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Efficacy of a nutrient association on hair cycle regulation and keratinogenesis: molecular basis

Treatment of rosacea with botulinum toxin

Chronic suppurative folliculitis of the scalp: a therapeutic challenge

Favre-Racouchot syndrome: optimal response to surgical treatment

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The effects of an association of nutrients on human follicular dermal papilla: an in vitro study

Efeito de uma associação de nutrientes na papila dérmica folicular humana: estudo in vitro

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.201810311024

ABSTRACT

Introduction: The skin aging process includes a functional decline of the scalp's structures, with progressive atrophy of the dermis and follicular dermal papillae, which are crucial to the nutrition and metabolism of the hair follicle. These phenomena are directly related to a poor quality of the hair shaft.

Objective: To evaluate the influence of a combination of nutrients on the keratinogenesis in the follicular dermal papilla.

Methods: Cell cultures of human dermal papillae were incubated with a combination of A, C, D, E and B-complex vitamins, in addition to trace elements and keratin amino acids during 72 hours, in three different concentrations. These cultures were compared to an untreated control-culture. The papilla's fibroblasts cell proliferation rate was determined after 72 hours.

Results: The diverse concentrations evaluated promoted significant increase in cell proliferation as compared to the control group, however there was no significant difference between the concentrations studied.

Conclusion: The studied association of nutrients was capable to significantly act on the proliferation of cells in the human hair follicle's dermal papilla, restoring more favorable conditions for the synthesis of the hair shaft. These findings demonstrate the presence of a significant potential in the approach strategy various causes of alopecia, including alopecia related to aging (senescent).

Keywords: Alopecia; Aging; Dermis; In vitro techniques; Nutrients

RESUMO

***Introdução**: O processo de envelhecimento cutâneo inclui um declínio funcional das estruturas do couro cabeludo, com atrofia progressiva da derme e das papilas dérmicas foliculares, essenciais à nutrição e metabolismo do folículo piloso. Esses fenômenos estão diretamente relacionados a pior qualidade da haste capilar.*

***Objetivo**: Avaliar o impacto de uma associação de nutrientes na papila dérmica folicular influenciando a queratinogênese.*

***Métodos**: Culturas celulares de papilas dérmicas humanas foram incubadas com uma associação de vitaminas A, C, D, E, as do complexo B, oligoelementos e aminoácidos constituintes da queratina durante 72 horas, em três concentrações distintas, contra uma cultura-controle, não tratada; foi então determinada a taxa da proliferação celular de fibroblastos da papila.*

***Resultados**: As diferentes concentrações avaliadas promoveram aumento significativo da proliferação celular em relação ao grupo-controle, mas sem diferença significativa entre as concentrações estudadas.*

***Conclusão**: A associação de nutrientes estudada foi capaz de atuar significativamente na proliferação das células da papila dérmica do folículo piloso humano, restabelecendo condições mais adequadas para a síntese da haste.*

Esses achados demonstram um potencial relevante na estratégia de abordagem em alopecias de causas variadas, incluindo a alopecia relacionada ao envelhecimento (senescente).

***Palavras-Chave:** Alopecia; Derme; Envelhecimento; Nutrientes; Técnicas in vitro*

Originals Articles

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INTRODUCTION

Hair follicle aging is among the most common causes of hair loss and with the lengthening of human life expectancy, there has been an increase in the incidence of the so-called senescent alopecia – also referred to as aging hair – as well as in the number of studies on this subject. [1]

In senescent alopecia, diffuse rarefaction is observed in the scalp, that might aggravated by androgenetic alopecia. In this condition, there is predominance of thinned hair, with presence of some other rougher and thicker fibers that are more difficult to comb. Also, progressive graying of hairs aggravates the sensitivity of the strands. [2,3]

There is concomitant and progressive atrophy of the dermis that supports hair follicles, in addition to a progressive reduction of its thickness and the weakening of the adjacent microvasculature, with a negative influence on the follicular dermal papilla.[4]

More recently, the follicular dermal papilla region has received increased attention in the understanding of the various etiologies of hair loss. The dermal papillae, which constitute a projection of the superficial dermis, are intensely vascularized, allowing the enlargement of the area of exchange with the epidermis. The follicular dermal papillae are responsible for nourishing the hair follicles, being vital structures for their integrity and function.

The hair follicle's dermal portion can be divided into two compartments: dermal papilla and dermal sheath. [5]

The dermal papilla is located at the base of the follicle; while the dermal sheath (or connective tissue sheath) follows the follicle's epithelium at the bulb's level. These portions are separated by a basal membrane.

The follicular dermal papilla is therefore in close contact with the hair bulb in a region of intense mitotic and metabolic activity, being thus responsible for synthesis of the hair shaft

Dermal papilla fibroblasts are located at the base of the hair follicles, and are known to induce regeneration of these follicles during the anagen phase. [6]

The presence of correlation between length of the hair shaft and the number of cells of the dermal papilla has already been verified. This can be observed both in the variation among follicles of different individuals and in processes of follicular decline, when progressive telogenization occurs in successive hair cycles.[7]

The dermal papilla has the ability to specify hair morphology and regulate the resumption of the capillary cycle's growth phase.[8]

The decline of the synthesis of dermal elements due to the aging of the scalp then further combines with the functional decline of hair follicles, with changes in the keratinogenesis of hair shafts.

With advancing age, nutrient intake and absorption may be reduced and in situations that require economy of energy and nutrient, they will be prioritized for vital functions and organs, further worsening the degenerative process. As a result, nutritional deficiency of amino acids, vitamins that are metabolic processes' cofactors (such as vitamins C and E), and trace elements (such as iron and zinc), therefore worsen the clinical symptoms of senescent alopecia. [9]

The diffuse loss of hair, known as telogen effluvium, results from some stimulus that changes the hair cycle, causing the acceleration of the anagen into the telogen phase (telogenization). This phenomenon modifies the physiological proportion of hair fibers between these two phases, leading to significant losses in relatively short time intervals, causing great distress to the patient. [10]

Among the most common causes of telogen effluvium are deficiency of nutrients, such as protein, iron, zinc and biotin, which are important elements in the synthesis of hair fibers, as well as for cellular functions of keratinocytes. [11,12]

In alopecia areata there is also involvement of the dermal papilla, with an increase in the expression of ICAM-1. [13]

Nutritional supplements that somehow act on keratinogenesis and dermal papilla cells may have a relevant effect on the integrity of the hair fibers and their synthesis. In light of that, this study was aimed at evaluating the effects of a new association of nutrients on the dermal papilla zone.

MATERIALS AND METHODS

The studied product is a combination of micronutrients and amino acids (Eximia Fortalize Kera D) composed of vitamins A, C, D, E, as well as those of the B complex (folic and pantothenic acids, biotin, niacin, pyridoxine and thiamine), in addition to trace elements, magnesium and zinc), all at concentrations compatible with the recommended daily intake (RDI), and a pool of essential amino acids: aspartic and glutamic acids, serine, glycine, histidine, arginine, threonine, alanine, proline, tyrosine, valine, methionine, cystine, isoleucine, tryptophan, leucine, phenylalanine, lysine and hydroxyproline.

The product was previously prepared for culture evaluation of dermal papilla cells at non-cytotoxic concentrations.

Human dermal papilla cells (ScienCell Research Laboratories, USA) were seeded in 75cm2 bottles (Nunc®, Denmark), cultured and expanded in an incubator at 370ºC in the presence of 5% CO2, using specific culture medium. Upon reaching confluence, the cells were seeded in 96-well plates (Nunc®, Demmark) for further evaluation of cell proliferation.

Human dermal papilla cell cultures were incubated for 72 hours with the three predetermined non-cytotoxic concentrations: 0.316mg / ml, 0.100mg / ml and 0.0316mg / ml. Concomitantly, a culture without treatment was evaluated as a control. Subsequently, the rate of cell proliferation was measured based on a trial of incorporation of bromodeoxyuridine (BrDU) in the cell's DNA using a commercially available kit (Cell Signaling Technology Inc., Danvers, MA, USA).

Bromodeoxyuridine is a synthetic nucleoside analogous to thymidine, used to detect proliferating cells in living tissues. [14]

The reading of the absorbance for the evaluation of proliferating cells was performed by spectrophotometry (Multiskan, GO, USA).

Statistical evaluation

In the statistical evaluation, the ANOVA test (GraphPad Prism v6) was used to compare the data between the groups. The Bonferroni post-test was then applied, to confirm the ANOVA test result. A 5% significance level was used.

RESULTS

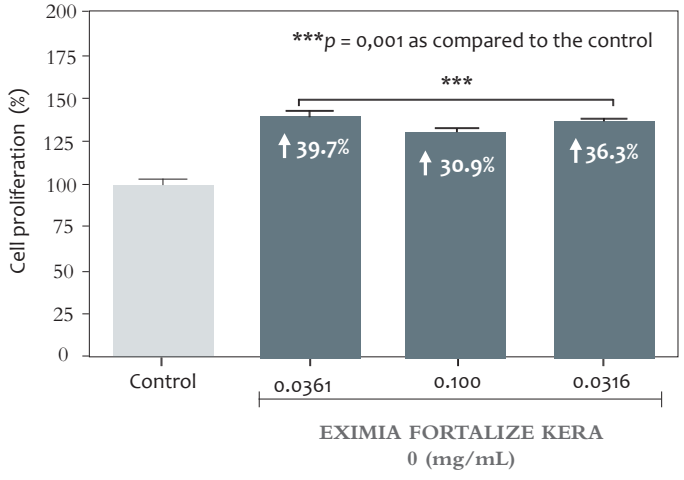
The different evaluated concentrations (0.316, 0.100 and 0.0361mg / ml) led to respective increases of 39.7%, 30.9% and 36.3% in cell proliferation regarding the control group. There was no significant difference between the studied concentrations regarding the rate of cell proliferation, all of which with statistical superiority when compared to the control group. Graph 1 demonstrates the effect of the studied nutrient association on the proliferation of cells in culture of follicular dermal papilla cells.

DISCUSSION

Hair loss is among the most frequent complaints in dermatological practices. About 80% of males and 50% of females are expected to experience hair loss during the course of their lives.[15]

In the aging process there is a tendency of loss of dermal papillae due to the flattening of the dermoepidermal junction throughout the integument. A series of phenomena also occur in the hair dermal papillae, which are differentiated structures closely related to the hair follicle. Although the role of follicular dermal papillae in hair aging has not yet been fully elucidated, an *in vitro* study has demonstrated that follicular dermal papillae experimentally induced into aging lose their ability to induce hair follicle neogenesis and epidermal differentiation, in addition to suppressing the growth of stem cells. They also produce higher levels of inflammatory cytokines that, in addition to inhibiting cell growth (particularly IL-6), block the transition from the telogen into the anagen phase *in vivo*. [16]

Although dermal cells seem to be resistant to oxidative stress, it has been observed that in androgenetic alopecia, dermal papilla cells from the frontoparietal rarefaction areas have higher levels of calatase and total glutathione, nevertheless appear to be less able to cope with oxidative stress, when compared to cells of the dermal papilla from the occipital region. These findings demonstrate that oxidative stress has a role in the pathogenesis of androgenetic alopecia, suggesting that bald area cells are more sensitive to environmental oxidative stress than cells from non-bald areas.[17]



Graph 1: Increased rate of cell proliferation: human follicular dermal papilla cells

The proliferation of dermal papilla cells significantly demonstrates that the association of nutrients contained in the studied compound is capable of positively stimulate the proliferation of dermal papilla fibroblasts. It is through the dermal papilla that the hair bulb receives and absorbs the nutrients that are crucial for the development of hair. Evidence suggests that the dermal papilla and its fibroblasts have influence on follicular growth, especially on the proliferation and differentiation of hair follicle matrix cells.[18]

In androgenetic alopecia, the primary target of androgen action in the hair follicle is probably also the dermal papilla, with its binding occurring through specific receptors.[19]

A cross-sectional study investigating the correlation of vitamin D deficiency and alopecia areata demonstrated that serum vitamin D levels were significantly lower when compared to the control group. The lowest values were found in cases of total / universal alopecia areata as compared to plaque and in ophiasis cases.[19]

Another study involving 80 women with telogen effluvium showed significantly lower levels of vitamin D than those in the control group, nevertheless the precise mechanism of action is not yet established.[20]

Regarding oxidative stress, hair is also exposed to environmental factors, as is the case for the remaining of the skin. Ultraviolet radiation, smoking habits and nutritional aspects, which are recognized as major factors in extrinsic cutaneous aging, also lead to an equal impact on dermal integrity and functionality, as well as on the function of the hair follicle, interfering in the synthesis and differentiation of keratin, and in the hair cycle, accelerating the telogenization phenomenon and progressive miniaturization of the shaft. Experimental evidence supports the hypothesis that oxidative stress plays a role in hair aging.[21]

These factors generate a state called microinflammation – a nomenclature that makes reference to the slight, indolent inflammation that is not destructive as the inflammation observed in cicatricial alopecias, nonetheless leads to slow and progressive damage of the follicle.[22]

The synthesis of the hair fiber also depends on an adequate protein supply: α-keratin – which receives this denomination because its structure is α-helical in shape – is formed by sulfur bridges. Although keratin is composed of the almost 21 amino acids occurring in nature, sulfur amino acids – such as cystine (composed of two cysteine molecules) and methionine – are crucial for the hairs' structure and the combination of resistance and other physical properties of the strands, such as brightness, elasticity, and color are linked to the balance between the amino acids involved.[23]

In the present study, the association of nutrients that stimulated the follicular dermal papilla was capable of:

- Stimulating keratinogenesis, not only based on the supply of nutrients, such as the amino acids contained in keratin (cystine and methionine), but also on elements involved in keratinocyte metabolism (B-complex vitamins, including biotin, and oligoelements such as iron, magnesium and zinc) and on the stimulus caused by the proliferation of dermal papilla cells, which are fundamental for the synthesis of hair stems, thus offering a multiple mechanism

- Regulating keratinogenesis (vitamins A and D) and collagenesis (vitamin C) with vitamins that also help to inhibit damages caused by oxidative stress

Epidermal vitamin D receptors regulate the expression of many genes related to the hair cycle in mammals. [24] Antioxidant micronutrients, such as vitamin C and E, as well as factors that regulate inflammation, could also act on the prevention and assist in reducing the degenerative damage resulting from the inflammatory process.[24, 25]

CONCLUSION

The association of nutrients found in the studied formulation was able to significantly act on the proliferation of the human hair follicle's dermal papilla, lending conditions for the synthesis of the hair shafts. The observed stimulation of the dermal papilla – favoring keratinogenesis – has a relevant potential in the approach strategy in alopecias of varied causes, such as androgenetic, areata, senescent alopecia or even telogen effluvium.

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Implementation of the study, data compilation and review, statistical evaluation oversight, preparation of the report.

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Originals Articles

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Conflict of interests: None.

