigeminal that innervates the vasculature of the meninges and runs towards the trigeminal caudate nucleus. The pain is described in extracranial regions innervated by somatic afferent fibers that protrude in the homologous regions in the trigeminal caudate nucleus. This viscerosomatic conversion leads to the onset of pain in the meningeal afferent fibers to the extracranial dermatomes. The use of botulinum toxin in these dermatomes has been showing effectiveness in the treatment of chronic migraine headaches.

In 2010, the use of botulinum toxin type A was approved by the FDA (US Food and Drug Administration) for the prevention of chronic migraine, becoming the second choice treatment for adult patients who do not respond to drug therapy. The mechanism involved is the action of botulinum toxin in nociceptive mediators such as glutamate, substance P, and calcitonin gene-related peptide, in controlling the pain.[52]

Several randomized, placebo-controlled studies have shown the us of botulinum toxin for the treatment of chronic migraine. Blumenfeld et al., described a technique in which 155U of botulinum toxin A are distributed in 31 injections of 5U (applying 5U in each corrugator muscle, 5U in the procerus, 10U on each side of the frontalis muscle, 20U in each temporal muscle, 15U on each side of the occipital, 10U in each side of the cervical paraspinal region, and 15U on each side of

the trapezius muscle. One thousand, three hundred and eighty four (1,384) patients with chronic migraine were treated in this study, received at least 155U botulinum toxin each in 7 muscles of the neck and head every 12 weeks for 5 cycles, with an outcome of effectiveness and safety in the prophylaxis of chronic migraine. [52]

Lin et al. evaluated 98 patients with chronic migraine who received 100U of toxin injected in 21 points or 155U injected in 31 points of seven muscles of the head and neck. Around 40% of patients reported a 30% reduction of chronic migraines in the 12 weeks after a single application. [53] In another study, Aurora et al. showed improvement in the treatment of chronic headache with botulinum toxin when compared to a placebo, also demonstrating the need for maintenance treatment and the benefit accumulated over time with continued prophylaxis. [54]

Thus, it is possible to conclude that botulinum toxin can be used in the treatment of chronic migraine with positive results due to its analgesic action, especially in patients with difficulty in accepting the pharmacological treatment or even in those who are refractory to clinical therapy.

Bruxism

Bruxism is a condition characterized by the non-functional contact of the teeth of the mandible with those of the maxilla, generating the gnashing of teeth due to the repetitive and unconscious contraction of the masseter and temporalis muscles, leading to discomfort and damage to the teeth. The causes are poorly defined, however may involve behavioral, genetic, or functional alterations of the central nervous system.

No permanent therapy has proven effective in the treatment of bruxism. Current treatments focus on the management of symptoms and the prevention of complications, with oral appliances, and pharmacological and behavioral treatments the most frequently used methods. Some studies demonstrate positive results obtained with the use of botulinum toxin in the treatment of bruxism, what can be attributed to the decrease in the intensity of the contraction of the jaw occlusion muscles. [55]

Alonso-Navarro et al. treated 19 patients with severe bruxism with botulinum toxin injections in the masseter and temporalis muscles, at doses of 25 - 40U per muscle. These patients were followed up with for periods ranging from 6 months to 11 years. The result suggested success in the treatment of bruxism, with the effect's duration ranging from 13 to 26 weeks.

In a review study on the effectiveness of botulinum toxin in bruxism, Long et al. concluded that botulinum toxin injections could reduce the frequency of bruxism events, decrease the level of pain induced by this disease and meet the needs of the patients treated. When compared with oral appliances, botulinum toxin is equally effective. [56] In light of this, botulinum toxin arises as a safe, easy to use therapeutic option with great results in bruxism.

Depression

Depression affects about 121 million people worldwide, and is often a disabling disease. Although there are several treatments available, in many cases the therapeutic response is not satisfactory, with the condition becoming chronic in a number of patients. New therapeutic techniques are required to improve the prognosis of depressive disorders. [57] Finzie and Wasserman first described the use of botulinum toxin for the treatment of depression: 9 out of 10 patients treated with toxin did not present a depression picture after two months of treatment, with all patients showing improvement in mood. [58]

Negative emotions such as anger, fear, and sadness, which prevail in depression, are associated with the activation of the corrugator and procerus muscles in the glabellar region of the face. The treatment of the glabellar region with botulinum toxin produces a relative change in facial expressions of nervousness, sadness, and fear into a happiness expression, and can have an emotional impact. Patients who underwent this treatment reported improved emotional well being, in addition to an aesthetic benefit. The treatment is responsible for attenuating the activation of the limbic region of the brain, which was caused during voluntary contraction of the corrugator and procerus, thereby indicating that the feedback from facial muscles can modulate the processing of emotions. [57]

In a randomized, controlled study, 15 patients with depressive disorder underwent botulinum toxin injections in the glabellar region, while another 15 underwent injections of 9% NaCL0, as a placebo. The female patients received a total of 29U (7U in the procerus muscle, 6U in the medial region of the corrugators, and 5U in the lateral region of the corrugators). The male patients received an additional 2U in each of the sites (totaling 39U) due to their more abundant muscle mass. It was possible to observe an improvement of 47.1% in the symptoms of depression in the control group and 9.1% in the placebo group, at six weeks after the treatment. The authors state that a single treatment in the glabellar region with botulinum toxin is associated with the relief of depression, and that the facial muscles not only express, but also regulate emotional states. [57]

In a randomized, double-blind, placebo-controlled study, Magid et al. followed up with patients with depressive disorder who underwent injections of botulinum toxin (29U in women and 39U in men) and of placebo, concluding that there was a significant improvement in symptoms of depression in patients treated with botulinum toxin as compared to the placebo. [59] More recently, Wollmer et al. also demonstrated in a randomized controlled trial that botulinum toxin injections in the glabellar region produce improvements in the symptoms of depression, stating that although the mechanism of action is unknown, hypotheses associated with the feedback caused by the facial muscles should be considered. [60]

Furthermore, it is known that substance P levels are intimately involved in the pathogenesis of depression. Recent studies have reported the antidepressant effect of substance P's antagonist's receptor. Guiard et al. concluded that high levels of substance P in the brain have an important role in the pathophysiology of depression. [61] The transmission of substance P is also stimulated in stress and anxiety situations. Just as botulinum toxin is responsible for inhibiting the neurotransmission of substance P, the success in treating depression with botulinum toxin

can also be explained by this mechanism of action.

In this manner, it is possible to conclude that botulinum toxin injections can be applied to the glabellar region by dermatologists not only for aesthetic treatment, but also as a therapy in depressed patients, especially when they do not respond to pharmacological treatments.

CONCLUSION

The present study explored the many uses of botulinum toxin in dermatology, which go beyond aesthetics. The authors included various dermatological diseases that find in botulinum toxin an effective and differentiated therapeutic option, exploring its mechanism of action and results in the long run. Through extensive literature review, it was possible to gather information that is crucial to the conscientious dermatologist in his or her permanent search for new treatment options for his or her patients.

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Surgical treatment of the subungual glomus tumor guided by Doppler ultrasonography

Tratamento cirúrgico do tumor glômico subungueal orientado pela ultrassonografia doppler

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ABSTRACT

The subungual glomus tumor is a benign neoplasia of glomus cells and is clinically characterized by paroxysmal pain and hypersensitivity to cold, which causes functional impairment to patients. Diagnosis is based on history and physical examination, and can be better guided based on radiologic study – with ultrasound and Doppler. The authors demonstrate clinical and ultrasonographic aspects of a case, describing the surgical procedure.

Keywords: glomus tumor; ultrasonography, doppler, color; ambulatory surgical procedures.

RESUMO

O tumor glômico subungueal é uma neoplasia benigna de células glômicas sendo caracterizado clinicamente por dor paroxística e hipersensibilidade ao frio, o que gera prejuízo funcional ao paciente. O diagnóstico é baseado na anamnese e exame físico, podendo ser melhor orientado com base no estudo radiológico, com o ultrassom e doppler. Demonstramos os aspectos clínicos e ultrassonográficos de um caso, descrevendo o procedimento cirúrgico.

Palavras-chave: *tumor glômico; ultrassonografia doppler em cores; procedimentos cirúrgicos ambulatoriais.*

INTRODUCTION

In dermatology, lesion diagnosis is essentially a clinical matter. However, for the diagnosis of subungual lesions such as glomus tumors, exostosis, mucoid pseudocysts and fibrokeratomas, further assessment through imaging methods is necessary. In addition to identifying alterations, it is possible to assess the precise size and location of these tumors pre-operatively. Ultrasonography is a noninvasive method, which when performed with skill can describe tumors as small as 3 mm.

CASE REPORT

A 38-year-old Caucasian female patient from Nova Iguaçu, RJ - Brazil, who worked as a homemaker, sought care complaining of pain in the left thumb for about three years, accompanied by the sensation of "electric shock" when coming into contact with low temperatures and local trauma. She

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described progressive worsening, denying comorbidities or family history. On physical examination, erythronychia with undefined limits measuring roughly 3 mm, was observed in the central region of the nail plate, best seen on dermoscopy (Figure 1). The needle puncture test caused local discomfort.

Clinical suspicion of a glomus tumor was raised, with the ultrasound examination revealing a correlation between the pain symptoms and the observed location of the lesion. The analysis showed a nodular, hypoechoic image with well-defined contours (Figure 2) that was hypervascularized under power Doppler examination (Figure 2), occupying the medial ungual bed and causing bone remodeling of the underlying distal phalanx.