Efficacy of a nutrient association on hair cycle regulation and keratinogenesis: molecular basis

Eficácia da associação de nutrientes na regulação do ciclo pilar e na queratinogênese: bases moleculares

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ABSTRACT

Introduction: Associated nutritional elements in physiological doses have demonstrated beneficial effects on capillary synthesis.
Objective: To evaluate the impact of the association of nutrients on parameters related to the follicular unit's integrity.
Methods: An evaluation of the interaction of a nutritional Suplement versus an in vitro control was carried out in culture of human hair follicles, under four diverse markers: quantification of keratins 10 and 14; immunofluorescence evaluation of 17A1 collagen (COL17A1) protein expression; determination of β-catenin; and quantification of ATP synthesis.
Results: There was a significant improvement ($p < 0.005$) of all evaluated parameters. Histologic analysis demonstrated a significant increase in the presence of the collagen 17A1 under immunofluorescence.
Conclusions: The parameters evaluated in this study have highlighted the positive impact of the association of nutrients in the hair follicle and follicular papillary dermis, with an increase of cell proliferation and metabolism, as well increased presence of collagen 17A1.
Keywords: Beta Catenin; Collagen; Hair follicle; Keratin-10; Keratin-14

RESUMO

***Introdução**: Elementos nutricionais associados em doses fisiológicas demonstraram efeitos benéficos sobre a síntese capilar.*
***Objetivo**: Avaliar o impacto de uma associação de nutrientes em parâmetros relacionados à integridade da unidade folicular.*
***Métodos**: Foi realizada uma avaliação de interação do suplemento nutricional versus um controle in vitro, em cultura de folículos pilosos humanos, sob quatro marcadores distintos: quantificação das queratinas 10 e 14; avaliação por imunofluorescência da expressão proteica do colágeno 17A1 (COL17A1); determinaçao de β-catenina; quantificação da síntese de ATP.*
***Resultados**: Houve melhora significativa ($p < 0,005$) de todos parâmetros estudados; a histologia demonstrou aumento significativo da presença do colágeno 17A1 sob imunofluorescência.*
***Conclusões**: Os parâmetros avaliados neste estudo permitiram evidenciar o impacto positivo da associação de nutrientes analisada no folículo piloso e derme papilar folicular, com incremento das proliferação e metabolismo celular, além de maior presença do colágeno 17A1.*
***Palavras-Chave:** Beta Catenina; Colágeno; Folículo piloso; Queratina-10; Queratina-14*

INTRODUCTION

Hair growth depends on the close interaction between different cell populations in the follicular compartment. [1]

Dermal papilla cells originate from the mesenchymal dermis and are located at the base of the hair follicles. These cells play a crucial role in the hair morphogenesis and cycle through mechanisms involving the Wnt signaling pathway. [2]

The Wnt signaling pathway is responsible for the development and regeneration of hair follicles and is mediated by β-catenin, which is a key signal for the cell nucleus, in which it binds to the TCF/LEF transcription factor to activate the transcription of genes that produce hair fibers. [3]

Hair aging is a multifactorial process in which intrinsic factors are associated with extrinsic factors, as is the case for the skin as a whole: solar radiation – particularly ultraviolet (UV) radiation – is the most studied, however other oxidative and mutagenic factors, such as diet and pollution, influence that process. Likewise, there is progressive decline in epidermal renewal, with changes in the scalp's cutaneous barrier. [4]

The hair aging process is intrinsically connected to the hair follicle, and this to the follicular papillary dermis. [5] The gradual reduction of the cellular population in these structures, together with oxidative and DNA damaging mechanisms, is a crucial event in hair aging that is described and phenotypically correlated with hair. [6]

There is evidence that this reduction in stem cells correlates with the gradual proteolysis of a specific collagen – type XVIIα1 (COL17A1). [7]

This process is clinically characterized by depigmentation and loss of hairs. From the histological point of view, it is possible to observe the miniaturization of the hair follicle. [6]

Nutritional elements combined in physiological doses have demonstrated beneficial effects on the hair synthesis. Keratinogenesis-linked nutrients associated with antioxidants have been demonstrated to have positive effects on keratinocytic proliferation and differentiation. [8] Additionally, the clinical effect of this association was demonstrated in another study, according to which patients with telogen effluvium in use of nutritional supplementation showed a significant improvement in the anagen/telogen ratio after the isolated use for 12 weeks. [9]

Some of the nutritional supplements may also possibly lead to a better metabolic function of the keratinocytes involved in the hair follicle, justifying the improvement of the hair loss and structure. Moreover, they may have a relevant effect on various etiologies of alopecia, such as telogen effluvium or senescent alopecia (aging hair). The objective of the present study is to evaluate the impact of a new association of nutrients on parameters related to the follicular unit's integrity.

MATERIAL AND METHODS

The studied product was an association of micronutrients and amino acids (Exímia Fortalize Kera D®, FQMMelora, Rio de Janeiro, Brazil) constituted by vitamins A, C, D and E, as well as those of the B complex (folic and pantothenic acids, biotin, niacin, pyridoxine and thiamine); iron trace elements, magnesium and zinc, all at physiological concentrations (100% IDR), in addition to a pool of essential amino acids (aspartic and glutamic acids, serine, glycine, histidine, arginine, threonine, alanine, proline, tyrosine, valine, methionine, cystine, isoleucine, tryptophan, leucine, phenylalanine, lysine and hydroxyproline).

The product was previously prepared for evaluation in the media at non-cytotoxic concentrations, previously determined by *in vitro* cytotoxicity evaluation.

The interaction of the nutritional supplement was evaluated under four different markers:

- keratins 10 and 14 quantification;
- 17A1 collagen protein (COL17A1) expression evaluation by immunofluorescence;
- β-catenin determination (this molecule is a subunit of the cadherin protein complex, and is a marker in the Wnt signaling pathway, associated with cell proliferation);
- ATP synthesis quantification (stimulation of cellular metabolism).

Aiming at evaluating the quality of epidermal and follicular keratinogenesis, scalp fragments obtained from elective plastic surgery were treated with three concentrations of the studied product and evaluated for 72 hours for subsequent immunoenzymatic quantification of keratins 10 and 14. The scalp fragments were also subjected to five consecutive doses of UVA/B radiation and treated with three concentrations of the product for five days for evaluation of COL17A1 by immunofluorescence, using fluorescence microscopy (OLYMPUS BX53, Japan) and the cellSens Standard software (©2010 OLYMPUS CORPORATION).

After obtaining the immunofluorescence images, its intensity was quantified with assistance of the ImageJ (Arbitrary Units - UA) software.

For evaluation of cell metabolism and hair growth quality, human follicular dermal papilla cells were incubated with three concentrations of the product (0.316, 0.100 and 0.0316mg/ml) for 72 hours for later quantification of β-catenin and ATP.

Cell cultures with equal concentrations were irradiated with UVB/A spectrum (UV meter, Honle UVAmerica Inc. MA, USA).

Concentrations of ATP, β-catenin and keratins 10 and 14 were measured by Elisa (enzyme-linked immunosorbent assay-USCN-USA).

The statistical evaluation of the obtained quantitative data was performed using the ANOVA test (GraphPad Prism v6 software), which allowed measuring the variation level of the results, comparing the data between the groups. The Bonferroni post-test was used to confirm the results, with a significance level of 5%.

RESULTS

Quantification of keratins 10 and 14 in *ex vivo* scalp cultures.

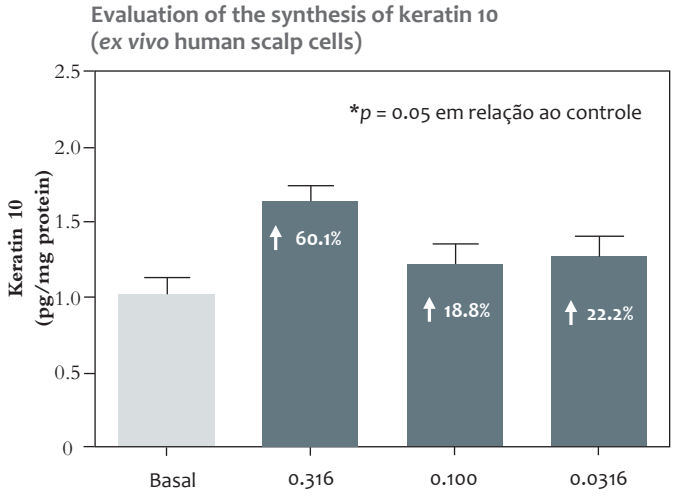
The 0.316mg/ml concentration promoted a significant increase ($p < 0.05$) in the production of keratins 10 and 14 (60.1% and 27. 8%, respectively, as compared to the baseline) as shown in Graphs 1 and 2.

The results regarding the quantification of β-catenin evidenced that the 0.16 mg/ml concentration was also able to stimulate the production of this mediator in 41.3% when compared to the baseline, as shown in Figure 3.

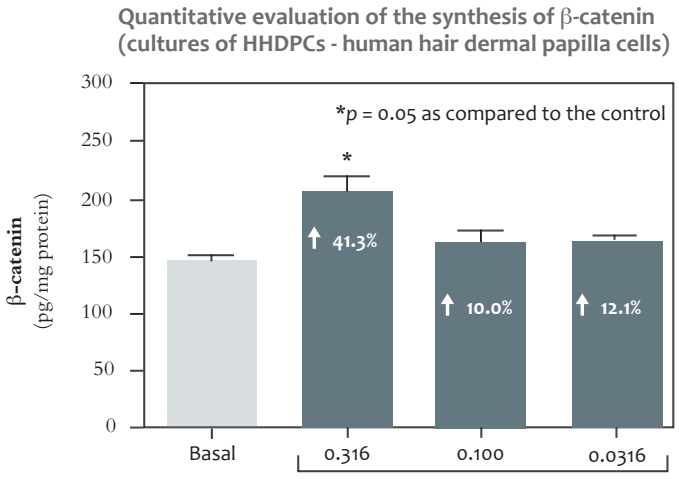
In addition, the 0.100 and 0. 0316 mg/ml concentrations promoted significant increases ($p < 0.001$) in ATP synthesis in HHDPCs (human hair dermal papilla cells) cultures. Increases of 53.2% and 50.6% were observed in the 0.100 mg/m and 0.0316 mg/ml concentrations, as shown in Figure 4.

Regarding the effect of radiation on COL17A1, immunofluorescence demonstrated that cumulative exposure to UVA/B significantly reduced the protein synthesis of COL17A1 by 42.3% ($p <0.001$) in an untreated area (COL17A1 protein is immunomarked in green; the exposed cellular nucleus-DNA is represented by blue marking) while the treatment with the studied product was capable to preserve the synthesis of COL17A1 in the scalp fragments subjected to UVA/B radiation in 70.5%, 48.9%, and 43.6%, in the 0.316, 0.100 and 0.0316 mg/ml concentrations, respectively, as depicted in Figure 1.

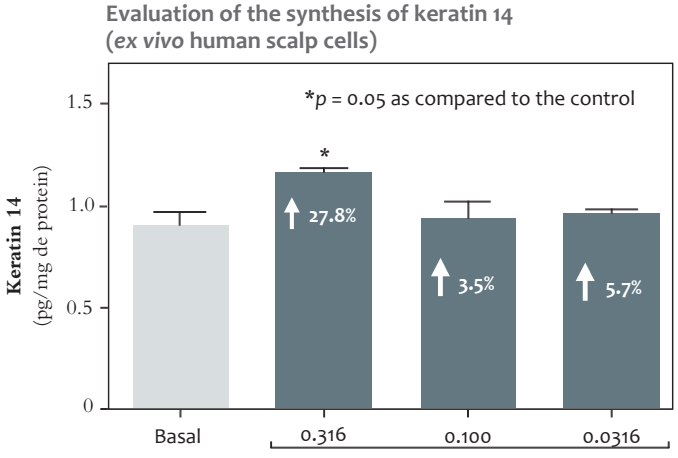
Graph 5 shows the result of the immunofluorescence staining quantification, demonstrating the significant effect of the three evaluated concentrations on the synthesis of COL17A1.



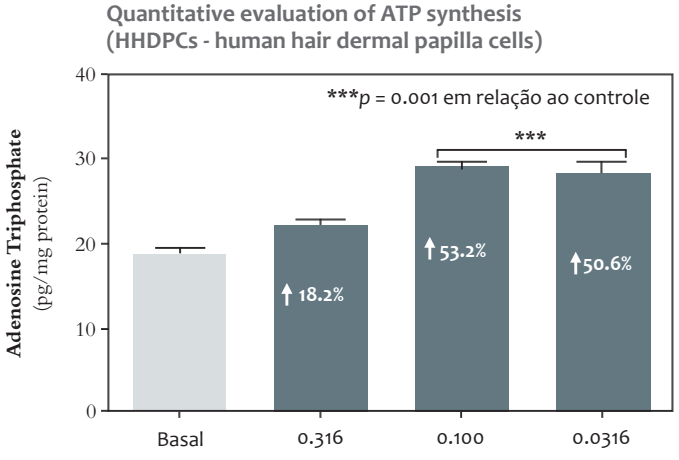
Graph 1: Light bar: mean value of the control area; dark bars: mean value of the synthesis of keratin 10 with treatment using 0.316, 0.1 and 0.0316 mg/ml concentrations, respectively. (*p*<0,005*)



Graph 3: Legend: white bar: control area's mean value; pink bars: average percentage of β-catenin synthesis with treatment using 0.316, 0.1 and 0.0316 mg/ml concentrations respectively. (*p*<0,005*)



Graph 2: Light bar: control area's mean value; dark bars: mean value of the synthesis of keratin 10 with treatment using 0.316, 0.1 and 0.0316 mg/ml concentrations, respectively. (*p*<0,005*)



Graph 4: Legend: white bar: control area's mean value; pink bars: average percentage of ATP synthesis with treatment using 0.316, 0.1 and 0.0316 mg/ml concentrations respectively. (*p*<0,001***)

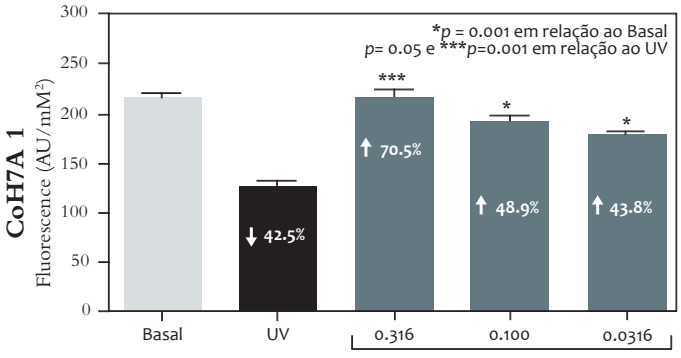
DISCUSSION

The parameters evaluated in the present study allowed to evidence the impact of the association of the nutrients present in the analyzed formulation on the keratinogenesis mechanisms of the perifollicular epidermis, reflected in the greater integrity of the epidermal (hair follicle) and dermal (follicular papilla) components.

The expression of keratins 10 and 14 increased significantly in the presence of the association, demonstrating increased hair keratin synthesis. The expression of these keratins physiologically increases during the anagen phase, for they are proliferative markers of the interfollicular epidermis' basal layer.[10]

An animal model study showed that in hyperglycemic situations there is a reduction of keratin 14 expression and ectopic induction of keratin 10, which demonstrates a change in keratinocyte proliferation and differentiation in these patients. These findings justify the alterations found in the cutaneous barrier of these patients.[11]

Graph 05: Semi-quantitative evaluation of immunomarked COL17A1 (human hair dermal papilla cells), in arbitrary units



Graph 5: Light bar: control area's mean value; black bar: untreated area irradiated with reduction of COL17A1 ($p < 0.001$ as compared to the baseline #) mean value bars: average percentage of COL17A1 presence under treatment using 0.316 ($p < 0.001$ ***), 0.1 ($p < 0.05$ *) and 0.0316 mg/ml ($p < 0.05$ *) concentrations respectively

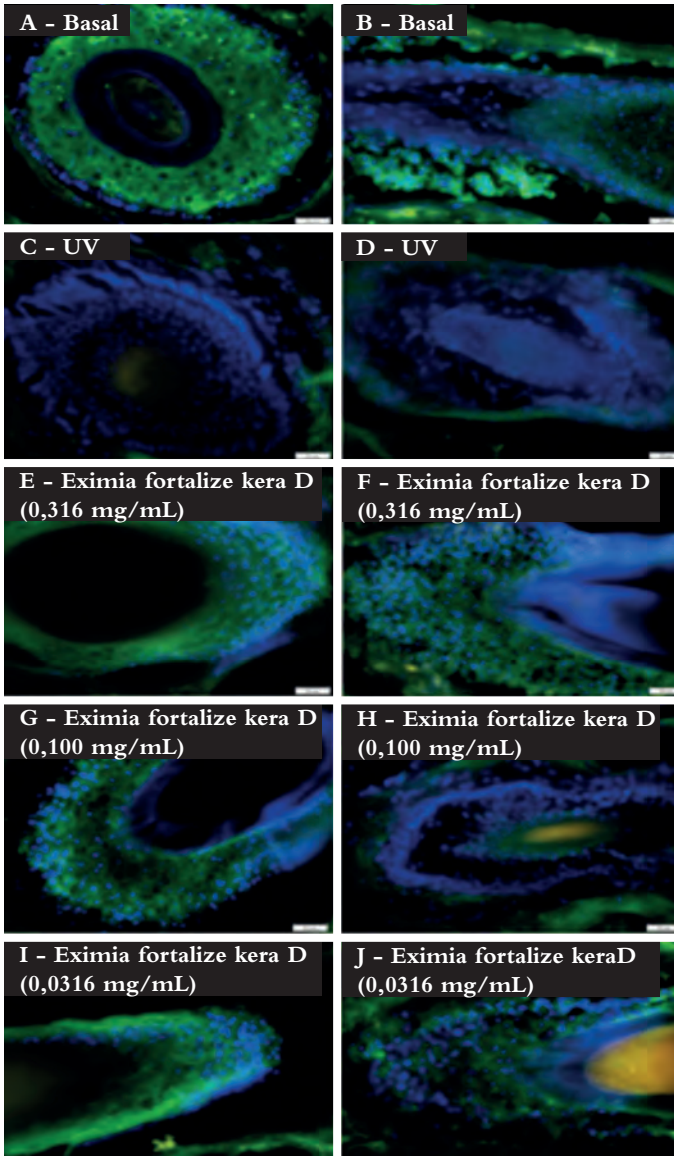


Figure 1: Histological evaluation based on the immunofluorescence of COL17A1 protein synthesis (ex vivo human scalp fragments)

The association of sulfur amino acids contributes to this synthesis of hair keratin, specifically methionine and cysteine. [12]

Another marker was also used to measure the rate of cell proliferation: beta-catenin, which is a Wnt pathway mediator protein (wingless type MMTV integration site Family). This signaling pathway is crucial in the cell proliferation events, being involved in the interaction of the hair follicle's epithelial-mesenchymal cells, meaning that its reduction implies a decrease in keratinocyte differentiation. [13]

The Wnt/beta-catenin pathway is also involved in the modulation of cell migration in the processes of epithelial healing, and hair follicle development and regeneration. [14]

Regarding the collagen type XVIIα1 (COL17A1), Matsumura et al. described the hair follicles aging process step by step, elucidating mechanisms of DNA damage and aging of stem cells associated with the aged hair phenotype, that leads to the miniaturization of the follicle, as well as of the surrounding cell populations. In that study, the marker was the collagen 17A proteolysis, related to the renewal of stem cells. [7]

The authors of the present study evaluated the impact of ultraviolet radiation on COL17A1, demonstrating that the photodamage is also capable of inducing its proteolysis, which would be an acceleration mechanism of aging, in addition to the oxidative damage inflicted.

The association of nutrients studied in the present paper was capable of preventing excessive degradation of COL17A1 in the hair follicle exposed to UVA/B radiation, thus preventing the UV-induced hair aging process. This is the first study to demonstrate this protective effect of COL17A1, suggesting the possibility of preventing the aging of the hair caused by extrinsic factors.

The reduction of the synthesis of hair strands is also associated with the decline in cellular function observed in aging.

Concomitantly, the oxidative stress inherent to cellular metabolic processes is increased by the already mentioned extrinsic factors, such as cutaneous oxidative damage, generating microinflammation in the follicle and perifollicular area.

The observed increase in ATP shows that the studied association was able to stimulate the cellular metabolism in the dermal papilla cells, increasing its synthesis.

In this setting, it is important to note that the dermal papilla plays an important role in the dermoepidermal interaction that controls hair synthesis and hair cycle events, which are altered not only in hair senescence, but also in androgenetic alopecia. [15]

The association of nutrients contained in the product Eximia Fortalize Kera D was proven to have a positive action on some of the main molecular parameters involved in keratinogenesis and in the hair cycle, meaning therefore that it can act positively on hair senescence and strand miniaturization.

CONCLUSION

The parameters evaluated in the present study evidenced the positive influence of the evaluated association of nutrients in the hair follicle and follicular papillary dermis, being clinically characterized by:

- improvement of the hair strand structure (greater resistance and brightness) and epidermal integrity, preserving the scalp's barrier function (less predisposition to irritations and proliferation of microorganisms), due to the greater expression of keratins 10 and 14
- regulation of the hair cycle (preventing telogenization) due to β-catenin expression
- preservation of the dermoepidermal support and interaction in the hair follicle due to the preservation of collagen 17A 1 under UV stress
- protection against stimulation of the cellular metabolism, due to the greater production of ATP ●

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DECLARATION OF PARTICIPATION:

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Study design and planning, drafting of the manuscript.

Evaluation of the moisturizing and protective activity of a topical product containing saccharide isomerate and hydroxyethyl urea, on the skin barrier

Avaliação da atividade hidratante e protetora da barreira cutânea de produto para uso tópico contendo isomerato de sacarídeo e hidroxietil ureia

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.201810311039

ABSTRACT

Introduction: The proteins involved in the process of epidermal differentiation play a key role in retention of water and maintenance of the stratum corneum.

Objective: To assess the compaction of the skin barrier and protein expression of filaggrin, involucrin, loricrin and sphingomyelin after the use of a moisturizing cream containing saccharide isomerate and hydroxyethyl urea.

Materials and methods: *Ex vivo* evaluations were performed in skin culture in addition to immunofluorescence in order to identify proteins, as well as in vitro analysis with tissue culture in culture medium and histological sections, all of which compared with a control group.

Results: In the *ex vivo* evaluation, the protein markers increased in the group treated with the moisturizing cream as compared to the skin culture model with atopic dermatitis. In the *in vitro* evaluation, it was possible to observe an improvement in the skin barrier compaction with the application of the cream on a reconstituted three-dimensional epidermis model, as compared with the control.

Conclusions: The moisturizing cream promoted a significant increase in the production of filaggrin, involucrin and loricrin, as well as in the compaction of the skin barrier, thus suggesting a positive effect on skin hydration and protection of the cutaneous barrier, preserving and restoring the skin.

Keywords: Administration; Amino acids; Carbohydrates; Cutaneous; Fluid therapy; Keratins; Keratinocytes; Skin; Skin care; Skin cream; Peptides; Proteins; Urea; Wetting agents

RESUMO

Introdução: *As proteínas envolvidas no processo de diferenciação epidérmica apresentam papel fundamental para a retenção de água e manutenção da camada córnea.*

Objetivo: *Avaliar a compactação da barreira cutânea e expressão proteica de filagrina, involucrina, loricrina e esfingomielina após utilização de creme hidratante contendo isomerato de sacarídeo e hidroxietil ureia.*

Material e Métodos: *Foram realizadas avaliações ex vivo em cultura de pele e imunofluorescência para determinação das proteínas e análise in vitro com tecido cultivado em meio de cultura e cortes histológicos que foram comparados com um grupo-controle.*

Resultados: *Na avaliação ex vivo os marcadores das proteínas aumentaram no grupo tratado com o creme hidratante, em comparação ao modelo de cultura de pele com dermatite atópica. Na avaliação in vitro foi observada melhora na compactação da barreira cutânea com a aplicação do creme sobre um modelo tridimensional de epiderme reconstituída, em comparação ao controle.*

Conclusões: *O creme hidratante promoveu aumento significativo da produção de filagrina, involucrina e loricrina, assim como da compactação da barreira cutânea, sugerindo, assim, efeito positivo na hidratação cutânea e proteção da barreira cutânea, preservando e restaurando a pele.*

Palavras-Chave: *Agentes molhantes; Aminoácidos; Carboidratos; Creme para a pele; Hidratação; Higiene da pele; Pele; Peptídeos; Proteínas; Queratinas; Ureia*

Originals Articles

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This study was performed at Kosmoscience Ciência & Tecnologia Cosmética Ltda - Campinas (SP), Brazil. (*In vitro* efficacy study via immunofluorescence) and Tridskin Laboratórios Ltda - São Paulo (Brazil.) (*In vitro* evaluation of the skin barrier in the epidermis model).

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Conflict of interests: None.

INTRODUCTION AND OBJECTIVE

The skin barrier is an important means of protection and defense of the skin; it regulates the transepidermal water loss and prevents aggression by external agents, such as microorganisms.[1-3] The stratum corneum is the main component of this barrier, and is based on a "brick and mortar" structure, where the bricks are corneocytes, and the mortar, lipids.[1, 4] This model is accepted as the most adequate for the understanding of the cellular arrangement and tortuous pathways for cutaneous permeability.[4-6] The stratum corneum is a metabolically active structure that exerts adaptive functions, and has great interaction with the underlying epidermal layers. Physiologically, the formation of the stratum corneum occurs based on a sequence of events: The granular layer's keratinocyte's cell membrane becomes more permeable to ions, especially those of calcium, which, by activating peptidases, converts pro-filaggrin into filaggrin.[6]

Cutaneous barrier's proteins with functional relevance (Filaggrin, Involucrin and Loricrin): During epidermal differentiation, several proteins are involved in the formation of the corneal envelope, among them are loricrin, involucrin, filaggrin and keratins.[7] Filaggrin is a protein contained in the keratohyaline granules, which activates the triglyceridase enzymes and bundles keratin filaments into macro fibrils. This protein is then degraded into free amino acids, which are later used in the constitution of the natural hydration factor or converted to urocanic acid or pyrrolidone carboxylic acid (PCA).[4] It originates from pro-filaggrin, produced by keratinocytes, and is the main component of keratohyaline granules that can be observed by optical microscopy in the granular layer. The conversion of pro-filaggrin into filaggrin – both of them intracellular proteins – occurs by means of dephosphorylation and proteolysis by serine proteases, releasing multiple active monomers of filaggrin. With the decrease of the water gradient in the outer layers of the epidermis, hydrolysis of filaggrin into hygroscopic amino acids takes place.[1, 8-10] Filaggrin is responsible for aggregating keratin and other proteins in the more superficial layers of the epidermis to form the stratum corneum; the process of conversion of pro-filaggrin into filaggrin ensures the epidermis' integrity.[4, 11] With the degeneration of the cell nucleus, cells become flattened, and the keratin molecules align in parallel, creating a cornified envelope connected with the extracellular lipids. This layer's cohesive strength depends on the formation of covalent glutamine bonds, in which precursor proteins are incorporated into keratin: involucrin, SPRP (small proline-rich peptides), cornifin, loricrin, keratolinine and desmosomal proteins, such as envoplakin and periplakin. Lamellar bodies originating in the granular layer also contribute to the formation of the lipid matrix, where the corneocytes are located. Any disruption of the skin barrier triggers a repairing response that can last hours to days, depending on the stimulus' intensity. Initially there is secretion of a pool of pre-formed lamellar bodies, followed by increased synthesis of cholesterol and free fatty acids, in addition to ceramides. Concomitantly, there is an increase in enzymes and mRNA levels for these same enzymes, with primary activation by phosphorylation of HMG CoA reductase and sterol regulatory element binding proteins (SREBPs), as regulators of cholesterol synthesis and epidermal fatty acids.[4, 11] Loricrin and involucrin are important proteins that facilitate the terminal differentiation of the epidermis and formation of the cutaneous barrier. Human loricrin is an insoluble protein, initially expressed in the granular layer of the epidermis during cornification, comprising 80% of the cornified envelope's total protein mass. In addition, it functions as the main reinforcing protein for the stratum corneum. Involucrin is also a common component of the stratum corneum and provides a skeleton to which other proteins subsequently become crosslinked. In the cornified envelope's structure, involucrin is adjacent to the cell membrane, forming its outer surface. Current studies have investigated the expression of loricrin and involucrin in eczematous skin lesions and in unlesioned skin of individuals with topical dermatitis, having demonstrated that this gene expression is regulated by the IL-4 and IL-13 interleukins and cytokines, suggesting that skin sensitization by several allergens and pathogens in topical dermatitis occurs partially due to a defect in the cutaneous barrier and may result in skin inflammation and infection. Cornification is characterized by the elimination of all organelles and nucleus by the aggregation of intermediate filaments to form an intracellular fibrous matrix and by the constitution of a tough protein at the keratinocytes' periphery – the cornified cell envelope. Concomitantly, the desmosomes and intercellular junctional structures are transformed into corneodesmosomes after addition of corneodesmosin. This is a network of complex, highly insoluble proteins, 15nm thick, with a ω-hydroxyferamides monolayer attached to its extracellular surface. The cell envelope replaces the plasma membrane of terminally differentiated keratinocytes. This is the result of the formation of very stable ε-(γ-glutamyl) lysine isopeptide bonds between several precursors of protein nature, including involucrin and loricrin. This reaction is catalyzed by calcium-dependent enzymes called transglutaminases. The cornified cell envelope, together with corneodesmosomes, is critical for the stratum corneum's barrier functions, as it confers resistance to the layer. In addition, it is involved in the structural organization of lipids that fill intercorneocyte spaces in the form of lamellae, after their secretion by lamellar bodies. This extracellular hydrophobic matrix, enriched in cholesterol, ceramides and free fatty acids, plays an important role in protecting the stratum corneum.[11] The moisturizing compound provided by the composition of the test substance – Dermovance S (Farmoquímica S/A, São Paulo, Brazil) – improves its water retention capacity in the epidermal barrier (hygroscopy) and can also prevent irritations.

Aiming at evaluating the skin barrier's moisturizing and protective activity, *ex vivo* and *in vitro* evaluations were performed with the product.

Ex vivo evaluation: The primary objective of the present study was to evaluate the preclinical effectiveness of the product in hydration and protection of the skin barrier. The secondary objective was to evaluate the protein expression of filaggrin, involucrin, loricrin and sphingomyelinase using immunofluorescence in an *ex vivo* skin atopic dermatitis (AD) model.

In vitro evaluation: To evaluate the compaction of the skin barrier of human equivalent epidermis using histology after the application of the product as compared with the untreated epidermis (control group).

MATERIAL AND METHODS

Ex vivo evaluation:

Culture of human skin: The specimens used in the present study were obtained from a healthy 48-year-old, phototype III, woman who underwent elective plastic surgery in the abdominal region (abdominoplasty). After the surgical procedure, the specimens were harvested and stowed in plastic vials containing 0.9% saline solution and kept at low temperature for up to 24 hours. This project did not include the storage of the biological material for future use, with the unused specimens having been adequately discarded as infectious waste. The use of human skin specimens originated from elective surgeries for the purpose of the present study was approved by the Research Ethics Committee of the Universidade São Francisco - SP (CAAE: 55951916.9.0000.5514).

Skin specimens treatment protocol and induction of AD: The specimens were fractionated into pieces of approximately 1.5cm^2, placed in culture dishes (NUNC, Thermo Fisher Scientific), and treated with the product in the amount of 25-30mg / cm2, being massaged for 30 seconds and incubated at 37oC in the presence of 5% CO2 for 24 hours before the induction of AD and for additional 48 hours during the induction process. For the induction of AD in *ex vivo* skin, the epidermal barrier was ruptured using 4% sodium lauryl sulfate (SDS) for later exposure to *Dermatophagoidesfarinae* (Df) mite extract (International Pharmaceutical Immunology do Brasil Ltda) at the concentration of 20,175 UBE.

Immunofluorescence: After treatment, the *ex vivo* skin specimens were fixed in 4% paraformaldehyde (pH 7.4) for 24 hours and cryoprotected in 30% sucrose solution for 72 hours. Then, serial cuts of 10μm were collected directly on slides marked with the assistance of a Cryostat (Leica). At the end of the cuts, the specimens were rinsed with 0.1M PB phosphate buffer incubated overnight with primary anti-filaggrin antibodies (Novus), anti-involucrin (Bioss), anti-loricrin (Novus) and anti-sphingomyelinase (Bioss,). The cuts were later rinsed with 0.1M PB and incubated for 1 hour with Alexa Flour 488 - Goat anti-Rabbit secondary antibody (Thermo Fisher Scientific). Immediately after completion of the steps described above, a further incubation (1 minute) was performed with Dapi (4′,6-diamidino-2-phenylindole; DNA marker; Sigma) followed by three 10-minute rinses with 0.1 M PB.

The slides were mounted on specific device and analyzed under a fluorescence microscope (Olympus) with assistance of the cellSens Standard software (©2010 OLYMPUS CORPORATION). The evaluated parameter was the fluorescence's intensity emitted by the specific antibody marker. After the images were obtained, the fluorescence's intensity was quantified using the ImageJ software (Arbitrary Units - AU).

Statistical analysis: The ANOVA test allowed to measure the variation of the results, comparing the data between groups. The Bonferroni post-test was then applied, reinforcing and making even more precise the result obtained in the ANOVA test. A 5% significance level was used (GraphPad Prism v6).

In vitro evaluation:

Equivalent epidermis preparation: Primary human keratinocytes (NHK) were trypsinized at passage 1 e and resuspended in a 2,000,000 density in culture medium. This cell suspension was transferred to the polycarbonate membrane, which was submerged in fresh medium. Each membrane (with the cells) was subsequently incubated for 24 hours at 37 °C and 5% CO2. After the incubation period, the tissues were emerged and cultured in contact with liquid air for another 16 days.

Application of test substance: The application of the test substance to the equivalent epidermis can lead to contamination of the tissue by micro-organisms, since the test substance has not undergone any sterilization process. Therefore, two protocols were performed.

Protocol A - without filtration, with application of 10ml of the product directly on the epidermis, aiming at reproducing the normal use of the product on the skin: after 16 days of incubation, 10μ of pure test substance (unfiltered) was applied on the epidermis. Treated (with the test substance) and untreated (control) tissues were incubated for 15 minutes at 37°C and 5% CO2. Subsequently to this period all tissues were rinsed with phosphate buffered saline (PBS) and incubated for another 5 days at 37°C and 5% CO2. The tissues were then prepared for histological sections, aiming at evaluating the effect on the compaction of the cutaneous barrier in the equivalent epidermis, comparing them to the control (without the product or untreated).