The excision of the lesion was carried out through a longitudinal incision in the nail plate, (Figures 3 and 4) which was replaced and sutured. The histological report revealed proliferation of perivascular round cells with eosinophilic cytoplasm and central vesicular nucleus, and a conclusive diagnosis of glomus tumor. (Figure 5)

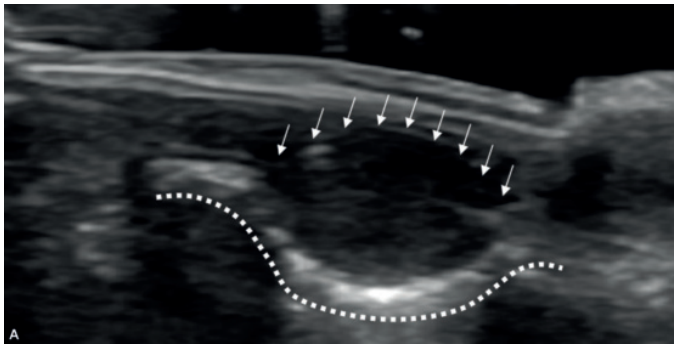

Figure 1: Ultrasound examination performed in the sagittal plane, B mode, with 18 MHz probe, showing a nodular, hypoechoic image with well-defined borders (arrows) in the medial nail bed, causing bone remodeling in the underlying distal phalanx (dotted line).

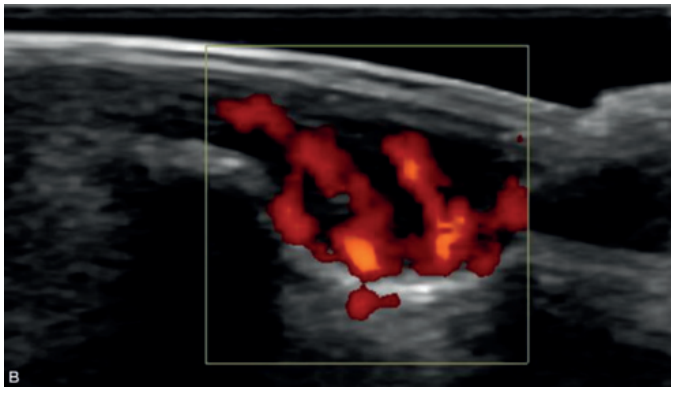

Figure 2: Power Doppler assessment – signs of hypervascularization of the lesion (red).

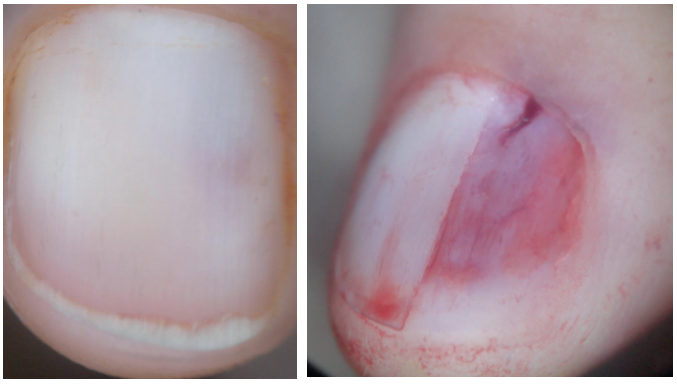

Figure 3: Intraoperative dermoscopy –bluish erythematous tumor measuring around 3mm, more clearly viewed with the exposure of the nail bed

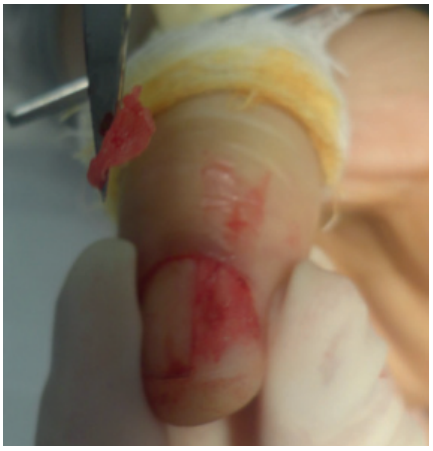

Figure 4: Surgical treatment – simple tumor exeresis

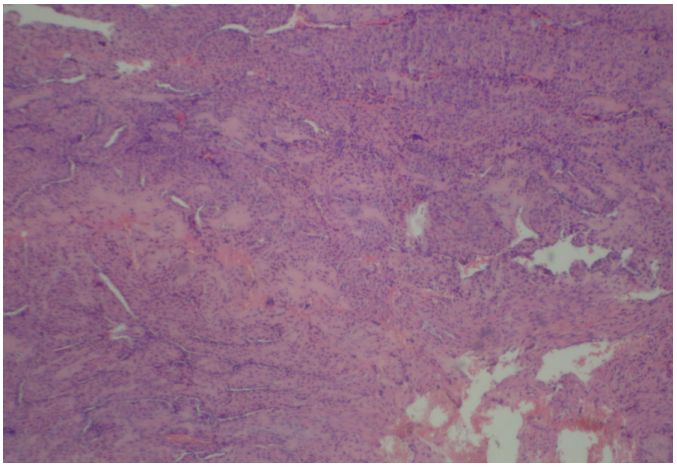

Figure 5: Histolopathologic study – proliferation of perivascular round cells with eosinophilic cytoplasm, consistent with glomus tumor

DISCUSSION AND CONCLUSION

Glomus tumors are benign neoplasms of glomus cells derived from neuromyoarterial glomus bodies. In about 75% of cases the lesion is located in the hand, especially in the subungual region where glomus bodies are found in higher concentrations. [1,2] They occur with any age group and are rare, account-

ing for only 1-5% of all tumors of the hand. [2] Multiple lesions are infrequent (2-3%), and are more common in children. [3]

Most lesions of this type present clinically with the classic triad (paroxysmal pain, hypersensitivity to temperature changes, and local sensitivity). Physical examination reveals bluish erythematous lesions of small dimensions (3-10 mm in diameter). However, due to the fact that they are located beneath the nail plate, it is difficult to assess their exact size and location, sometimes resulting in incorrect diagnoses. [3, 5]

Ultrasonography is a useful tool for diagnosis and preoperative localization of the tumor, which facilitates surgery and decreases recurrence rates and is currently the method of choice for the evaluation of lesions that affect the nail bed and plate. Another function of this examination is to dismiss differential diagnoses such as epidermal inclusion and mucous cysts, which are avascular cystic lesions, i.e. devoid of flow under Doppler examination and generally without remodeling of the adjacent bone. [2, 4, 5]

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New Techniques

Surgical treatment of the aging reversal lip

Tratamento cirúrgico da inversão labial do envelhecimento

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ABSTRACT

One of the signs of perioral aging is the lengthening of the upper lip followed by perioral sagging that leads to the depressed angle of the mouth. Various perioral rejuvenation techniques – such as the use of fillers and ablative techniques – are described, however the inversion of the lip does not usually fully improve with those treatment modalities. The authors describe three patients with depressed angles of the mouth that were surgically corrected through a simple, however little used technique, which produces satisfactory aesthetic results.

Keywords: mouth; aging; surgery, plastic.

RESUMO

Um dos sinais do envelhecimento perioral é o alongamento do lábio superior seguido de flacidez perioral que ocasiona a queda do ângulo da boca. São descritas várias técnicas de rejuvenescimento perioral, tais como preenchimentos e técnicas ablativas, observando, porém, que a inversão labial não costuma melhorar totalmente com essas modalidades de tratamento. Relatam-se três casos de queda do ângulo da boca corrigidos cirurgicamente por técnica simples, mas pouco utilizada, que apresenta resultados estéticos satisfatórios.

Palavras-chave: *boca; envelhecimento; cirurgia plástica.*

INTRODUCTION

Particularly evident in the perioral area, facial aging results from changes in the skin, subcutaneous tissue, muscles, and bones. [1-5] In the lower third of the face, facial aging entails the lengthening of the upper lip followed by perioral sagging and the resulting fall of the angle of the mouth, [1] which can be called frowning mouth and is associated with the formation of marionette lines. [2] The youthful, aesthetically ideal mouth resembles a rhombus-shaped diamond, with smooth contours extending between the commissures, with the cupid's bow well demarcated and protruding the philtrum. [2] With age, however, the loss of curvature and the fall of labial commissures lend a senile and saddened appearance. [2]

Among the techniques for perioral rejuvenation, the following can be highlighted: injections of cutaneous fillers (such as hyaluronic acid, which reconstruct lip volume and soften the grooves), dermabrasion and deep peels (which soften the rhytids), and botulinum toxin. Nevertheless, the improvement of the frowning and sad appearance of the mouth is not usually completely achieved with these modalities. [2,3]

The authors report on three cases of patients who underwent surgical correction of the fall of the labial commissures with a simple and rarely used technique, which nonetheless leads to satisfactory aesthetic results.

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METHODS

The correction of the frowning mouth is carried out by removing the excess of skin with an incision in the shape of a triangle (Figure 1). The base of the triangle (the line joining the points A and C) must be demarcated on the marionette line, starting at the edge of the skin with the semi-mucosa of the upper lip, taking care not to surpass the lower limit of the fold. After evaluating where and by how much it is necessary to raise the corner of the mouth, aiming to obtain a good aesthetic result, point B (the apex of the triangle) is marked. The end points of the line A-C (base of the triangle) are linked to point B. The exeresis of the marked skin is carried out, followed by hemostasis with cautery and simple suture using 5.0 mononylon. The suture must be started at point B, which should be joined to another point on the triangle's base (at the point where the greater elevation is intended), without the necessity of undermining the skin.

Post-operatively, the patients were instructed to restrict movement of the mouth during the first 24 hours. Sutures were removed after 7 days and the use of micropore tape over the scar was prescribed for 30 days.