Protocol B - with filtration, diluting the product to 0.1mg/ml and 1mg/ml in the culture medium: 30mg of the test substance were weighed and resuspended in 10ml of culture medium, resulting in a suspension of 3mg/ml of test substance. This 3mg/ml suspension was strained in a 0.22 μm filter. The 1mg/ml and 0.1mg/ml solutions were prepared from this filtered suspension, in culture medium. The tissue's culture medium was replaced with the 1 mg/ml and 0.1 mg/ml solutions, using standard culture medium for the control tissue. Thereafter, the treated (with the test substance) and untreated (control) tissues were incubated for 5 days at 37°C and 5% CO2. Next, the tissues were prepared for the histological sections aiming at evaluating the effect on the compaction of the cutaneous barrier in the equivalent epidermis, comparing them to the control (without product or untreated).

RESULTS

Ex vivo evaluation

The results of the study revealed that the atopic dermatitis (AD) experimental *ex vivo* skin model was able to satisfactorily mimic the characteristics of the skin of an individual with AD, based on the statistically significant reduction of the synthesis of filaggrin, involucrin and loricrin ($p < 0.05$, $p < 0.01$

and p<0.05), respectively) when comparing the AD group with the control group (Figures 1, 2 and 3). Although the reduction of sphingomyelin synthase was not significant based on the immunofluorescence semiquantitative method, the outcomes evidenced a decrease tendency in this mediator (Figure 4). The sign for the evaluated markers is revealed in green in the histological sections and exhibits localized marking/distribution in the epidermis, more specifically in the granulosum layer, as well as in the stratum corneum. As shown in Figures 1, 2 and 3, the intensity of the marking for filaggrin, involucrin and loricrin was strongly increased in the test substance group as compared to the *ex vivo* model of culture with AD ($p < 0.05$, $p < 0.01$ and $p < 0.05$, respectively). Although the increase in sphingomyelin synthase synthesis was not statistically significant (Graph 4), the treatment with the test substance showed a tendency towards the increase of this mediator when compared to the AD group.

In vitro evaluation

No microorganism contamination was observed in any of the tissues used, either in Protocol A or in Protocol B.

Protocol A – The test substance was applied without filtration (10µl) directly on the epidermis in order to reproduce the normal use of the product on the skin. There was no significant improvement in the compaction of the stratum corneum with the epidermis treated with the test substance, as compared to the untreated epidermis (Figures 5A and B). The product, however, remained between the stratum corneum and the stratum granulosum, forming a protective film in the epidermis. The formation of the protective film is one way of protecting the skin from excessive loss of water to the environment.

Protocol B – The test substance was resuspended at 3mg/ml and then filtered on a 0.22mm filter. Based on this resuspension, 0.1mg/ml and 1.0 mg/ml dilutions were prepared in

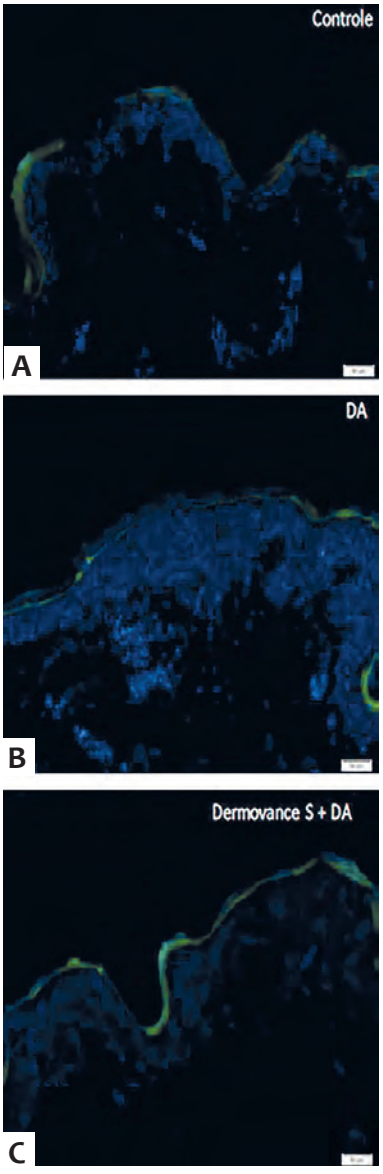


Figure 1: Immunofluorescence photographic evaluation of filaggrin synthesis in *ex vivo* human skin specimens incubated with test substance
A - Histological section of *ex vivo* skin under treatment (control)
B - Histological section of ex vivo skin with AD
C - Histological section of *ex vivo* skin with AD treated with test substance; the green marking represents the synthesis of filaggrin protein, while the blue marking represents the cell's nucleus (DNA); the reference bar corresponds to 50µm

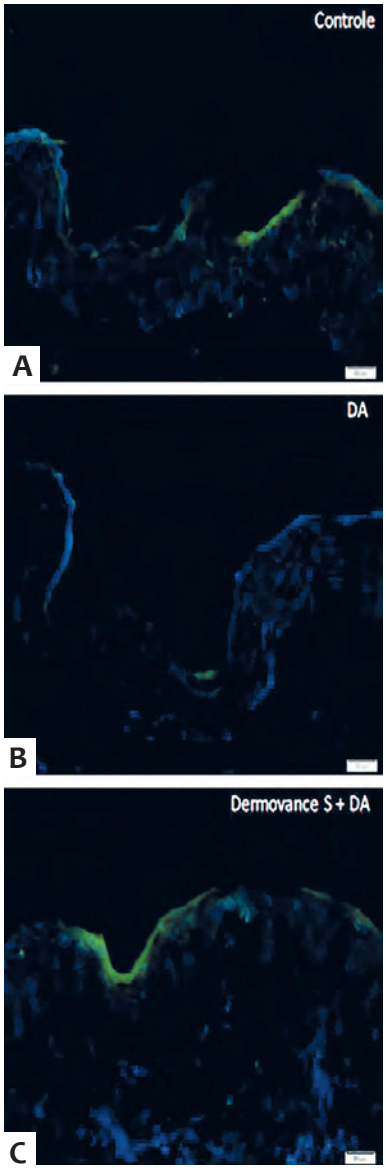


Figure 2: Immunofluorescence photographic evaluation of involucrin synthesis in *ex vivo* human skin specimens incubated with the test substance
A - Histological section of *ex vivo* skin without treatment (control)
B - Histological section of *ex vivo* with AD
C - Histological section of *ex vivo* skin with AD treated with the test substance; the green marking represents the synthesis of involucrin protein, while the blue marking represents the cell's nucleus (DNA); the reference bar corresponds to 50µm

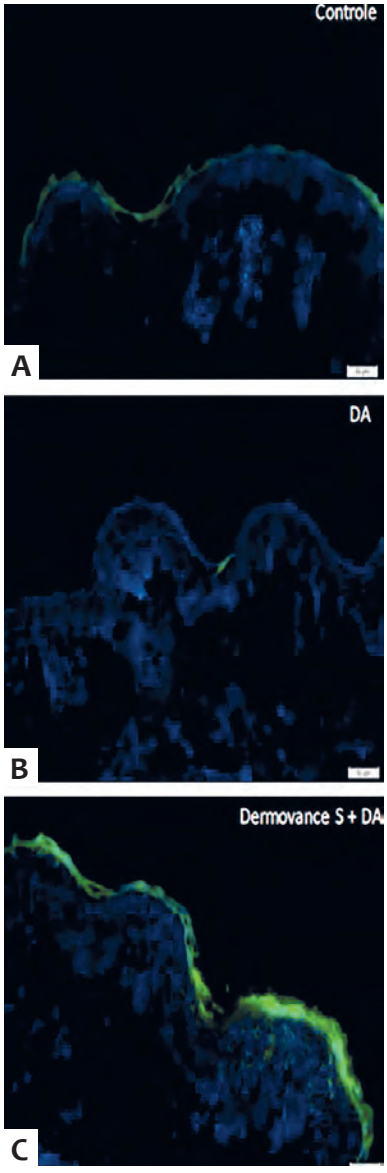


Figure 3: Immunofluorescence photographic evaluation of loricrin synthesis in *ex vivo* human skin specimens incubated with the test substance
A - Histological section of *ex vivo* skin under treatment (control)
B - Histological section of *ex vivo* skin with AD
C - Histological section of *ex vivo* skin with AD treated with the test substance; the green marking represents the synthesis of loricrin protein, while the blue marking represents the cell's nucleus (DNA); the reference bar corresponds to 50µm

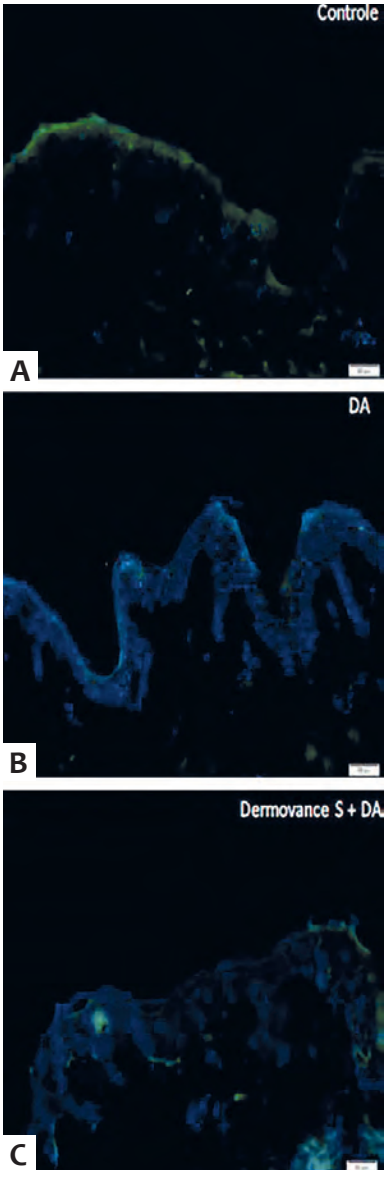
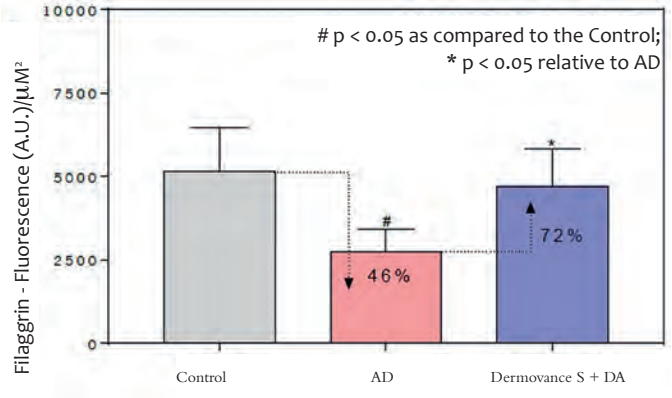


Figure 4: Immunofluorescence photographic evaluation of synthase synthesis in *ex vivo* human skin specimens incubated with the test substance
A - Histological section *ex vivo* without treatment (control)
B - Histological section *ex vivo* skin with AD
C - Histological section of *ex vivo* skin with AD treated with test substance; the green marking represents the synthesis of the enzyme sphingomyelinase synthase, while the blue marking represents the cell's nucleus (DNA); the reference bar corresponds to 50µm

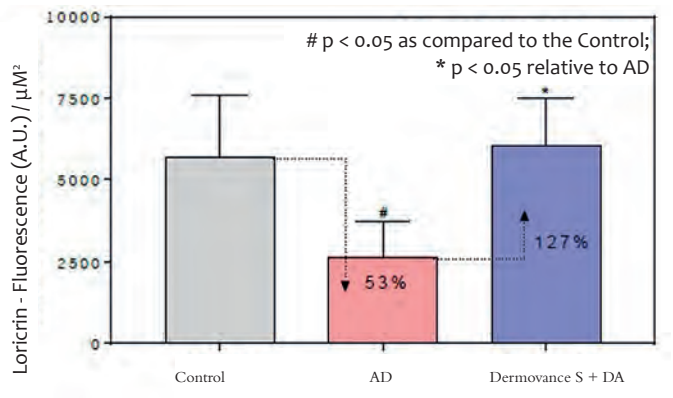
culture medium. In Protocol B there was an improvement in the reorganization of the epidermal layers when the test substance's concentration was 0.1mg/ml to 1.0mg/ml (Figures 5C and D). It is possible to observe some empty "spaces" between the cells of the epidermis' layers in Figure 5C (control). These spaces can no longer be seen after treatment with the test substance. The stratum corneum becomes more homogeneous, and the epidermis presents a healthier appearance.

DISCUSSION

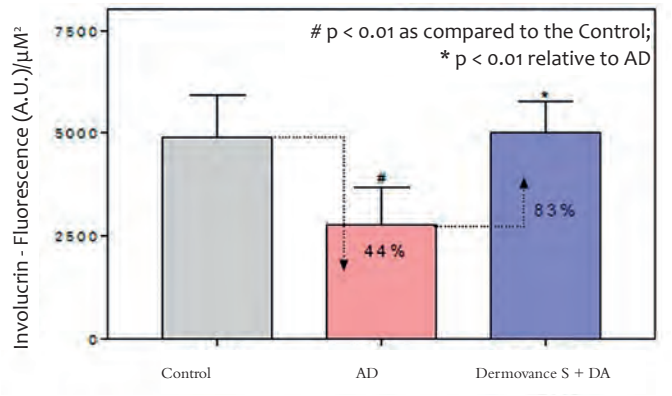
Alterations of the skin barrier, proteins (such as filaggrins, involucrins and loricrins) or abnormal ceramides can promote xerosis, predisposing to the development of pruritus and microcracks in the epithelium. Filaggrin, involucrin and loricrin contribute to the formation of substances that are important to the maintenance of pH, hydration and protection of the skin against microbial agents.[1, 9] These proteins play a key role in the retention of water in the stratum corneum, cell differentiation and maintenance of the skin barrier.[8, 13] Moisturizers restore the ability of intercellular lipid bilayers to absorb, retain and redistribute water. These agents can penetrate and contribute to the reorganization of the structure of the skin layers. Moisturizers can be classified into several groups, such as humectants, occlusive and emollients, according to their ingredients, and may have more than one action in a same product. [7] Moisturizing creams are semi-solid emulsions (mixtures of oil and water) that are miscible in water. They are classified into two types: oil-in-water creams, which are composed of small oil droplets dispersed in a continuous water phase; and water-in-oil creams, which are composed of small droplets of water dispersed in a continuous oily phase. Oil-in-water creams are more pleasant and cosmetically acceptable, since they are less greasy. Emollients are fats



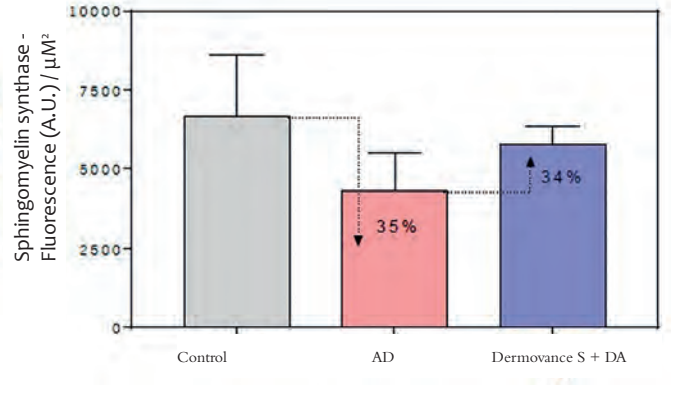
Graph 1: Semiquantification of the fluorescence's intensity (Arbitrary Units – A.U.) of filaggrin synthesis in specimens of human *ex vivo* skin in the presence or absence of AD, treated or not with the test substance. The data represent the mean value ± standard deviation of five experimental areas (ANOVA, Bonferroni)



Graph 3: Semiquantification of fluorescence's intensity (Arbitrary Units - AU) of loricrin synthesis in *ex vivo* human skin specimens in the presence or absence of AD, treated or not with the test substance. The data represent the mean value ± standard deviation of five experimental areas (ANOVA, Bonferroni)



Graph 2: Semiquantification of the fluorescence's intensity (Arbitrary Units - AU) of involucrin synthesis in *ex vivo* human skin specimens in the presence or absence of AD, treated or not with the test substance. The data represent the mean value ± standard deviation of five experimental areas (ANOVA, Bonferroni)