RESULTS

The authors report 3 cases of surgical correction of the frowning mouth through the described technique: Patient 1 (47 years old), Patient 2 (45 years old), and Patient 3 (58 years old). Figure 2 depicts a satisfactory aesthetic result – both from the physician's and the patients' assessments. After 2 years of follow-up, the patients reported satisfaction with the good results achieved from the surgery.

DISCUSSION

Perioral aging is caused by a number of factors, such as collagen degeneration, atrophy of facial muscles and maxillary and mandibular bone absorption. [1,3,4] In addition, the repeated movement of the muscles of facial expression, combined with the effects of the exposure to the sun, contributes to the alterations seen in aging. [1]

The literature describes several ways to surgically correct the fall of the angle of the mouth. 1-3 In the described cases the authors used the technique of Fereydoun Don Parsa et al.. These authors classified patients with labial reversal as follows: Type I (those who only have a fall of the labial commissures), Type II (in addition to the fall of the labial commissures there is a formation of marionette lines). Type I patients are treated with a triangular excision adjacent to the vermilion of the upper lip. In Type II patients, the excision is extended along the marionette lines, also with the aim of correcting them. As the patients studied did not have marked aging, the authors chose the Type I technique. [2]

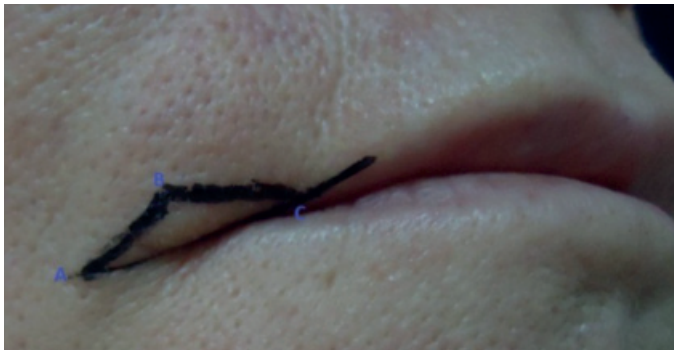

Figure 1: The correction of aging-related labial reversal is carried out with the removal of the excess skin in the shape of a triangle, as depicted here

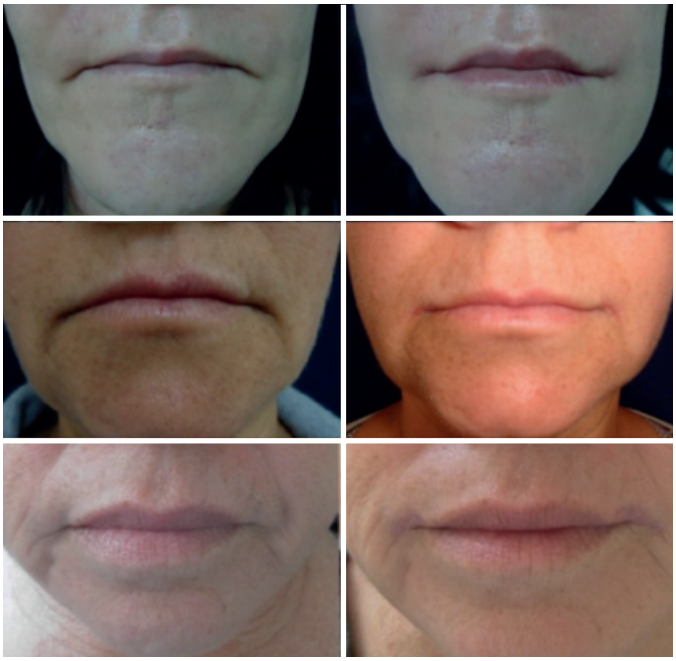

Figure 2: Pre-operative and 14thday post-operative, with satisfactory aesthetic results both in the physician's and the patient's evaluation

The main complication reported post-operatively was the formation of visible scars, sometimes hypertrophic. [2,3] In most cases, however, there was significant improvement with this issue after a few weeks of follow-up. The studied patients presented normal healing with an almost unnoticeable scar.

CONCLUSIONS

The frowning mouth lends a heavy facial expression, which in many cases cannot be corrected using only less invasive procedures. Often, surgical intervention is also required, which, as in the cases reported in the present study, proves to be effective, safe for ambulatory execution, and leads to excellent aesthetic results for the correction of aging-related labial reversal.

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Multiple eruptive dermatofibromas associated with systemic lupus erythematosus: a case report and brief literature review

Dermatofibromas eruptivos múltiplos associados a lúpus eritematoso sistêmico: relato de caso e breve revisão da literatura

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ABSTRACT

The solitary dermatofibroma or benign superficial fibrous histiocytoma is a common tumor that arises in the lower limbs of young women. Multiple eruptive dermatofibromas constitute a rare presentation of dermatofibromas (0.3%), often associated with underlying diseases. They are defined by the presence of 15 or more lesions or the appearance of five to eight tumors within less than four months. On PubMed/MEDLINE, to date, there are about 40 published cases of multiple eruptive dermatofibromas related to systemic diseases such as systemic lupus erythematosus, Sjögren's syndrome, hepatitis C, AIDS and the use of imunossupressants. The authors report a case where the emergence of multiple eruptive dermatofibromas preceded the onset of systemic lupus erythematosus by 20 years.

Keywords: histiocytoma, benign fibrous; lupus erythematosus, systemic; immunosuppressive agents.

RESUMO

O dermatofibroma solitário ou histiocitoma fibroso benigno superficial é tumor comum que surge nos membros inferiores de mulheres jovens. Dermatofibromas eruptivos múltiplos constituem rara apresentação de dermatofibromas (0,3%), frequentemente associada com doenças subjacentes. São definidos pela presença de 15 ou mais lesões ou surgimento de cinco a oito tumores em período inferior a quatro meses. No PubMed/Medline, até o momento, há cerca de 40 casos publicados de dermatofibromas eruptivos múltiplos relacionados a doenças sistêmicas, como lúpus eritematoso sistêmico, síndrome de Sjögren, hepatite C, Aids e uso de imunossuperessores. Os autores relatam um caso em que o surgimento de dermatofibromas eruptivos múltiplos precedeu em 20 anos a instalação de lúpus eritematoso sistêmico.

Palavras-chave: *histiocitoma fibroso benigno; lúpus eritematoso sistêmico; imunossupressores.*

INTRODUCTION

Solitary dermatofibromas or superficial benign fibrous histiocytomas are common and benign dermal fibrohistiocytic tumors that have the appearance of papules or nodules of a brownish erythematous color. Appearing as a single tumor, or in small numbers, they are generally asymptomatic. The diagnosis is clinical and histologic, and surgical treatment is recommended only for aesthetic reasons and if there are any symptoms – which is unusual. [1] Its etiology is unknown, and it is usually located in the lower limbs, with an absence of association with systemic diseases.

Multiple eruptive dermatofibromas (MED) constitute a variant, which occurs in 0.3% of patients, with the presence of 15 or more lesions, or the appearance of 5 to 8 tumors in less than four months. [1] The lesions are usually painful and widespread, and have been associated with autoimmune diseases, immunosuppressive drugs, and hormonal alterations. [2] Many patients have alterations in their immune status –more commonly AIDS and systemic lupus erythematosus (SLE) [3,4] – nevertheless other immune disorders (dermatomyositis, Sjögren's syndrome, hepatitis C) or myeloprolifarerative disorders (cutaneous t-cell lymphoma) can be associated with MED. [4] Furthermore, antiretroviral agents, immunobiological drugs (Efalizumab), and anti-tumor necrosis factor alpha may also be involved. Therefore, the emergence of this type of entity should prompt the investigation of the underlying disease. Various histological subtypes of dermatofibromas have been described in the scientific literature, however in general MED arises histologically as poorly circumscribed lesions, exhibiting epidermal hyperplasia, prominent collagen bundles and diffuse proliferation of fibrocytes. [5] The present report describes a case in which MED developed 20 years before the diagnosis of SLE.

CASE REPORT

A 47-year-old mulatto female patient, born and raised in the city of Juazeiro, Bahia State, Brazil, describe the emergence of approximately 5 nodular erythematous-brownish lesions on the lower limbs (LL), 25 years earlier, denying a history of local or systemic symptoms or medication use. The gradual emergence of other lesions with the same feature in the LL, upper limbs (UL) and abdomen ensued. New lesions have continued to appear up until the present time.

For the previous 5 years, the patient had been having protracted courses of fever for about 60 days, polyarthralgia, swelling in joints of the hands and feet, myalgia, loss of appetite, chest pain, and diffuse alopecia, which led her to seek care at the Rheumatology Department.

Laboratory tests revealed: ANF 1:1,500 (nuclear fine speckled pattern); hemangioma (Hb 10.7, leucocytes 8,000/ml, platelets 435,000; alpha-1 acid glycoprotein 241, N ≤ 117; alpha-1 antitrypsin 282, N ≤ 174); native anti-DNA 1:10, N = non-reactive; ESR 52mm in the first hour; echocardiography: limited pericardial effusion with cardiac chambers and normal diastolic function; normal renal and liver functions; negative PPD.

Once SLE was diagnosed, the patient was treated with 15 mg/day meloxicam, 30 mg/day famotidine, 200mg/day chloroquine diphosphate, 20mg/day prednisone and 10mg/week methotrexate, progressing to resolution of the fever and a progressive improvement in symptoms.

Two years after the onset of the systemic picture, the patient sought out the Dermatology Service due to the fact that the lesion presented a significant increase of brownish nodules, then numbering greater than 40, predominantly in the LL, UL, and abdomen (Figures 1 to 3). The biopsy of one of the lesions characterized the presence of dermatofibroma (Figure 4).