Graph 4: Semiquantification of the fluorescence's intensity (Arbitrary Units - AU) of sphingomyelin synthase synthesis in *ex vivo* human skin specimens in the presence or absence of AD, treated or not with the test substance. The data represent the mean value ± standard deviation of five experimental areas (ANOVA, Bonferroni)

or oils in a two-phase system (a liquid is dispersed in the form of small droplets in another liquid), which softens the skin by forming a protective film over the stratum corneum, avoiding drying by evaporation of the deeper layers of the skin and making it more flexible. As described, filaggrin is responsible for aggregating keratin and other proteins in the most superficial layers of the epidermis to form the stratum corneum, and the cohesive strength of that skin layer depends on covalent glutamine bonds, in which precursor proteins, such as loricrin and involucrin, are incorporated into keratin. [4, 9] The literature reports that in AD there is a reduction in important proteins of the epidermal barrier, such as filaggrin, loricrin and involucrin, as well as a reduction of sphingomyelin synthase enzyme, which is directly related to the synthesis of ceramides in the skin. The maintenance of the cutaneous barrier occurs by proliferation and differentiation of keratinocytes in the skin layers, which contain keratins and lipids that constitute the stratum corneum. During this terminal differentiation, keratinocytes express various proteins such as keratins, profilaggrins, filaggrins, involucrins, small proline-rich proteins, loricrins, cystatin A and elafin, which form the cornified envelope of mature corneocytes.[14, 15] The lamellar structure of the stratum corneum results from a reorganization and accumulation of lipid-rich organelles, which are lamellar bodies that excreted into the intercellular spaces at the interface

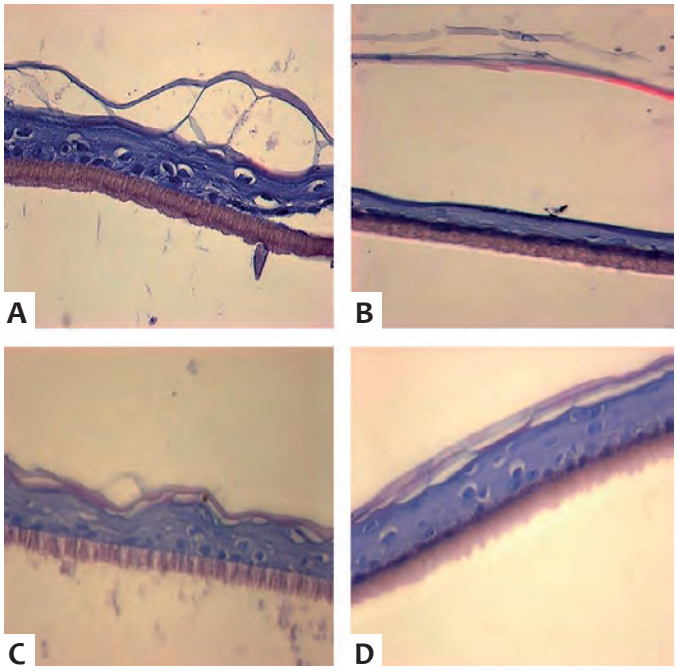


Figure 5: A - Control tissue specimen stained with Hematoxylin and Eosin
B – Tissue specimen of treated with 10µl of pure test substance (unfiltered)
C – Tissue specimen treated with 0.1mg/ml of the test substance
D – Tissue specimen treated with 1.0mg/ml of the test substance (filtered)

between the stratum corneum and the stratum granulosum. This lipid organization has been reported to be responsible for the barrier function, with the loss of this lamellar structure after the application of a solvent or its absence in some diseases being associated with the impairment of the barrier properties.[16] Due to this fact, the compaction of the skin barrier becomes relevant in the process of avoiding the penetration of microorganisms and the excessive loss of transepidermal water. Cosmetic formulations can improve the stratum corneum's function by supplying water molecules and lipids. [17]

CONCLUSION

According to the results obtained in the present study, it is possible to conclude that the moisturizing cream containing saccharide isomerate and hydroxyethyl urea significantly increased the production of filaggrin, involucrin and loricrin in an *ex vivo* skin model with atopic dermatitis. In the *in vitro* evaluation, the images obtained from the samples treated with the test substance suggest there is an effect in the restructuring of the layers of the epidermis, in the compaction of the stratum corneum and formation of a protective film. The results demonstrated in the two analyses allow inferring that the compound evaluated in the present study, exerts a positive effect on the hydration and protection of the cutaneous barrier, protecting and restoring the skin.

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In vitro evaluation of the anti-inflammatory activity of an oral administration product containing collagen peptides, Delphinol®, vitamin C and hibiscus

Avaliação da atividade anti-inflamatória in vitro de um produto de administração oral contendo peptídeos de colágeno, delphinol® vitamina C e hibiscus

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ABSTRACT

Introduction: The term inflammaging refers to the increase of the inflammatory response due to aging, resulting in a low level chronic pro-inflammatory state. High levels of proinflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor occur. Thus, the use of active principles that modulate the inflammatory response assists in the reduction of cellular oxidative stress, also reducing or avoiding irreversible cellular and non-clinically detectable molecular damage.

Objective: To evaluate the action of a compound containing collagen peptides, Delphinol®, vitamin C and hibiscus on the modulation of the cutaneous inflammatory response.

Materials and methods: The release of inflammatory cytokines after treatment with the product was evaluated in keratinocytes exposed to an inflammatory response-inducing lipopolysaccharide.

Results: When keratinocytes were exposed to the studied compound, it was possible to observe an increase in the release of interleukin 6 and a reduction tendency in the levels of interleukin 1-alpha and interleukin-8. In addition, the release of basal tumor necrosis factor-alpha was reduced by 67.5% (P = 0.008).

Conclusions: The compound studied has a potential effect on inflammaging – and consequently on aging – by modulating the inflammatory cytokines interleukin-1 alpha, interleukin-6, interleukin-8 and tumor necrosis factor-alpha.

Keywords: Aging;Anti-Inflammatory agents;Antioxidants;Ascorbic acid;Collagen;Dietary Suplements; Hibiscus; Inflammation mediators; Skin; Skin aging

RESUMO

Introdução: *O termo inflammaging refere-se ao aumento da resposta inflamatória devida ao envelhecimento, resultando em estado pró-inflamatório sistêmico crônico em baixo grau. Ocorrem níveis elevados de citocinas pró-inflamatórias como interleucina-1, interleucina-6 e fator de necrose tumoral. Assim, o uso de ativos que atuam na modulação da resposta inflamatória auxilia na redução do estresse oxidativo celular e também reduz ou evita os danos celulares e moleculares irreversíveis não clinicamente detectáveis.*

Objetivo: *Avaliar a ação de um composto contendo peptídeos de colágeno, delphinol®, vitamina C e hibiscus na modulação da resposta inflamatória cutânea.*

Material e Métodos: *Foi avaliada a liberação das citocinas inflamatórias após tratamento com o produto, em queratinócitos expostos a um lipopolissacarídeo indutor de resposta inflamatória.*

Resultados: *Quando os queratinócitos foram expostos ao composto em estudo, observaram-se aumento na liberação de interleucina 6 e tendência de redução nos níveis de interleucina 1-alfa e de interleucina-8. Além disso, ficou reduzida em 67,5% (P=0,008) a liberação de fator de necrose tumoral-alfa basal.*

Conclusões: *O composto estudado tem efeito potencial sobre o processo de inflammaging e, consequentemente, sobre o envelhecimento, por meio da modulação das citocinas inflamatórias interleucina-1 alfa, interleucina-6, interleucina-8 e fator de necrose tumoral-alfa.*

Palavras-Chave: *Ácido ascórbico; Antioxidantes; Anti-Inflamatórios; Colágeno; Envelhecimento; Envelhecimento da pele; Hibiscus; Mediadores da inflamação; Pele; Suplementos nutricionais*

Originals Articles

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INTRODUCTION AND OBJECTIVE

Cytokines are extracellular water-soluble polypeptides or glycoproteins. They are produced by several types of cells at the lesion's site and by cells of the immune system by the activation of mitogen-activated protein kinase. Cytokines influence the activity, differentiation, proliferation and survival of the immune cell, as well as regulate the production and activity of other cytokines, which may increase the inflammatory response (pro-inflammatory) – such as interleukin-1b (IL-1b), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor-alpha (TNFα) – or attenuate that process (anti-inflammatory). Tumor necrosis factor-alpha is a proinflammatory cytokine produced mainly by monocytes, macrophages and T-lymphocytes, being abundant in the peritoneum and splanchnic tissue.[1] Aging is a complex and dynamic biological process characterized by continuous remodeling with DNA repair, apoptosis, immune response, oxidative stress, and inflammation. One of the most recent theories on aging is focused on the immune response and takes into account the activation of subclinical and low grade chronic inflammation called *inflammaging*.[2] This chronic inflammatory response may build up over time and gradually cause tissue damage. It is considered one of the main reasons for many age-related diseases such as diabetes, atherosclerosis, macular degeneration and aging skin.[3] There is also increasing evidence that inflammation plays an important role in cardiovascular disease, and may be considered a late consequence of evolutionary programming for a proinflammatory response.[4-6] Aging is driven by the pro-inflammatory cytokines and substances produced by the innate immune system. The macrophage system and complement system, two important components of the innate immune system, have attracted increasing attention since they seem to be involved in the pathogenesis of various diseases associated with inflammation. Studies show that innate immunity is important in this process, in which mononuclear phagocytes, such as macrophages, play a key role in several age-related diseases. Several global studies of the gene expression profile linked all immune system and inflammation genes to photoaging, regardless of ethnic type. Ultraviolet-induced photoaging can be seen as premature aging of the skin. Ultraviolet (UV) radiation induces a series of events that can lead to inflammation, inducing: a) epidermal keratinocytes to release inflammatory cytokines, such as IL-1 and IL-6 and TNF-α; b) mast cells to generate prostaglandins and other inflammatory mediators, such as histamine and leukotrienes; c) cutaneous cell death; and d) peroxidation of the lipid membrane. In the inflammaging process, there is an increase in inflammatory reactions due to age, characterized by high levels of proinflammatory cytokines: IL-1, IL-6 and TNF-α. Exposure to acute UV radiation leads to the infiltration of neutrophils in the epidermis and dermis to purify UV-induced apoptotic cells and eliminate cutaneous cells. It is also suggested that some enzymes, such as matrix metalloproteinases (MMP-1 and MMP-9), contribute to the photoaging process. It is likely that monocytes and macrophages actually play a more important role in this process for they attack infiltrates after a few hours to cleanse apoptotic cells and oxidized lipids.[3] C-reactive protein (CRP), produced in acute phases by the liver in response to IL-6, is also a useful marker of inflammation that is most commonly used in the clinical practice. Inflammation is believed to be a consequence of cumulative lifetime exposure to antigenic load caused by clinical and subclinical infections, as well as exposure to non-infectious antigens. The resulting inflammatory response, tissue injury and production of reactive oxygen species that cause oxidative damage also trigger the release of additional cytokines, mainly from cells of the innate immune system, but also from the acquired immune response. This results in a vicious cycle, stimulating the immune system, remodeling and favoring a chronic pro-inflammatory state, in which pathophysiological changes, tissular damage and healing occur simultaneously. Irreversible cellular and molecular damage that is not clinically evident slowly accumulates over decades. The population of T CD8+ cells is altered to a greater extent as compared to the CD4+ population. With age, increased numbers of antigen-specific cells are associated with an increase in the number of terminally differentiated senescent cells, which occupy a large proportion of the immune space. These cells, particularly CD8 +, are potent producers of inflammatory cytokines and have been strongly associated with reduced antiviral immunity and related inflammatory pathologies. These specific cells produce more IL-6 and TNF-α than their younger counterparts.[3, 7]

The present study evaluated the *in vitro* anti-inflammatory activity of the test-substance (a nutraceutical complex for oral administration containing collagen peptides, vitamin C, Hibiscus sabdariffa and Delphinol® - Exímia Firmalize Age Complex® - Farmoquímica, Rio de Janeiro, Brazil) by modulating the release of inflammatory cytokines IL-1α, IL-6, IL-8 and TNF-α by keratinocytes.

MATERIAL AND METHODS

An *in vitro* comparative, controlled study was carried out.

Cell viability test

A cell viability test was performed, determining the highest non-toxic dose to be used in subsequent experiments. For this purpose, 3T3 Balb / C murine fibroblasts were maintained in culture and exposed to various concentrations of the test substance. The cultures were visually examined after 24 hours, and the number of viable cells and / or total cell content was determined by the uptake of neutral red (OD 540nm). The number of cells in the test sample was compared with that observed in the control. The analysis of IC50 was performed using the software Sigma Plot 9.01 (2004), using a four-parameter logistic curve equation (Hill Curve). Based on the data generated by this curve it was possible to determine the non-cytotoxic concentrations of the test substance.

Elisa Test (Enzyme-Linked Immunosorbent Trial): Sample Treatment

NHK cells were seeded in 24-well plates at a confluence of 28,500 cells per well. After 24 hours in a CO2 incubator, the cells were treated with test concentrations of the test substance in the presence of Escherichia coli extract (LPS, containing 5μg

/ ml equivalent protein) in Epilife Low calcium culture medium. The cell's supernatant was collected after 24 hours of exposure to treatments with the test substance + LPS, being subsequently stored in a freezer at -30 °C. The amount of IL-1α, IL-6, IL-8 and TNF-α in primary human keratinocyte culture's supernatant was evaluated by Elisa, according to the manufacturer's specifications (Human IL-1α: Thermo Scientic- Code: EH2IL1A; Human IL-6: Sigma-Aldrich - Code RAB0306; Human IL-8/CXCL8: Sigma-Aldrich - Code RAB0319; Human TNF-α: Sigma-Aldrich - Code RAB0476). In summary, specific antibodies fixed to a 96-well plate and the supernatants, including recombinant protein standards with known concentrations of IL-1α, were applied to the wells. Then, biotinylated secondary antibody was added. During the first incubation, the human antigen binds to the antibody immobilized on the plate, while the biotinylated antibody binds to a second site. After removal of the secondary antibody excess, the streptavidin-peroxidase (HRP-linked antibody) enzyme is added. After the washing process aimed at removing excess free enzyme was completed, a substrate solution is added (TMB), which binds to the enzyme to produce a blue coloration. After the addition of H2SO4, the blue color is converted into yellow, and the reading is performed at a 450 nm wavelength using a spectrophotometer. The intensity of the product's coloration is directly proportional to the concentration of the inflammatory cytokines IL-1α, IL-6, IL-8/CXCl8 and human TNF-α present in the supernatant. First, the standard curve was calculated on an absorbance plot as a function of the amount of secreted inflammatory cytokine. The absorbance values obtained for the sample trials are plotted in the first-degree equation obtained from the standard curve for the determination of the concentration of each cytokine present in the sample. The adjustments of the equation and determination of parameters were performed using Microsoft Excel software.

Statistical analysis

The trials were expressed as mean ± standard deviation and the statistical analysis was performed using Student's t-test, obtained with assistance of the Microsoft Excel software.

RESULTS

Cell viability test

The test substance was prepared at an initial concentration of 200,000 μg/ml, and the other concentrations were prepared by serial dilutions using a 1:10 factor. As shown in Graph 1, the concentrations chosen for subsequent trials were 1,000 and 100 μg/ml. In this trial the reference substance SDS (Sodium Dodecyl Sulfate) was used in order to ensure the toxic effectiveness of the test substance in the cell lineage (Graph 2).

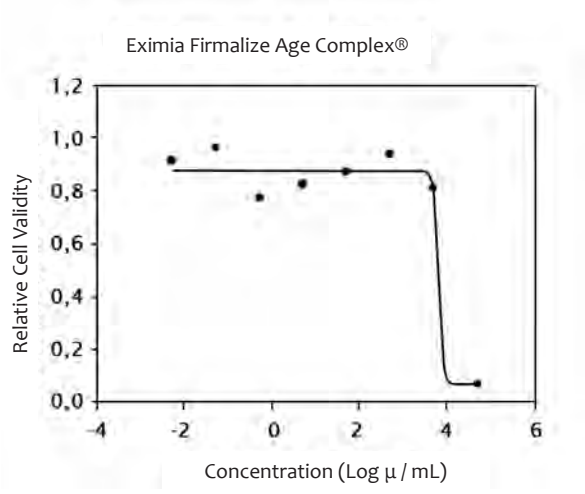
Release of inflammatory cytokines by NHK

When keratinocytes were exposed to LPS, there was an increase in the release of IL-1α (2.8x, p = 0.002), IL-6 (25.4x, p = 0.001) and IL-8 / CXCL8 (7.3 times, p = 0.0001); however LPS did not induce a significant increase in TNF-α (p = 0.412).

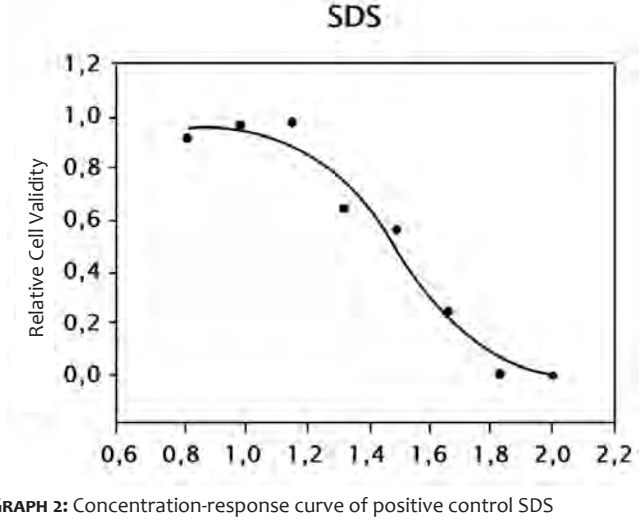
The test substance did not show a significant reduction in the release of IL-1α and IL-8 at the tested concentrations, nevertheless there was a trend towards a reduction in IL-1α and IL-8 levels (Table 1). On the other hand, an increase in the release of IL-6 (105%) was observed in the samples treated with 1,000 μg/ml of the test substance when compared to the LPS control (Table 1; Graph 3). The release of TNF-α by keratinocytes is directly related to cell death, and given that the used concentration of LPS does not induce death, no increase in TNF-α was also observed. Nonetheless, the test substance reduced the release of basal TNF-α at the highest tested concentration (1,000μg/ml) by 67.5% (p = 0.008), when compared to the LPS control (Table 1, Figure 3).

DISCUSSION

Aging is associated with elevated levels of circulating cytokines and proinflammatory markers such as IL-6, IL-1 and TNF-α. Bone, nutritional and muscle metabolism are affected by the inflammatory state intrinsic of aging, including its immune, hormonal and adipose changes, resulting in a chro-



Graph 1: SBT's concentration-response curve of the test substance



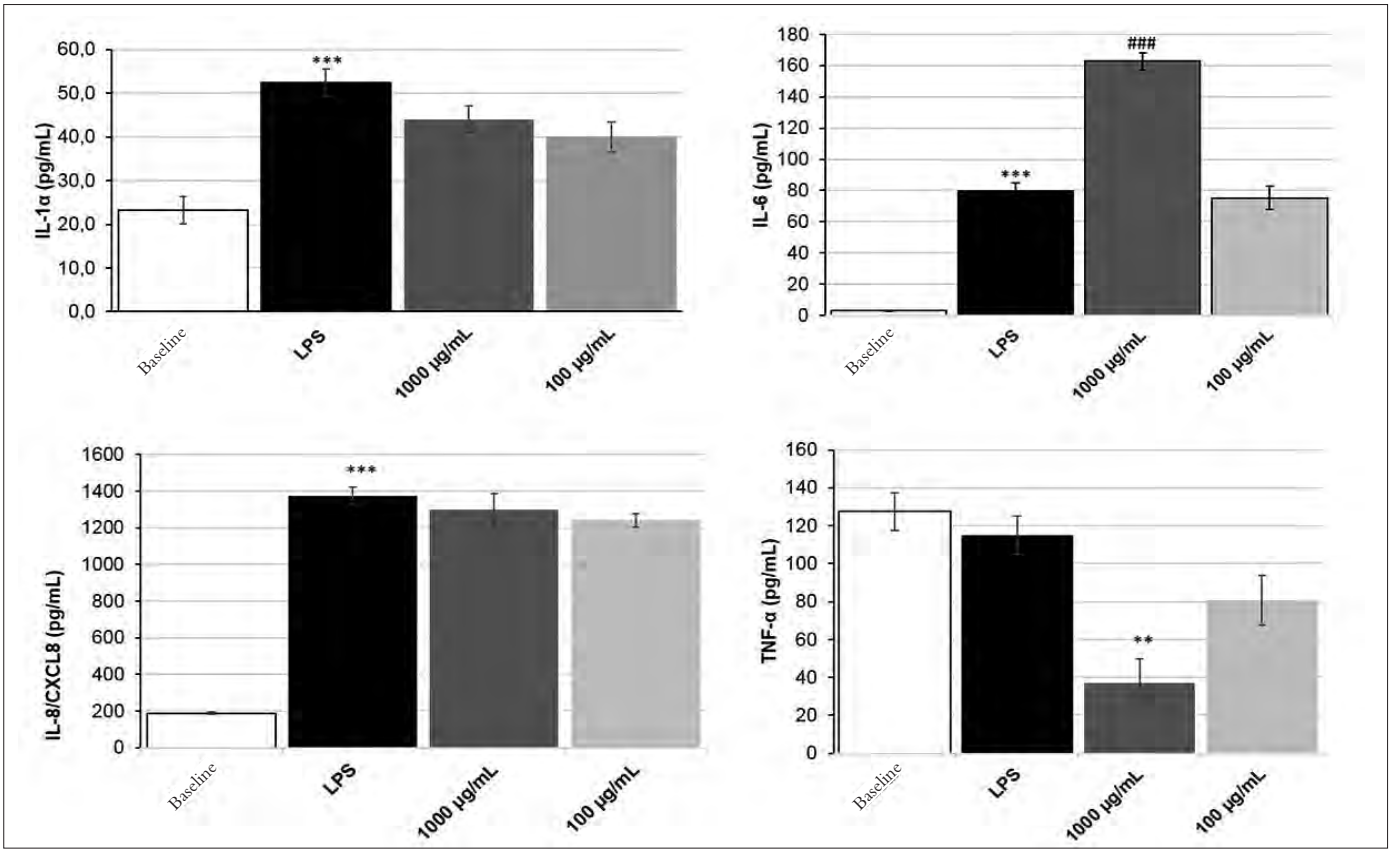
Graph 2: Concentration-response curve of positive control SDS

nic inflammatory state in which the levels of pro-inflammatory cytokines, especially TNF-α and IL- 6, have destructive effects on the skin. This phenomenon, known as immunosenescence, is accompanied by increased pro-inflammatory cytokines levels and reduced anti-inflammatory cytokines, resulting in the chronic low-grade inflammation known as inflammaging.[7-10] In the inflammaging process, there are increased inflammatory reactions due to age, characterized by high levels of proinflammatory cytokines IL-1, IL-6 and TNF-α. [7] Since interleukins and metalloproteins are linked to inflammation and oxidative stress response, their genes are suitable candidates for aging and age-related diseases and infections. Inflammation and the deconstrolled production of inflammatory cytokines play an important role in this process, which is characterized by high levels of proinflammatory cytokines, interleukins and TNF-α, which have been shown to increase with age and to be involved in the pathogenesis of most associated diseases.[5, 7, 11] IL-6 is a reliable marker of inflammation, whose circulating level increases with time. IL-6 gene is highly polymorphic and expressed in lymphocytes, fibroblasts and macrophages in response to different types of inflammation stimuli. In addition, IL-6 also controls the induction and expression of metalloproteins that maintain zinc and copper homeostasis. During stress and inflammation, the gene expression of metalloproteins is induced by proinflammatory cytokines IL-1 and IL-6, which might be deleterious in the aging process.[11-13] The inflammatory response system not only provides protection against exposure to inflammatory and infectious agents, but also contributes to the reduction of tissular damage, improving longevity, which is characterized by the balance between pro and anti-inflammatory agents.[2, 5, 7]

Several *in vitro* and *in vivo* studies confirm the antioxidant activity of vitamin C and Hibiscus. Hibiscus extract has a potent antioxidant effect, eliminating reactive oxygen and free radical activity. It also has a protective action against oxidative damage induced by tert-butyl hydroperoxide (t-BHP), protects the cell

Table 1: Statistical analysis (Student's t) and percentage of variation between the mean values of the LPS control and treatments with the test substance

Markers	1000µg/ml		100µg/ml	
	p value	variation	*p value*	variation
IL-1α	0.144	-18.80%	0.08	-27.60%
IL6	0.0004	105%	0.662	-5.30%
IL8	0.491	-5.50%	0.077	-9.70%
TNF-α	0.008	-67.50%	0.085	-29.80%



Graph 3: Release of cytokines exposed to the test substance. Release of IL-1α (A), IL-6 (B), IL-8/CXCL8 (C) and TNF-α (D) by primary human keratinocytes exposed to LPS and treated with the test substance.
The graph depicts mean ± MSE (mean standard error) values obtained for the release of inflammatory cytokines, in pg/ml.
Values differ from the baseline by *** for p <0.001 and by ** for p <0.01; and from LPS control by ### for p <0.001, based on the Student's t-test.

from lipid peroxidation and promotes inhibition of oxidation mediated by Cu2 + LDL, in addition to the formation of substances that are reactive to thiobarbituric acid (TBAR), inhibition of malondialdehyde content formation (100-300mg / kg), reduction of glutathione depletion and decrease of superoxide dismutase and catalase blood activity. [14] Vitamin C has a known antioxidant action, besides exerting photoprotective function, being capable of reducing the erythema caused by UVB irradiation.[15] Delphinol® also has antioxidant capacity, reducing intracellular oxidative stress. In addition, it eliminates pro-inflammatory stimuli, increases autophagy regulated by sirtuin-1 and restores nitric oxide synthase activity, with consequences on vasodilation, improving microcirculation, normalizing platelet activity and contributing to anti-inflammatory activity. [16] This substance inhibits lipid peroxidation mediated by UVB, oxidative and DNA damages, thus protecting cellular apoptosis. [17] As with all complex organisms, unique biological systems rarely work in isolation. Neuronal cells within the HPA axis contain multiple cytokine receptors, particularly IL-1, IL-6 and TNF-α. Reducing their circulating levels leads to the control of the inflammation process. [7] Oral supplementation with collagen peptides promotes the improvement of the skin's properties. Collagen increases the fibroblasts' density, regenerates the extracellular matrix and stimulates hyaluronic acid synthesis, improving skin hydration and sagging.[18, 19]

Based on the results obtained and taking into account the composition of the test substance, the authors of the present study can state that the product assists in the reduction of inflammaging and has antioxidant action, reducing the inflammation and slowing down the aging mechanisms of the skin.

CONCLUSION

According to the experimental conditions and methodology used, the test substance reduced TNF-α release in the presence of a stressor, showed a tendency to reduce IL1-α and IL-8 release and promoted increased IL-6 release. Due to the observed *in vitro* effects on the modulation of pro and anti-inflammatory cytokines, the authors of the present study can conclude that the test substance has a potential effect on the inflammatory process and, consequently, on aging.

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Rare and severe complication in a superficial peeling

Complicação rara e grave de peeling superficial

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ABSTRACT

One of the resources available aimed at improving skin quality are chemical peels, that can include the use of several active substances. Superficial peels reach the epidermis only and usually cause a slight desquamation for cell renewal, however they are not free of complications. The authors present a report of a patient who had contact dermatitis linked to retinoic acid, after undergoing a combined peeling procedure with Jessner's solution followed by 5% retinoic acid.

Keywords: Chemexfoliation; Receptors, retinoic acid; Skin aging

RESUMO

Um dos recursos para melhorar a qualidade da pele são os peelings químicos, utilizando várias substâncias ativas. Os peelings superficiais atingem apenas epiderme e normalmente causam uma leve descamação para renovação celular, porém não são isentos de complicações. Os autores apresentam o relato de uma paciente que apresentou dermatite de contato ao ácido retinóico, após peeling combinado com solução de Jessner seguido de ácido retinóico 5%.

Palavras-Chave: *Abrasão química; Envelhecimento da pele; Receptores do ácido retinoico*

INTRODUCTION

Among the resources aimed at improving skin quality are chemical peels containing active substances such as glycolic, retinoic and trichloroacetic acids, among others, which provide skin exfoliation and subsequent cell renewal. [1], [2] Depending on the formulations' concentrations and pH, these peels can be superficial, medium or deep. [3] Superficial peels are performed with relative safety in medical practices, reaching only the epidermis with the resulting desquamation being usually thin and clear, without implying changes to the patient's daily routine. [4] Nevertheless, these peelings are not free of complications. The authors of the present paper report a rare and serious complication of superficial peeling combined with Jessner's solution (JS) and retinoic acid (RA) in a patient who presented contact dermatitis linked to RA.

CASE REPORT

A 27-year-old female patient from the city of São José do Rio Preto (SP), Brazil, dermatologist resident physician, with no comorbidities, underwent a combined peeling containing JS and 5% RA, aimed at treating mild photoaging.

The procedure was performed without intercurrences and was characterized by the application of two layers of JS and a homogeneous layer of 5% RA on the patient's face. The substance was removed after 5 hours, with the aid of water and soap.

Case Reports

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Twelve hours after the removal of the acids, the patient developed with significant erythema and vesicles with serous contents on the face, in addition to intense edema, especially in the palpebral region (Figure 1).

After the diagnosis of contact dermatitis, 2g cephalexin per day was introduced for prophylaxis of bacterial infections, 0.5mg / kg prednisone, 10mg loratadine per day, topical methylprednisolone aceponate, and thermal water.

There was improvement of edema and erythema within 48 hours (Figure 2), and complete resolution of the condition after 14 days, without sequelae (scarring or dyschromia).

Two months after the remission of the picture, a contact test with 0.05% RA was performed on the patient's right forearm, with the emergence of pruritic erythematous papules 12 hours after the removal of the substance, with worsening of the eczema after 24 hours. The authors of the present report also performed a test with JS and the RA's vehicle (a nonionic cream), both without alterations, confirming the diagnosis of allergic contact dermatitis to RA.

DISCUSSION

The therapeutic and controlled desquamation caused by chemical peels is a powerful tool aimed at treating various diseases and aesthetic disorders. Among its main indications are the treatment of spots, scars and fine wrinkles. It can be performed on the face and also in other areas of the body. [5] Retinoic acid peeling is used in concentrations ranging from 5% to 12%. It is indicated in cases of mild to moderate photoaging, melasma, acne, superficial scars and postinflammatory hyperpigmentation. [5] Complications are rare, with references in the literature to acneiform eruption, telangiectasias and superficial keratitis. [6]

The solution developed by Max Jessner is composed of 14% salicylic acid, 14% lactic acid and 14% resorcin in 95% alcohol, and is used as a keratolytic agent in the treatment of comedonian acne, postinflammatory hyperpigmentation, melasma and mild photoaging. Penetration depends on the number of layers and can be used to carry out medium depth peels. When used in other body areas, only one area should undergo application per session, in order to avoid the risk of salicylism. It causes significant erythema, with areas of frosting, and moderate burning sensation. Complications are linked to resorcin's and salicylic acid's systemic toxicity, and are based on the absorbed amount of these substances, which varies with the extent of the treated area and the number of layers applied. Resorcin can cause contact dermatitis, [7] however this was not the case in the present report.

Combined peels associate different chemical substances in the same procedure, aiming at obtaining the best effects from each of them, meaning a more efficient action without unnecessary deepening. [7]

The complications of JS and RA combined peelings vary according to the depth of the procedure, the skill of the professional who used it and the specific characteristics of the patient.[8] The most common complications are pigmentary alterations (postinflammatory hyperpigmentation and hypopigmentation), bacterial infections (Staphylococcus, Streptococcus, Pseudomonas), viral (herpes simplex) and fungal infections (*Candida sp*), allergic reactions, milia, acneiform eruptions, and persistent erythema – all of which should be treated properly and incisively. Prior skin preparation, correct choice of peeling agent, and post-operative care can help in the prevention of these complications.

In the present case, the patient had allergic contact dermatitis to RA, with intense erythema and edema that could

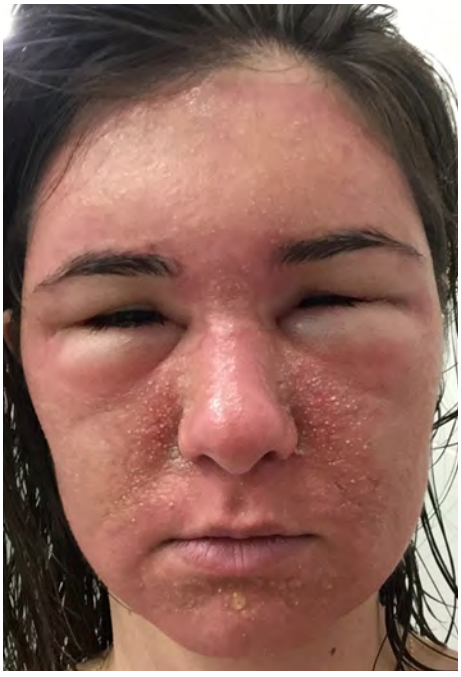

Figure 1: Intense erythema and edema 12 hours after the application of Jessner's peeling with 5% retinoic acid

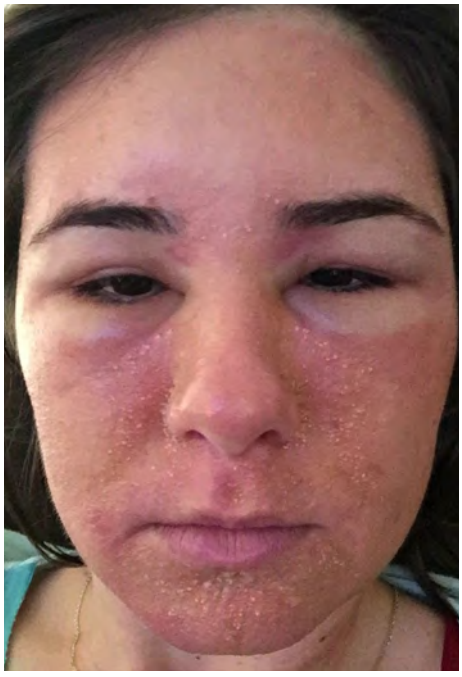

Figure 2: Improvement of erythema and edema after 48 hours

evolve with severe complications, such as facial cellulitis. The good doctor-patient relationship was crucial for the good development of the condition.