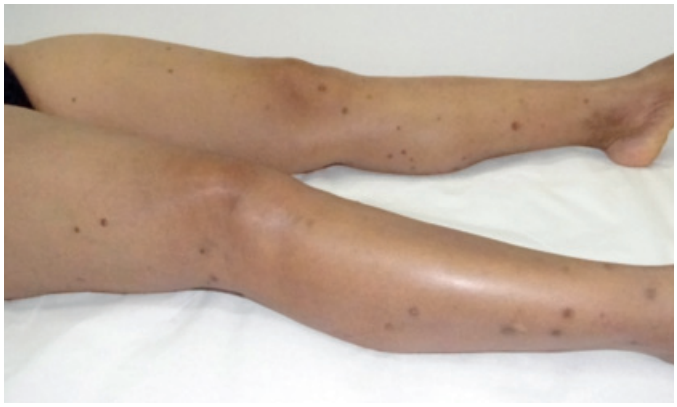

Figure 1: Presence of multiple dermatofibromas in LL

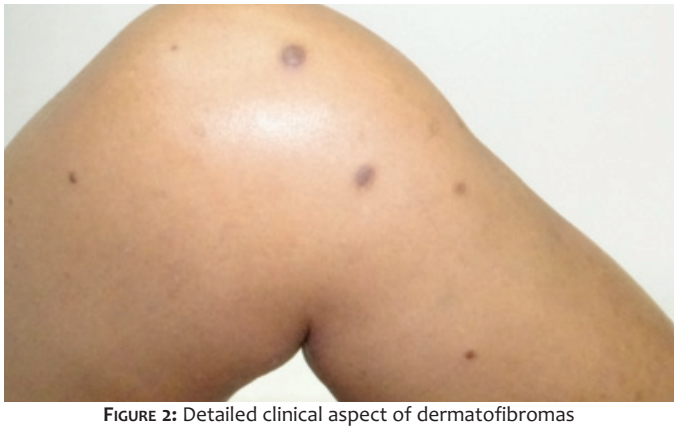

Figure 2: Detailed clinical aspect of dermatofibromas

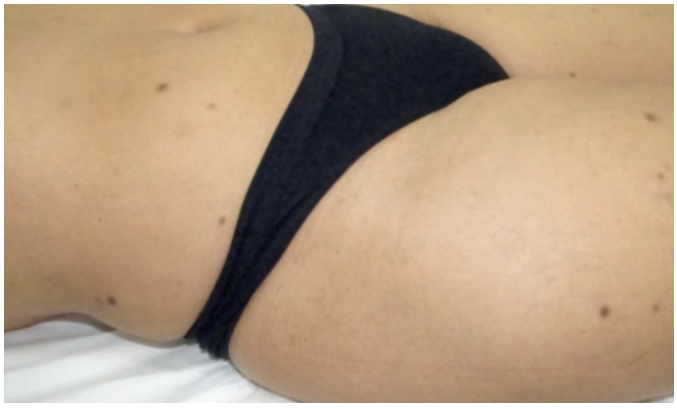

Figure 3: Presence of dermatofibromas in LL and abdomen

The patient had FAN 1:1,280 on the occasion, normal protein electrophoresis and echocardiogram, and was taking meloxicam, famotidine and 6mg/day deflazacort.

The patient has been followed up with by the Rheumatology and Dermatology departments to date, showing decreased ANF (1:320), thus confirming the control of the systemic involvement. She has, however, a progressive increase of the MED. After having been made aware of the benignity of the tumor, the patient chose not to undergo exeresis.

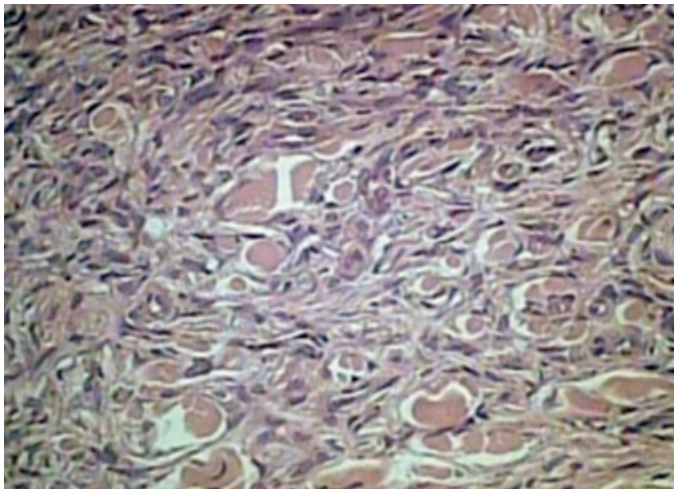

Figure 4: Histology - HE staining: Proliferation of fibrous histiocytic spindle cells interspersed among the collagen fibers of the reticular dermis

DISCUSSION

MED has been associated with several comorbidities (56%) [4] and autoimmune diseases treated with immunosuppressants – especially SLE (46%), HIV infection, ulcerative colitis, pemphigus vulgaris, acute myeloid leukemia, and organ transplants, and also congenital and family cases. [5] It occurs more frequently in female patients, which may be explained by the occurrence of autoimmune diseases being more predominant in women, particularly SLE.

Histologically it is characterized by proliferation in the dermis of non-encapsulated spindle cells with the periphery composed of bundles of collagen. The overlying epidermis is acanthotic and has hyperpigmentation in the basal layer. The presence of lymphocytic inflammatory infiltrate is common. [6]

In the present case, the patient was diagnosed with MED 20 years after its onset and, in the course of this, was diagnosed with SLE due to the presence of non-scarring alopecia, arthritis in two or more peripheral joints, serositis, positive for FAN and anti-DNA. In this manner, the patient therefore met 5 of the criteria proposed by the Systemic Lupus International Collaborating Clinics, which set new criteria for SLE in 2012, basing the diagnosis on the presence of 4 of the 17 listed, with at least 1 clinical and 1 immune criterion, or a renal biopsy consistent with nephritis lupica associated with positive ANF or anti-DNA. [7]

Over 80% of MED cases are immunologically mediated,[3] including those clinically manifested even before the diagnosis of underlying pathologies. Some patients developed MED after beginning use of immunosuppressants, or with an increase in dose, suggesting that it was a reactive process rather than a simple benign neoplasia, and allowing for the establishment of a causal correlation between medication and the development of MED,[8] which could explain the progressive increase of these lesions in the patient.

Although its pathogenesis remains unknown, recent evidence demonstrates the existence of several fibroblast growth

Chart 1: Literature case reports - Underlying diseases and dermatofibromas according to authors and dates

Authors/date	Distribution of the lesions	Age/gender	Underlying disease
Taborda M.L., Buffon R.B., Bonamigo R.R. / 2007	- Abdomen, LL	- 62 years / M	- Hepatitis C
Pinto Almeida T., Caetano M., Alves R., Selores M. / 2013	- RLL (thigh) - Trunk, UL, LL	- 12 years / F - 42 years / F	- Congenital - Sjogren's Syndrome
García Millán C. / 2007	- LL (thighs) - Abdomen, LL	- 35 years / F - 45 years / F	- HIV - HIV, hepatitis C, hepatocellular carcinoma
Massone C., Parodi A., Virno G,.Rebora A. / 2002	- Trunk, UL, LL	- 46 years / F	- SLE
Huang P.Y., Chu C.Y., Hsiao C.H. / 2007	Left upper limb, LL	- 28 years / F	- Dermatomyositis
Kimura Y., Kaneko T., Akasaka E., Nakajima K., Aizu T., Nakano H. / 2010	- Gluteal region, LL	- 32 years / F	- Hashimoto's thyroiditis, myasthenia gravis
Alexandrescu D.T., Wiernik P.H. / 2005	- UL, LL	- 52 years / M	- Chronic myeloid leukemia
Accaria E., Rebora A., Rongioletti F. / 2008	- LL - Trunk	- 62 years / F - 47 years / F	- Sézary Syndrome - Multiple myeloma after bone marrow transplantation

factors derived from mast cells in patients with SLE and MED. [9]

Yamamoto has demonstrated an increased numbers of mast cells both in the solitary dermatofibroma and in the MED. Mast cells are rich in cytokines that may affect fibroblasts, keratinocytes or t-cells, and may possibly induce several pathological changes, including epidermal acanthosis, basal melanosis, and the onset of the fibrosis process. In solitary dermatofibromas and in those with spontaneous regression, the number of those cells is lower than that in MED. [9] Immunohistochemistry shows positivity for antibodies against factor XIIIa, vimentin and actin. The transforming growth factor-beta (TGF-beta) can be a trigger for fibrosis. [10]

CONCLUSION

The authors have described a case of a patient with MED, which began 20 years before the onset of SEL. No previous description of such a long period between the diagnosis of MED and that of an underlying disease could be found in the literature review carried out by the authors, which is presented in this paper. ●

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Gorlin-Goltz syndrome: report of an exuberant case

Síndrome de Gorlin Goltz: relato de um caso exuberante

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ABSTRACT

The basal cell nevus syndrome – also known as Gorlin-Goltz syndrome – is an autosomal dominant disorder that occurs with the development of basal cell carcinomas in young patients and other clinical and radiological findings. As this syndrome tends to be a systemic disease, a better understanding of it by the various medical specialties is important for early diagnosis, allowing appropriate treatment and secondary prevention. In the present case, the authors describe an adult patient with multiple exuberant basal cell carcinomas having spread through the body over 10 years.

Keywords: basal cell nevus syndrome; carcinoma, basal cell; epidermal cyst

RESUMO

A síndrome do nevo basocelular, também conhecida como síndrome de Gorlin Goltz, é doença autossômica dominante que se apresenta com o desenvolvimento de carcinomas basocelulares em pacientes jovens entre outros achados clínicos e radiológicos. Como essa síndrome tende a ser doença sistêmica, o melhor entendimento a seu respeito pelas diversas especialidades médicas é importante para o diagnóstico precoce, permitindo tratamento e prevenção secundária adequados. No caso descrito, apresentamos um paciente adulto com múltiplos carcinomas basocelulares exuberantes difusos pelo corpo há 10 anos.

Palavras-chave: *síndrome do nevo basocelular; carcinoma basocelular; cisto epidérmico*

INTRODUCTION

Gorlin-Goltz syndrome or basal cell nevus syndrome is a dominant autosomal disorder characterized by early onset of basal cell tumors, and may also present other phenotypic abnormalities, for instance palmoplantar punctate pittings, odontogenic mandible cysts, and abnormalities in the ribs.[1]

Basal cell carcinoma (BCC) cutaneous lesions, as well as other skin alterations, may be present from birth or develop during childhood, though their occurrence is more frequent between puberty and 35 years of age. The number and type of lesions can vary within the same family, and there are marked differences in clinical manifestation between individuals from dark and light skinned populations. [1,2]

In many cases, the BCC cutaneous lesions can resemble nevi or fibromas, and speculation about their actual diagnosis is sometimes possible only with the addition of thorough clinical and family histories, as well as other clinical and physical aspects associated with the patient.

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The present study was carried out at the Instituto National do Cancer (INCA) - Rio de Janeiro (RJ), Brazil.

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Conflict of interest: None

CASE REPORT

A 39-year-old Caucasian male patient, who was born and brought up in the northeast Brazilian State of Bahia and worked as a farmer, was referred to the Brazilian National Cancer Institute (INCA). He complained about the emergence of diffuse tumor lesions throughout the body, which had grown progressively for nearly 20 years. The patient reported prior excision of some lesions and denied both similar family history or other comorbidities.

The dermatological examination showed multiple tumor lesions on the face (Figure 1), trunk, and upper limbs (some of them ulcerated, suggestive of BCC), in addition to diffuse nodular cystic lesions on the dorsum and upper limbs (Figure 2: A, B and C). He also had a large number of palmar pittings. There was an absence of cognitive deficits or neurologic alterations (Figure 3).

During the investigation, a skull and face tomography showed cutaneous thickening of an exophytic aspect, with infiltration of the lacrimal fossae, malar region, and upper lip; ectasia of the supratentorial ventricular system; extensive calcification of the tentorium and falx cerebri; multiple lytic expansive formations, which were sparse in the maxilla and mandible, consistent with keratocysts and sessile osteoma in the anterior wall of the right frontal sinus.

Also, biopsies of the tumor and nodular cystic lesions were carried out with a histological outcome compatible with BCC and epidermal cyst, respectively. In light of the clinical, radiological, and histological findings, it was concluded that this was Gorlin-Goltz syndrome with exuberant clinical findings.

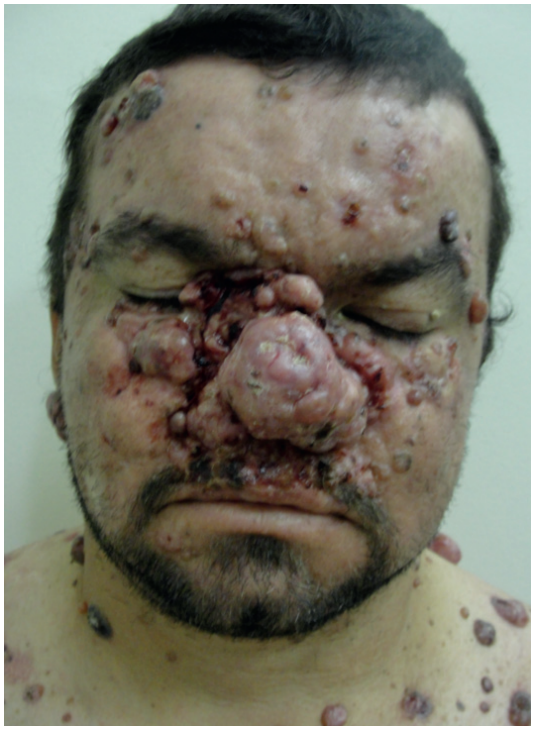

Figure 1: Multiple tumors in the face

DISCUSSION

The basal cell nevus syndrome (BCNS), or Gorlin-Goltz syndrome, is inherited through dominant autosomal transmission, has high penetrance and variable expressivity, and is characterized by the mutation of the PTCH1 gene, which is a tumor

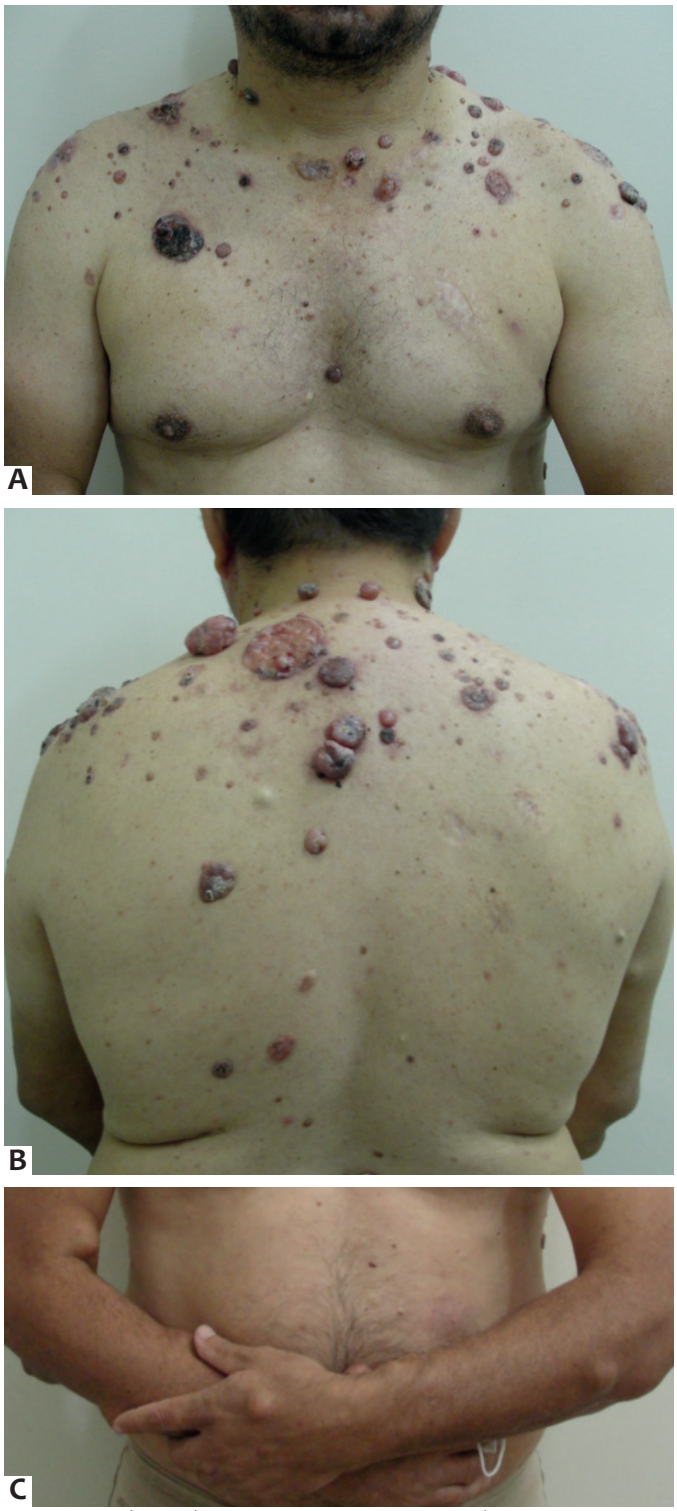

Figure 2: A) and **B)** Multiple tumors in the trunk. **C)** Multiple tumors in the upper limbs

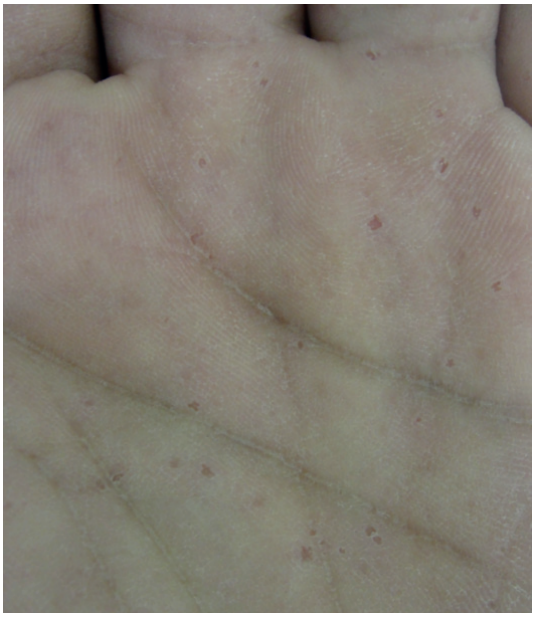

Figure 3: Palmar pittings

Chart 1: Diagnostic criteria of Gorlin-Goltz syndrome.