Peelings are contraindicated in cases of pregnancy, lactation, active herpetic lesions, bacterial or fungal infection, facial dermatitis, use of photosensitizing drugs, allergies to peeling components and unrealistic expectations. [9]

CONCLUSION

Peelings constitute an excellent therapeutic armamentarium, however they are not exempt of complications, meaning they should be performed by experienced professionals with ability to identify and treat possible complications.

The authors of the present report emphasize the importance of carrying out a good anamnesis, preparing photographic records before the procedure, obtaining the patient's signature for an informed consent term, and clarifying possible complications to the patient, including those linked to superficial exfoliations.

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Treatment of rosacea with botulinum toxin

Tratamento de rosácea com toxina botulínica

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ABSTRACT

Rosacea is a common chronic skin disease that has several clinical manifestations, with erythema and inflammation being predominant characteristics. Its presence is associated with psychosocial impact on patients' lives. Although there are several options for topical and systemic treatments, it is known that only the inflammation is treated and that the erythema persists in most cases. More recently, there have been some publications describing the treatment of rosacea with botulinum toxin associated with good results. In this manner, the authors sought to evaluate the action of botulinum toxin in the treatment of rosacea that is persistent and refractory to various clinical treatments.

Keywords: Rosacea; Botulinum Toxins; Therapeutics

RESUMO

Rosácea é uma doença crônica comum da pele que apresenta diversas manifestações clínicas sendo que o eritema e a inflamação são características predominantes. Sua presença está associada a um impacto psicossocial na vida dos pacientes. Embora existam várias opções de tratamentos tópicos e sistêmicos, sabe-se que eles tratam a inflamação e que o eritema é persistente na maioria das vezes. Recentemente surgiram algumas publicações relatando o tratamento de rosácea com toxina botulínica associando-o a bons resultados. Assim, buscamos avaliar a ação da toxina botulínica no tratamento da rosácea persistente e refratária a diversos tratamentos clínicos.

Palavras-Chave: *Rosácea; Terapêutica; Toxinas botulínicas*

INTRODUCTION

Rosacea is a common chronic skin disease that has several clinical manifestations and is classified into four subtypes, according to its characteristics: erythematous-telangiectasic rosacea (characterized by flushing and persistent central facial erythema); papulopustular rosacea (characterized by persistent erythema combined with transient papules and pustules with central facial distribution); phymatous rosacea (characterized by the thickening of the skin with irregular contours involving ears, cheek, mentum (gnatophyma), forehead and nose (rhinophyma); and ocular rosacea (characterized by symptoms of burning sensation, dryness, pruritus and redness in the eyes, as well as ocular sensitivity to light). [1]

The prevalence of rosacea varies from 1% to 22%, according to different studies and populations. The most common subtype is erythematous-telangiectasic rosacea, followed by papulopustular rosacea, both of which predominate in women, whereas phymatous rosacea predominates in men and ocular rosacea affects both men and women.[1,2,3] Although it is not known whether rosacea subtypes occur progressively or are only diverse variants, most patients report that symptoms begin with transient flushing that progress to persistent erythema.[4]

In this manner, facial erythema is the initial and most common characteristic in all subtypes of the rosacea, being also described as a crucial characteristic in the definition of its diagnosis. [4,5] Erythema is diffuse in nature and predominates even after the resolution of inflammatory lesions. Although persistent erythema's pathophysiological mechanisms are undetermined, it is known that it does not respond to systemic and topical treatments such as antibiotics and azelaic acid, remaining active despite the resolution of inflammatory lesions. This suggests that persistent erythema is not only associated with the inflammatory response, but that it also has a mechanism of action that acts directly on vessels, stimulating vasodilation through mediators such as VEGF, LL-37 and MMPs.[4,6]

In 2012, Dayan et al. observed that patients treated with botulinum toxin in the glabella and forehead regions presented not only reduction of wrinkles, but also improvement in the quality of the skin, a more homogeneous surface and reduction of erythema associated with acneic lesions in the treated area. In this way, the investigators performed intradermal application of botulinum toxin in some patients with rosacea diagnosis with a similar outcome. [7]

In light of this result, and also due to the availability of only a few publications on the subject, the authors of the present study report the case of a patient diagnosed with papulopustular rosacea, bearing persistent erythema refractory to various clinical treatments, who was treated with the application of intradermal botulinum toxin, developing with significant improvement of the picture.

CASE REPORT

A 35-year-old female patient undergoing clinical follow-up due to the diagnosis of papulopustular rosacea in the frontal, nose, malar and mentum areas, with some areas developing into phyma due to chronic local inflammation with little response to topical and systemic treatments (Figure 1A).

Therefore, the authors of the present study decided to evaluate the therapeutic response to botulinum toxin. One vial containing 100U of OnabotulinumtoxinA was diluted in 8ml of saline solution, and applied intradermally in injections of 0.05ml in multiple points (0.5cm distant from each other), in the affected areas (Figure 1B) of the following regions: forehead, nose, malar and mentum. A total of roughly 10 injections were applied per area. With this dilution, it was possible to obtain 1.25U per 0.1ml. Considering that 0.05ml was applied per injection, a total of 5.0 to 7.5U were applied per area.

Fourteen days after the procedure the patient returned with an important improvement of the picture, reduction of the center-facial erythema, papules and pustules (Figure 2). A further application was carried out with evaluation after 10 days showing an even greater improvement of the center-facial erythema and resolution of papulopustular lesions (Figure 3). Two months after the first application, the same outcomes remained, with almost total resolution of the erythema (Figure 4) and the patient reporting intense satisfaction with the treatment.

DISCUSSION

The use of botulinum toxin in the treatment of rosacea was shown to be an effective therapeutic option for facial erythema, which is a common feature in difficult-to-treat rosacea.

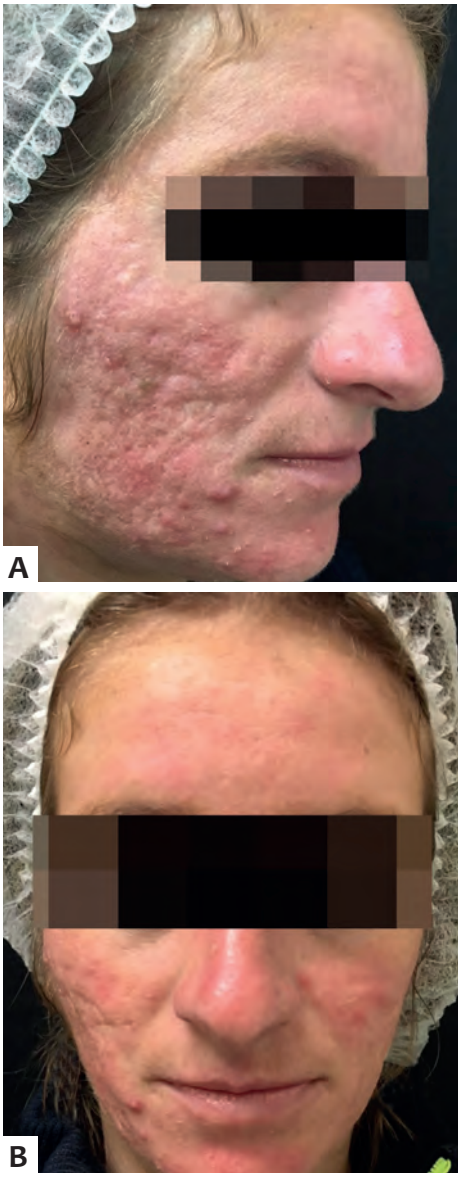

Figure 1: A and B - Before the facial application of botulinum toxin.

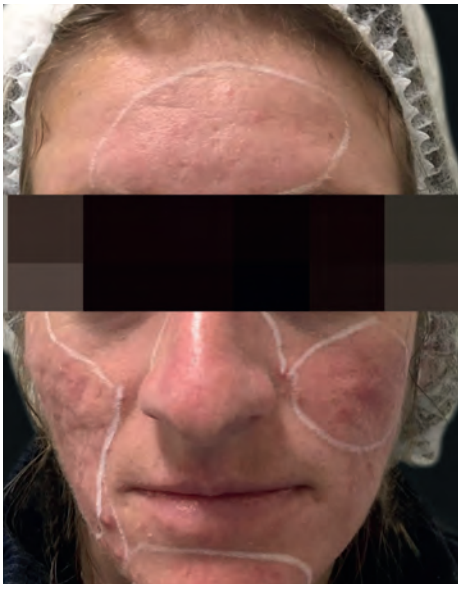

Figure 2: Application areas

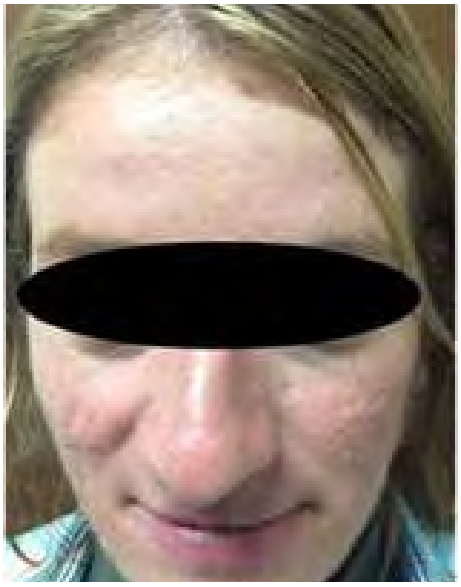

Figure 4: Two months after the first application

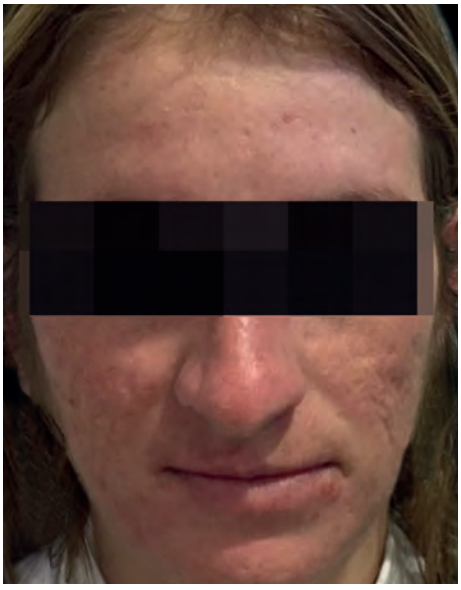

Figure 3: Fourteen days after the first application

In addition, it was possible to observe improvement of the inflammatory lesions, such as papules and pustules. Consequently, it is believed that the toxin applied in the dermis acts on both the inflammation and the vascular phenomenon present in rosacea.

Therefore, although not clearly explained, it is possible to verify that botulinum toxin has a mechanism of action responsible for reducing the symptoms of rosacea. It may be based on the inhibition of the release of neuropeptides associated with vasodilation and inflammation, such as VIP (vasoactive intestinal peptide) and acetylcholine, or yet on unidentified mechanisms in which the toxin prevents the release of various neuropeptides involved in the sebaceous activity, vascular homeostasis, and inflammation. [7]

Also, in a recent paper published by Park et al. in 2015, the successful treatment of two cases of rosacea patients with flushing and persistent facial erythema, refractory to other treatment options was described. The authors concluded that intradermal injections of botulinum toxin might be an effective option for cases of difficult treatment. [8] In 2015, Bloom et al. applied botulinum toxin in patients with persistent erythema on the nasal dorsum, tip and ala, also observing the ability of botulinum toxin to ensure effectiveness and safety in the treatment of rosacea's erythema. [9]

CONCLUSION

When confronted with a case of rosacea with little response to conventional therapy, taking into consideration the emotional impact that the picture has on the lives of the affected patients, seeking an effective therapeutic option is of paramount importance.

In this manner, the authors of the present paper can conclude that botulinum toxin has been proven a new therapeutic option in rosacea, for it brought satisfaction and improvement in the quality of life of the patient studied. The outcomes demonstrate that intradermal applications are effective both in reducing the rosacea's erythema and the inflammatory lesions.

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Case Reports

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Chronic suppurative folliculitis of the scalp: a therapeutic challenge

Foliculite supurativa crônica de couro cabeludo: desafio terapêutico

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ABSTRACT

Scalp folliculitis is a common condition in dermatological practice and a diagnostic and therapeutic challenge. The authors describe a case of chronic suppurative folliculitis in a 53-year-old man who had bore the condition for 18 years. The control of chronic staphylococcal infection with sulfamethoxazole-trimethoprim for 7 months, with progressive shaving of keloid lesions (5 sessions) and application of 90% trichloroacetic acid on wounds up until re-epithelialization (7 months), were successful in treating the disease.

Keywords: Folliculitis; Staphylococcus aureus; Trichloroacetic acid

RESUMO

A foliculite de couro cabeludo é condição comum na prática dermatológica e um desafio diagnóstico e terapêutico. Relata-se caso de foliculite supurativa crônica em homem de 53 anos evoluindo há 18 anos. O controle da infecção crônica estafilocócica com sulfametoxazol-trimetoprim (8-10mg/kg/dia/VO de TMP) por sete meses, shaving progressivo das lesões queloidianas (cinco sessões), aplicação de ácido tricloroacético a 90% nas áreas cruentas até reepitelização (sete meses) lograram êxito.

Palavras-chave: *Ácido tricloroacético; Foliculite; Staphylococcus aureus*

INTRODUCTION

Folliculitis decalvans is an inflammatory alopecia characterized by scalp induration with pustules, erosions, crusts and scales. Although *Staphylococcus aureus* can be isolated in these pustules, it is not known whether this process is primary or secondary. Histologically, an abscess can be observed in the center of the affected follicular infundibulum, followed by predominantly lymphocytic perifollicular inflammatory infiltrate with plasma cells, neutrophils, eosinophils and giant cells, follicular destruction and diffuse dermal fibrosis, with the possibility of hyperkeratosis and follicular occlusion ("plug"). Antibiotics, topical/systemic corticosteroids, and systemic retinoids may be beneficial. The dissecting folliculitis of the scalp begins with inflammatory nodules in the occipital region that progress to cicatricial alopecia. From a histological point of view, there is hyperkeratosis with obstruction and dilation of follicles, inflammatory infiltrate containing neutrophils, lymphocytes and histiocytes, destruction of adnexal structures, granulation tissue, giant cell foreign-body type reaction, formation of fistulas and extensive fibrosis. Surgical incisions/drainage, excision/grafting, and radiation therapy based epilation are used in refractory cases. *Folliculitis* keloidalis nuchea, more common in afro descendants, develops with

papules, pustules, keloids, and cicatricial plaques, mainly in the occipital region. Histology evidences a chronic inflammatory process with numerous plasma cells linked to the follicular structure, follicular destruction, microabscesses, and giant cell foreign-body type reaction around single hair shafts, fistulas, and intense dermal fibrosis with keloid fibers. Antibiotics and intralesional injections with triamcinolone are indicated. [1-4]

The objective of the present study was to highlight the therapeutic difficulty linked to chronic suppurative folliculitis and the excellent outcomes obtained with progressive shaving associated with the control of the infection with sulfamethoxazole-trimethoprim. [5]

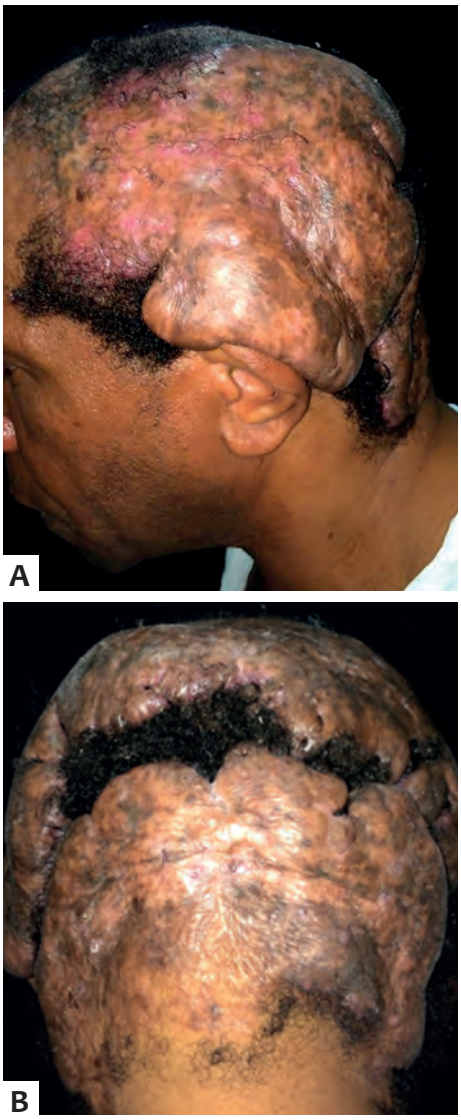
CASE REPORT

A 53-year-old, mulato male patient, cook by profession, originary from the state of Rio de Janeiro in Southeast Brazil, sought care at the Dermatology Service, Hospital Universitário Clementino Fraga Filho (HUCFF) of the Universidade Federal do Rio de Janeiro (UFRJ) in January 2014, complaining of a condition in the scalp that had emerged 18 years before. It began with pustules in the cervical region that progressed to the temporal regions, culminating with keloid scars throughout the scalp. On examination, a fetid pus draining could be observed in the occipital region, mainly when the patient was in the supine position, as well as cicatricial alopecia permeated by small hair tufts in the occipital region.