Major criteria:

- Two or more BCCs, or one before the age of 20
- Odontogenic keratocysts histologically confirmed
- Three or more palmar or plantar pits
- Bilamelar calcification of the falx cerebri
- Bifid, flattened, or fused ribs
- First-degree relative with Gorlin-Goltz syndrome

Minor criteria:

- Macrocephaly determined after adjustment for height (increased average height)
- Congenital malformations: cleft lip or palate, frontal bosses, coarse facies, mild or severe hypertelorism
- Skeletal abnormalities: Sprengel deformity, deformed chest, hemi vertebrae, fusion or elongation of vertebral bodies, defects of the hands and feet, syndactyly, bone cysts in the shape of candle flame in the hands
- Pontification of the sella
- Ovarian fibroma
- Medulloblastoma

suppressor. Its estimated prevalence ranges from 1/57,000 to 1/256,000 individuals and is more common in Caucasians. [2]

The PTCH1 gene, mapped on chromosome 9 (q22. 3q31), plays a fundamental role in the control of growth and development of normal tissues. The gene's product is a protein transmembrane component (Ptc, from *patched*), which in the presence of the Sonic Hedgehog protein, activates another protein transmembrane component (Smo, from *smoothened*). The activation of the latter promotes the transcription – in certain cells –of genes that encode signaling proteins belonging to the TGF-beta family (*Transforming Growth Factor-beta*) and WNT (*wingless-type MMTV integration site*), facilitating the cell decrease and differentiation processes. [3,4]

The characteristic signs and symptoms of the syndrome were recorded by Jarish in 1894. In 1960, Gorlin and Goltz described them as a triad, including the BCC and numerous keratocysts in the mandibles and skeletal abnormalities. Their work on this description is how the term Gorlin-Goltz syndrome was coined. [5]

The diagnostic criteria for the basal cell nevus syndrome, which were established by Evans et al. and modified by Kimonis et al. in 1997, are listed in Chart 1, with the diagnosis being confirmed when two major criteria, or one major and two minor criteria, are present. [6]

In the reported clinical case, the patient had three major criteria (multiple BCCs, palmar pittings, and calcification of the falx cerebri). The odontogenic keratocysts did not have a histological confirmation.

Epidermal cysts are infrequent findings in BCNS, however there are a few cases reporting this manifestation. [7] The mean age for the onset of BCC varies between 20 and 21 years. Variable in number – from just several to hundreds –they can occur in any area of the body, whether or not there has been exposure to solar radiation. [8] BCCs also have variable clinical behavior, and can be very aggressive from the onset, especially on the face. The predisposition to the development of BCC appears to be caused by the fact that the cells affected by the mutation are more susceptible to sunlight, due to the mechanism of DNA repair altered by the mutation. [9]

The mandible keratocysts occur in 75% of patients and have a recurrence rate of 60%. Seventy percent of patients had hypertelorism, which sometimes is associated with the widening of the nasal root. Approximately 80% have palmar or plantar pittings. [6]

Therapy aims at completely excising the tumors, especially BCCs and odontogenic keratocysts. Since the facilitation of the Sonic Hedgehog's signaling pathway is permissive for tumor development, the specific pharmacological treatment (Vismodegib) aimed at inhibiting that pathway is likely to be the future treatment strategy. [10]

In the case described, the therapeutic approach was not implemented in the dermatological service, due to the fact that the patient was transferred to his city of origin for treatment.

CONCLUSION

The diagnosis and treatment of Gorlin-Goltz syndrome require a multidisciplinary approach by dermatologists, plastic surgeons, head and neck surgeons, neurologists and neurosurgeons. Genetic counseling and screening of family members are essential. Awareness of the extreme sensitivity of such patients regarding ionizing radiation in necessary, with the presence of the potential to develop multiple tumors, in particular meningiomas and BCCs. ●

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Papilomatose confluente e reticulada de Gougerot e Carteaud: boa resposta à minociclina em dois casos

Confluent and reticulated papillomatosis of Gougerot and Carteaud: good response to minocycline in two cases

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ABSTRACT

Confluent and reticulated papillomatosis of Gougerot and Carteaud is a disease of uncertain etiology, the main differential diagnosis being pityriasis versicolor. The authors describe two cases of the disease – one in a man and one in a woman – both with good therapeutic response without recurrence after use of minocycline.

Keywords: hyperpigmentation; ceratosis; minocycline.

RESUMO

A papilomatose confluente e reticulada de Gougerot e Carteaud é doença de etiologia incerta, tendo como principal diagnóstico diferencial a pitiríase versicolor. Descrevem-se dois casos da doença, um em paciente do sexo masculino e outro em paciente do sexo feminino, ambos com boa resposta terapêutica e sem recidiva após uso de minociclina.

Palavras-chave: *hiperpigmentação; ceratose; minociclina*

INTRODUCTION

Confluent reticulate papillomatosis (CRP) was described by French dermatologists Gougerot and Carteaud in1927. Its etiology is unclear. Among hypotheses for the development of CRP are a disorder of keratinization and/or an abnormal response to microorganisms of the skin's biota. Lipophilic yeasts of the *Malassezia* genus are among the main suspects of involvement. [1,2] The disease is most common among women aged 10 to 35 years, with higher skin phototypes (IV to VI).

It is clinically characterized by verrucous, brownish papules approximately 5mm in diameter, which are confluent in the center and have a peripheral reticulate pattern. The most affected body sites are: the trunk, intermammary region, and dorsal and epigastric areas. It is possible for the lesions to extend to the shoulders, neck, and pubic region. Occasionally, the extremities can be affected. The palmar and plantar regions and mucous membranes are usually spared. There may be pruritus, however the greatest discomfort is of an aesthetic nature. [3,4]

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The three elements of CRP diagnosis are: 1) Clinical - papillomatous lesions of light-brown color, with confluent center and reticulate in the periphery; 2) Microbiological - direct-examination and biopsy without evidence of fungal elements; and 3) Histological - hyperkeratosis, papillomatosis, acanthosis, and occasional hypogranulosis, and sparse superficial inflammatory perivascular infiltrate. [5] Histology is nonspecific, and skin biopsy unnecessary in most cases. The most frequent findings are: hyperkeratosis and papillomatosis, thinning of the stratum granulosum and interpapillary focal acanthosis. Sometimes the vessels of the papillary dermis may show ectasia and perivascular lymphocytic inflammatory infiltrate. Basal layer hyperpigmentation can occur without alteration in the number of melanocytes. [6]

The main differential diagnosis is carried out with tinea versicolor (TV), which is more common than CRP. While CRP may not be as rare as reported in the literature, it is prone to under diagnosis –especially because some cases may respond to the usual therapy with TV. However, CRP should be suspected whenever a TV diagnosis does not improve after being treated with an antifungal. There is no standard therapy and several agents have been used with varying results. [7] Benzoyl peroxide, ammonium lactate, urea, tretinoin, clindamycin, sodium hyposulphite, and vitamin D analogues have been described with topical use. Among systemic treatments, minocycline, etretinate, and isotretinoin are among the most used. [8] The use of topical or systemic antifungals can be considered, especially when there is doubt about the differential diagnosis with TV. Although several drugs have been used with relative success, there is no uniformly effective agent due to the fact that it is a condition whose etiology is unknown. However, with the two present case reports it was possible to analyze the effectiveness of CRP treatment using minocycline, with a sustained therapeutic response, and therefore to help patients who have this diagnosis by providing a proven treatment option

CASE REPORT

Case 1: A 24-year-old Caucasian male patient, from the city of Curitiba (Paraná State, Brazil) had slightly scaly, hypo- and hyperchromic spots for four years in the abdominal, axillary, and dorsal regions (Figure 1). He underwent various topical and systemic treatments for tinea versicolor, with partial response and lesion recurrence.

Direct mycological examination and a culture of fungi taken from material swabbed from the anterior thorax were negative. The suspicion of CRP arose and minocycline was initiated at 100mg/day for eight weeks. The lesions disappeared at the end of treatment (Figure 2), and there was no recurrence after 12 months.

Case 2: A 20-year-old Caucasian female patient complained of scaly and hypochromic spots that she had in the abdominal region and on her back for three years (Figure 3). She had used ammonium lactate, with improvement and recurrence. Medications for tinea versicolor were also attempted without improvement. A biopsy was carried out (Figure 4), and fungi were not observed. The suspicion of CRP arose and minocycline was introduced at 100mg/day, for ten weeks. The lesions disappeared at the end of treatment and there was no recurrence for 36 months (Figure 5).

DISCUSSION

The emergence of CRP is generally more common in young adults, with an average patient age of 21 years. 6 Aligned with the data in the literature, the average age of onset of the dermatoses in both cases in this study was 18.5 years. Both patients had seborrheic skin, aggravated by excessive sweating during physical activity while wearing clothes without absorption capacity. The same characteristics had been verified in a previously reported case, 6 in which the presence of the symptoms were also correlated with sweat.

Most cases that have been described are of sporadic CRP, however there are some reports of the occurrence in two

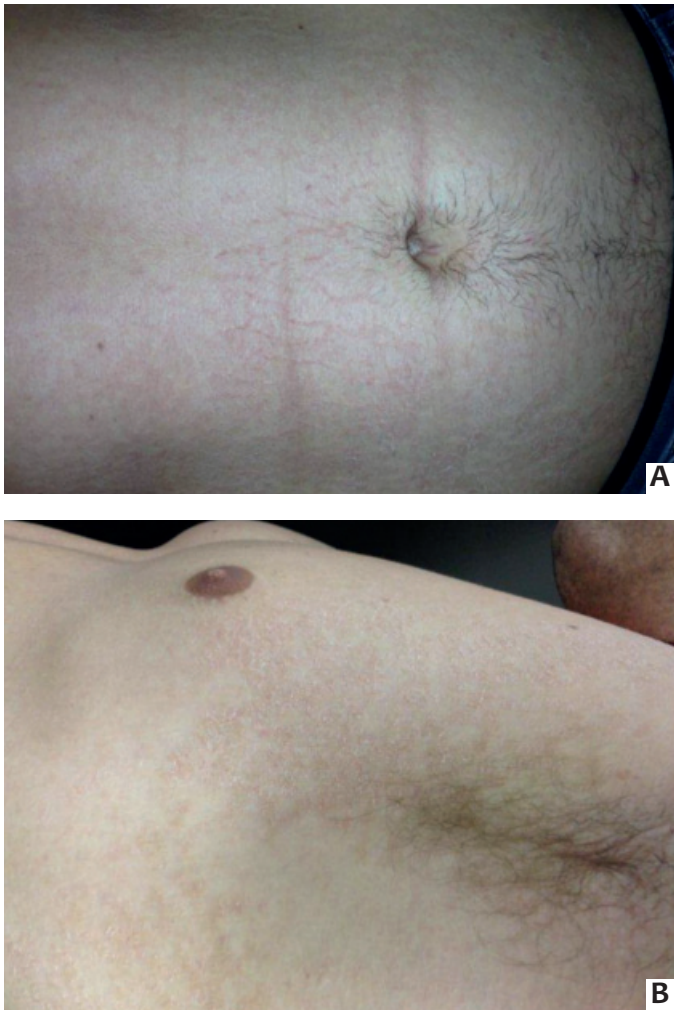
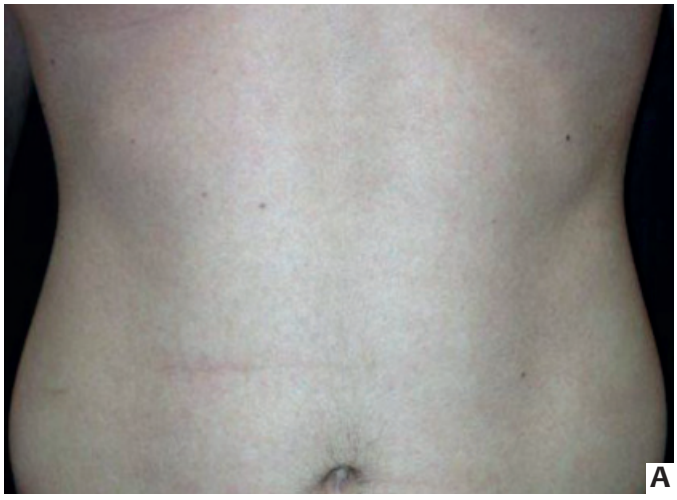


Figure 1: A) Hypochromic and hyperchromic, slightly desquamative spots in the abdominal region (Case 1)
B) Hypochromic and hyperchromic, slightly desquamative spots in the axillary region, extending to the dorsum (Case 1)



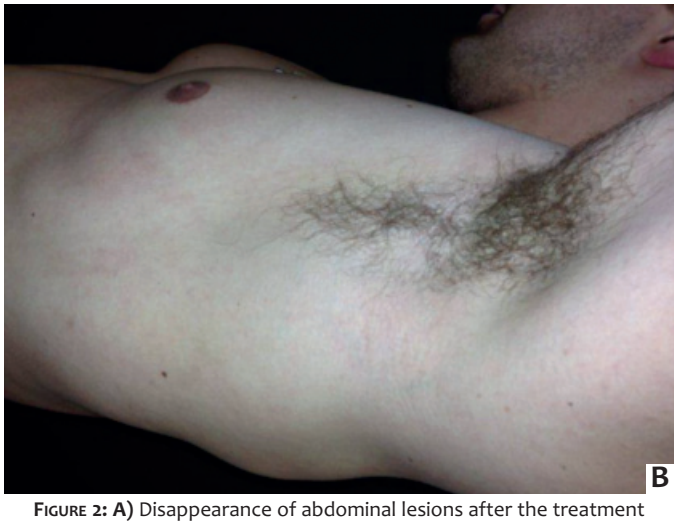
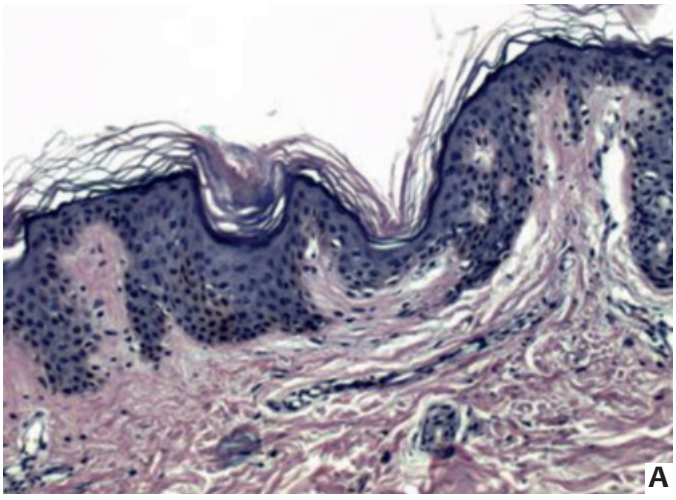


Figure 2: A) Disappearance of abdominal lesions after the treatment (Case 1). **B)** Disappearance of axillary and dorsal lesions after the treatment (Case 1)



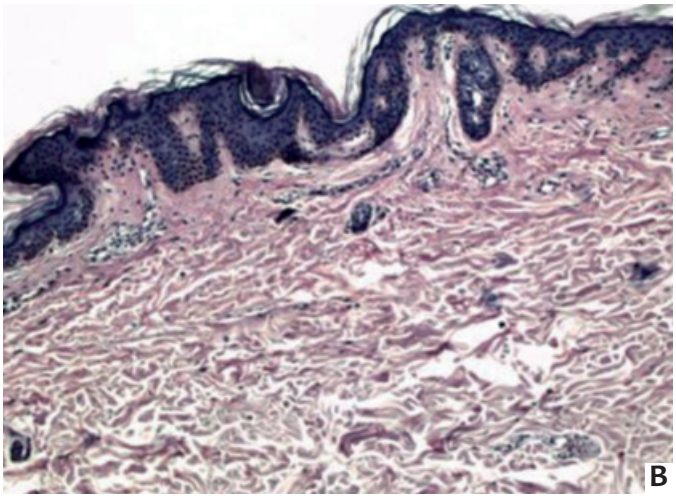


Figure 4: A) Patient's biopsy (Case 2)
B) Patient's biopsy (Case 2)

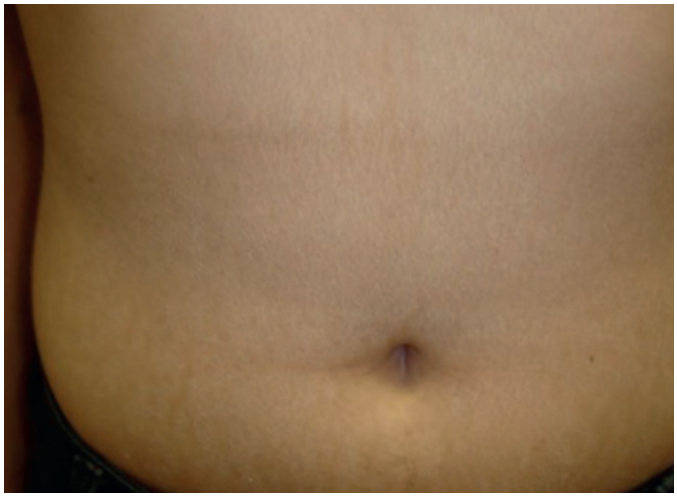


Figure 3: Hypochromic and slightly desquamative spots in the lower abdominal region (Case 2)

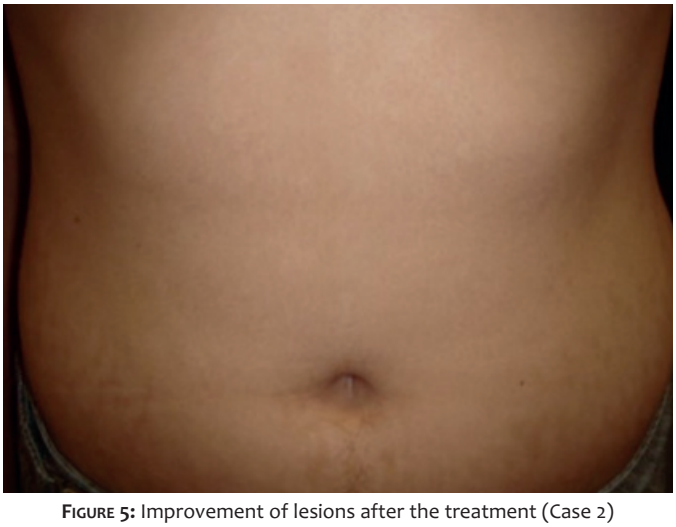


Figure 5: Improvement of lesions after the treatment (Case 2)

or more members of the same family. 3 In line with most cases reported in the literature, the two studied patients denied similar lesions in their families. Although records suggest a higher incidence of CRP in dark-skinned people, the patients studied in the present article were fair-skinned.

Regarding the treatment, in the studied cases there was a favorable response to the administration of minocycline at 100mg/day during a variable period of 8 to 10 weeks, with no recurrence after 12 months. That fact corroborated other reports, [7-10] leading the authors to conclude that this is a safe and effective alternative.

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Superficial acral fibromyxoma in a female patient: a case report

Fibromixoma acral superficial em paciente do sexo feminino: um relato de caso

ABSTRACT

The authors describe the case of a 75-year-old female patient, bearing a single asymptomatic, nodular lesion of fibroelastic consistency for three years, located on the left hallux. Following surgical excision of the lesion, the pathological examination and immunohistochemistry revealed a superficial acral fibromyxoma. This type of lesion was first described in 2001 and today there are approximately 100 cases in the literature. It is a benign mesenchymal tumor of slow growth, with a predilection for ungual and peri-ungual regions. There are no reports of malignant transformation and recurrence has been associated with incomplete resection.

Keywords: *fibroma; neoplasm; nail diseases.*

RESUMO

Descreve-se caso de paciente do sexo feminino de 75 anos, apresentando há três anos lesão única, assintomática, nodular, de consistência fibroelástica, localizada no primeiro pododáctilo esquerdo. Indicada a exérese cirúrgica da lesão, o exame anatomopatológico e a imuno-histoquímica revelaram fibromixoma acral superficial. Esse tipo de lesão foi descrito pela primeira vez em 2001, e hoje há aproximadamente 100 casos na literatura. Trata-se de tumor mesenquimal benigno, de lento crescimento, com predileção por regiões ungueais e periungueais. Não há relatos de transformação maligna, e a recorrência tem sido associada à ressecção incompleta.

Palavras-chave: fibroma; neoplasias; doenças da unha.

INTRODUCTION

Superficial acral fibromyxoma (SAF) was first described in 2001 by Fetsch et al. in a series of 37 cases. [1] Since then approximately 100 cases have been reported in the literature. [2] Yet this neoplasia is still poorly recognized by pathologists and dermatopathologists, partly due to its relatively uncommon occurrence, and partly because it has only recently been described. [3] It is a benign, slow-growing mesenchymal tumor, with no reports of malignant transformation or metastasis. The SAF has a clear tendency to involve the nail and periungual regions of the hands and feet. Middle-aged men are more frequently affected, with previously published case series suggesting that toes are more affected than fingers. [4] The usual treatment is complete surgical resection of the lesion, with a few cases of recurrence having been associated with incomplete resection. [2]

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The present study was carried out at the Instituto Lauro de Souza Lima (ILSL) - Bauru (SP), Brazil.

CASE REPORT

A 75-year-old mulatto female patient sought care complaining of a "callus" in the foot for three years. She denied pain or trauma preceding the onset of the lesion. The physical examination showed nodules of approximately 1 cm, with a color similar to that of the skin, fibroelastic consistency, and slight scaling located in the medial nail fold of the left big toe. It also presented with constitutional melanonychia and desquamation around the nail of that toe (Figures1 and 2). Dermoscopy showed intense subungual hyperkeratosis without the presence of specific structures and no vascularization (Figures 3 and 4). The patient underwent an excisional biopsy with the histology revealing a dermal mesenchymal lesion composed of stellate or spindle-shaped fibroblasts without atypia, permeated by capillaries a mid the myxoid matrix. The immunohistochemical analysis revealed diffuse expression of CD34, focal expression of CD99 and EMA with an absence of expression of the S-100 protein, or desmin and actin of the smooth muscle tissue. The clinical pathological features associated with the immunohistochemical profile defined the diagnosis of superficial acral fibromyxoma (Figures 5 and 6). The patient is still undergoing follow-up without signs of recurrence.

DISCUSSION

Superficial acral fibromyxoma affects more men than women (2:1), typically between the ages of 14- and 75-years-old, with a mean age at diagnosis of 43 years. [2,5] The SAF tends to present as a slow growing, firm mass or nodule, almost always located in the toes and fingers. [3] However, it can less commonly affect palms, heels, ankles, and thighs. [4] The nail is involved in 50% of cases, with hyperkeratosis or onychomycosis. A history of trauma preceding the appearance of the lesion is rare. [6] The SAF is characterized by being painless, a fact that explains the delay of patients in seeking medical care. [1] It is histologically characterized by a well-circumscribed dermal or subcutaneous tumor with increased vascularization, constituted by fusiform or stellate cells embedded in alternating areas of fibrous and myx-

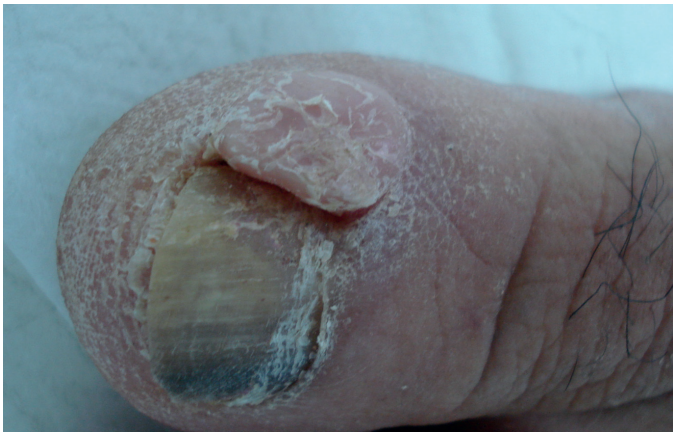

Figure 1: Skin-color nodular lesion of approximately 1 cm emerging from the medial nail fold of the left big toe

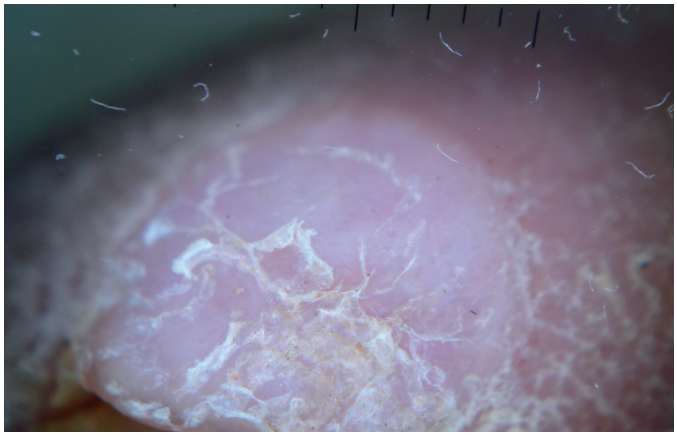

Figure 3: No structures or increased vascularity are seen under dermoscopy

Figure 2: Detail of the skin-color nodular lesion, with fibroelastic consistency and presence of desquamation on and around it

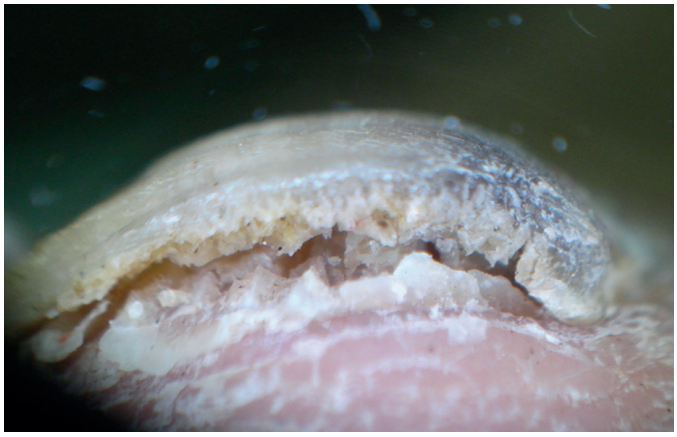

Figure 4: Intense subungual hyperkeratosis in seen under dermoscopy

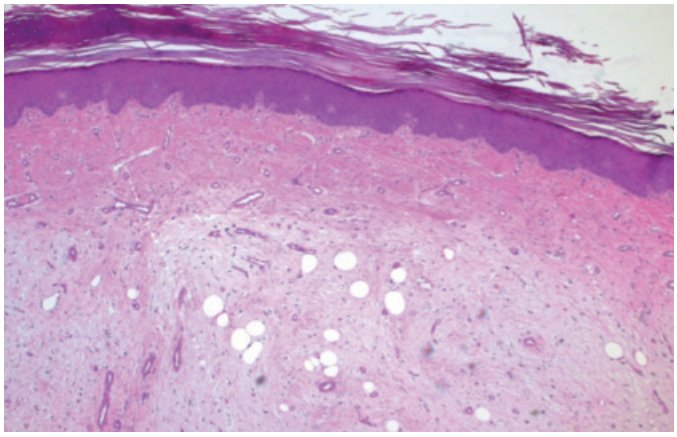

Figure 5: Circumscribed and well demarcated neoplastic proliferation located in the dermis (HE stain, 5x original magnification)

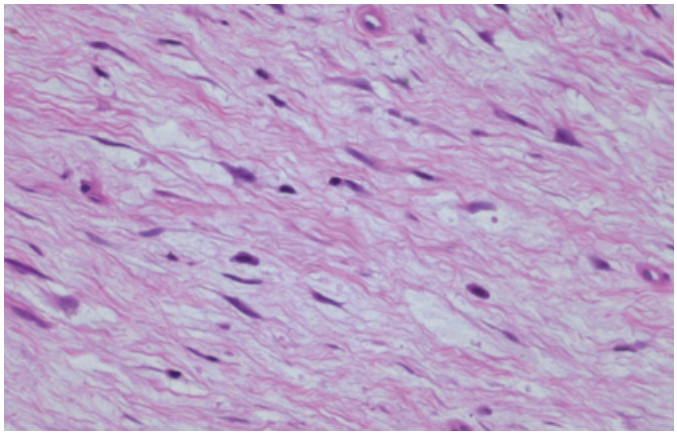

Figure 6: Neoplastic proliferation is composed of spindle cells without atypia, a mid myxoid stroma (HE stain, 40x original magnification)

oid stroma. The presence of significant nuclear atypia is rare and although it has been described in isolated cases, it causes concerns about the biological potential of the tumor. None of the tumors examined showed frank sarcomatous change, and no case of malignant transformation has been described in the literature. [2,3] The SAF is immunopositive for CD34, CD 99, and EMA, and negative for cytokeratin, melanocytic markers, SMA, and desmin. [3] The differential diagnosis of SAF should include consideration of ungual/periungual fibroma, acquired digital fibrokeratoma, low-grade fibromyxoid sarcoma, dermatofibroma, superficial angiomyxoma and myxoid neurofibroma.

The treatment of choice for SAF is surgical resection with free margins. Periodic monitoring is recommended after excision, and recurrence rates are estimated in the range of 10-24%. [6] Recurrence has been associated with incomplete resection. [2,5] The patient described showed no signs of recurrence of the lesion during a long follow-up. Although rare, SAF should be included in the differential diagnosis of tumors involving fingers and toes. [5]

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