(Figure 1: A, B and C). Under the suspicion of chronic suppurative folliculitis of the scalp, the patient was hospitalized (45 days) and underwent the following investigation routine: hemogram, biochemistry, urine type I and parasitological examination of feces without alterations; deep scalp biopsy for histological, microbiological (*Staphylococcus aureus* was isolated) and mycological examinations (which resulted negative).

The histological examination revealed an acute and chronic inflammatory process associated with the follicular lesion (isolated hair shafts sometimes involved by giant cell foreign-body type reaction) and dermal fibrosis (Figure 2). Aiming at controlling the chronic infection, sulfamethoxazole-trimethoprim- (8-10mg / kg / day / orally) was administered in two doses for 60 days, with half of that dose thereafter. The choice of sulfamethoxazole-trimethoprim (SMZ-TMP) – after negative G6PD laboratory test – was based on good tolerance to the drug at these doses as well as its prolonged permanence in patients with paracoccidioidomycosis, in addition to its recognized action against community staphylococci, despite the fact that the antibiogram had indicated several antibiotics. Prednisone was administered at 40mg / day orally for 14 days, aimed at reducing inflammation in the area, thus facilitating the surgical treatment in suppurative hidradenitis according to the present paper's authors' experience. [5]

Subsequently, the glycaemias remained high, having been treated with regular insulin and metformin (850mg / orally after the three daily meals). The patient developed multifactorial megaloblastic and iron deficient anemia (in association with the chronic disease), having been treated with ferrous sulfate



Figures 1: A and B - Extensive and deforming keloid masses, interspersed with hair tufts, encompassing occipital and parietotemporal regions

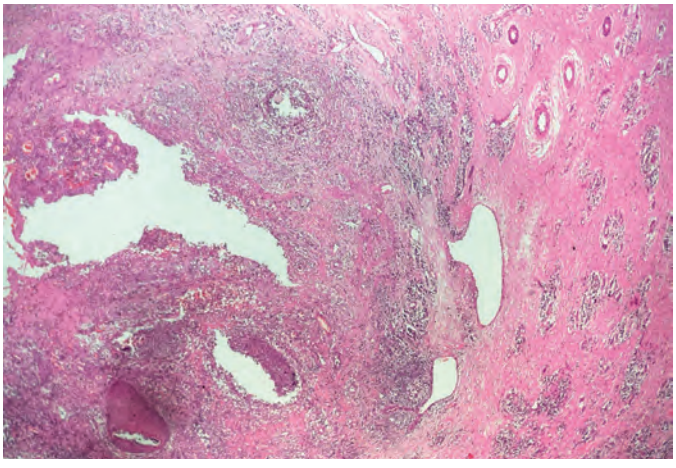


Figure 2: Follicular epithelium fragments surrounded by inflammatory cells, adjacent to clear space, suggesting the presence of a fistula. Microabscesses, separated follicular stem can be observed surrounded by leukocytes and dermal fibrosis (Hematoxylin & Eosin, 100x)

(109mg, 2 tablets / 3x / day and folic acid (5mg / day / orally). The patient was hospitalized and underwent weekly keloid mass excision (5 procedures in total) (Figure 3). The daily dressing procedures consisted of cleansing with degerming chlorhexidine and application of 90% trichloroacetic acid (TCA) in the morning [6] and of 1% silver sulfadiazine in the evening. Thirty minutes before the – very painful – application of TCA, 1g dipyrone plus a codeine paracetamol tablet (30/500) were administered, in addition to regular analgesia with the use of the same drugs. Following hospital discharge, the patient underwent weekly ambulatorial applications of 90% TCA and [6] SMZ-TMP up until complete re-epithelialization was achieved (in seven months) (Figure 4). The patient was discharged from the ambulatorial treatment after twelve months. The following events are noteworthy: intense postoperative pain, one moderate bleeding episode, and one heavy bleeding episode resolved with compressive dressing.

DISCUSSION

Scalp folliculitis is a common condition in dermatological practice and a diagnostic/therapeutic challenge due to the lack of precise guidelines. The authors of the present case hypothesized the superposition of the dissecting/keloid folliculitides based on the anamnesis data, and clinical and histopathological aspects. In a recent retrospective study of 23 cases of folliculitis decalvans, the authors indicate that there are no standard treatments, and recommend the administration of several antibiotics in a sequential manner, in addition to intralesional triamcinolone injections, with remission in half of the cases and a low recurrence/relapse rate. Nevertheless, they concede that it may take several years to discontinue antibiotics in some patients, and there may be recalcitrant cases. [1–3] Other authors [4] consider that oral isotretinoin was the best option in the study of 28 patients,[4] leading to stable remission up to two years after the discontinuation of the treatment. In the present case, the drug proved totally ineffective.

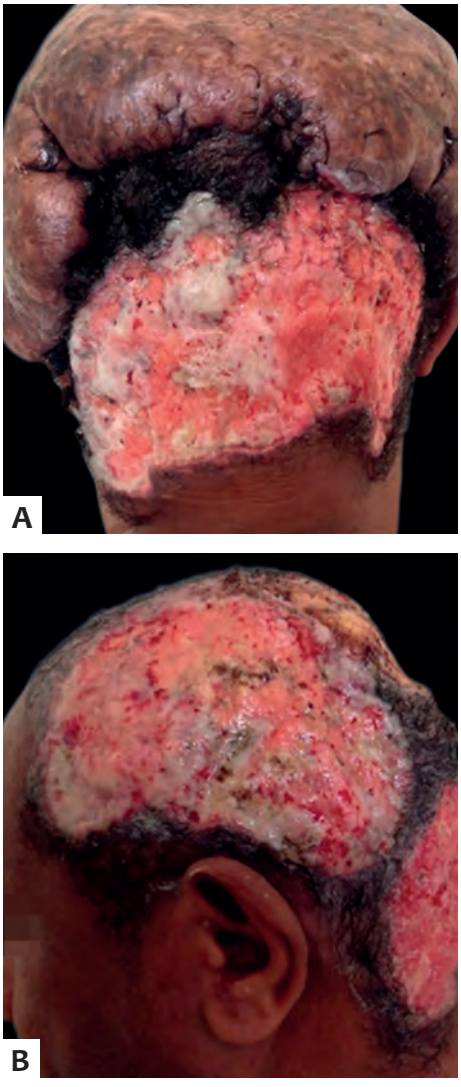


Figure 3: A and B - Surgical approach in five stages, with shaving of keloid masses by electrosurgery

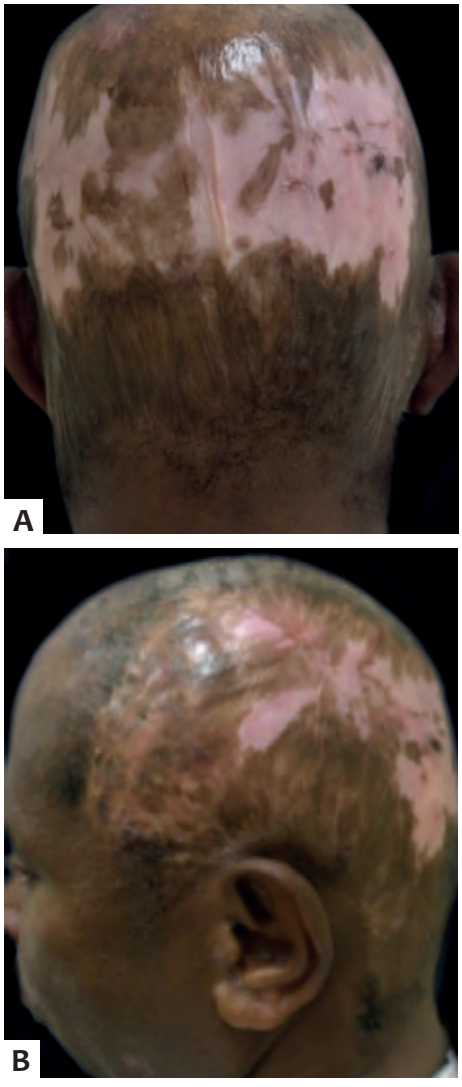


Figure 4: A and B - Complete healing of the scalp

The entities termed folliculitis decalvans, *Folliculitis* keloidalis nuchea and dissecting cellulitis of the scalp are considered deep cicatricial folliculitides and present a similar histological picture, characterized by acute and chronic inflammatory processes linked to the follicular structures and fibrosis, with often subtle variations in the intensity of the changes. Microscopically, there is a mixed inflammatory infiltrate with plasmocytes, possible formation of microabscesses and fistulae, follicular rupture, release of their contents (corneal material and hair shafts), giant cell foreign-body type reaction, transepidermal purging of cellular debris and fibrosis, sometimes with keloid fibers.

The present paper reports a case of folliculitis decalvans with a 20-year development (follicular abscess plus cicatricial alopecia) with tufted hair, without response to the used treatment scheme (topical and systemic corticosteroids, oral and systemic isotretinoin). The patient then decided to have his head shaved and noticed interruption in the formation of pustules. [7] The authors hypothesize that some modification occurred in the scalp with this measure, which influenced the inflammation: more ventilation and reduction of microbial colonization. [7] For keloids the following treatments are recommended: surgical excisions with primary closure in one or multiple stages, and excision with secondary intention healing. [8–10]

CONCLUSION

In the case described in the present paper, the interruption of the possible interaction between the bacterium (*Staphylococcus aureus*) and the host using the prolonged SMZ-TMP scheme allowed the resection of the keloid masses with satisfactory outcomes.

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Favre-Racouchot syndrome: optimal response to surgical treatment

Síndrome de Favre-Racouchot: ótima resposta ao tratamento cirúrgico

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ABSTRACT

The association of cysts and comedones in chronically sun-damaged skin characterizes the Favre-Racouchot syndrome. The authors report a case of a 64 year-old male patient with a history of smoking and tillage work activity. The patient had lesions in the malar, zygomatic and mandibular regions bilaterally, constituted by slightly erythematous cysts and large comedones in thickened skin with deep grooves. The condition was diagnosed as Favre-Racouchot syndrome, and treated by means of surgical excision. The objective of the present study is to describe an exuberant presentation of the syndrome, and its treatment via surgical excision.

Keywords: Facial dermatoses; Photosensitivity disorders; Skin aging

RESUMO

A síndrome de Favre-Racouchot é caracterizada pela associação de cistos e comedões em pele cronicamente danificada pelo sol. Relatou-se caso de paciente do sexo masculino, 64 anos, com antecedentes de tabagismo e atividade laboral em lavoura; apresentava lesões nas regiões malar, zigomática e mandibular, bilateralmente, constituídas por cistos levemente eritematosos e comedões grandes em pele espessada e com sulcos profundos. Foi feito diagnóstico clínico de síndrome de Favre Racouchot e tratamento por meio de excisão cirúrgica. O objetivo deste trabalho é demonstrar uma exuberante apresentação da síndrome e seu tratamento por excisão cirúrgica.

Palavras-Chave: *Dermatoses faciais; Envelhecimento da pele; Transtornos de fotossensibilidade*

INTRODUCTION

The Favre-Racouchot syndrome is characterized by the association of cysts and comedones in chronically sun-damaged skin. It is believed that there is also a correlation with smoking habits and radiotherapy. [1, 2] It mainly occurs in Caucasian men, although it has already been reported in dark skinned and aboriginal patients. [3, 4]

The diagnosis is clinical, and histological examination is rarely necessary. [5] Several treatments have already been proposed, including systemic and topical retinoids, mechanical extraction of comedones, curettage and cauterization, CO2 laser and surgical excision. [1, 2] The present case report is aimed at demonstrating an exuberant presentation of the syndrome and its treatment by surgical excision.

CASE REPORT

A 64-year-old male patient, with a history of smoking and working outdoors in the field, had lesions in the malar, zygomatic and mandibular regions on both sides of the face, consisting of slightly erythematous cysts and large comedones in thickened skin with deep furrows (Figure 1).

The patient described erythema, pain, and sporadic discharge from the cystic lesions. The clinical diagnosis was of Favre-Racouchot syndrome. The treatment was surgical and consisted of elliptical resection of most of the lesions (Figure 2A), followed by simple suture with nylon 5.0 thread (Figure 2B).

The histological examination revealed multiple epidermal cysts and comedones – some of them ruptured – with acute chronic inflammation and "foreign body" type gigantocellular reaction, associated with dermal elastosis. The outcome of the procedure was evaluated 45 days after (Figure 3).

DISCUSSION

The syndrome was first described by Thin in 1888, having been confirmed by Favre in 1932. In 1951, Favre and Racouchot named the disease, including solar elastosis and cysts as features.[1, 6] The Favre-Racouchot syndrome is estimated to be prevalent in 1.4% of the population, with a 6% incidence in the elderly with over 50 years of age, mainly in fair-skinned men.[1, 7] Its pathogenesis is unknown, however chronic exposure to ultraviolet radiation, smoking habits and radiotherapy have been identified as important triggers for promoting cutaneous atrophy, follicular hyperkeratosis, and comedones.[1, 5, 8] Exposure to the sunlight apparently exerts an aggravating effect on the development of cysts induced by smoking habits.[9]

The syndrome is characterized by open and closed comedones, papules, nodules and cystic lesions in association with marked solar elastosis of the surrounding skin, as seen in the reported case. [5] Its most frequent location are the periorbital and temporal regions, with symmetrical or asymmetric distribution, possibly due to irregular exposure to radiation.[10-12] In addition, it may affect the malar eminences, cervical region, retroauricular areas, ear lobes and forearms. [4] It is worth to note that there are some related conditions, such as cutis rhomboidalis nuchae, cutaneous myxoma, actinic keratosis, squamous cell carcinoma, trichostasis spinulosa, keratoacanthoma and eyelid papilloma.[4]

In most cases diagnosis is clinical. Histologically, there is diffuse solar elastosis, epidermal atrophy, basophilic degeneration in the upper dermis and absence or decrease in the size of sebaceous glands, which present a pilosebaceous infundibulum filled with keratin.[1, 8] The main differential diagnoses include: colloid milium, milia, syringoma and trichoepithelioma. [13]

Measures to attempt and prevent the progression of the disease include the use of broad-spectrum sunscreens associated with giving up smoking habits. There is no consensus on the treatment of this syndrome, meaning it is a challenge to dermatologist physicians. [14]

Due to its exfoliative and collagen-remodeling properties, topical retinoids (tretinoin and retinaldehyde) and systemic retinoids (oral isotretinoin) are quoted as important treatments. This therapy modality can improve comedones and facilitate their extraction. [15] A case series study based on the treatment of three patients with 0.05% tazarotene gel yielded good response, with skin irritation at the beginning of use being the main side effect. [2] Another study using daily oral isotretinoin (0.05-0.1mg / kg / day) combined with topical tretinoin was also effective. [4]

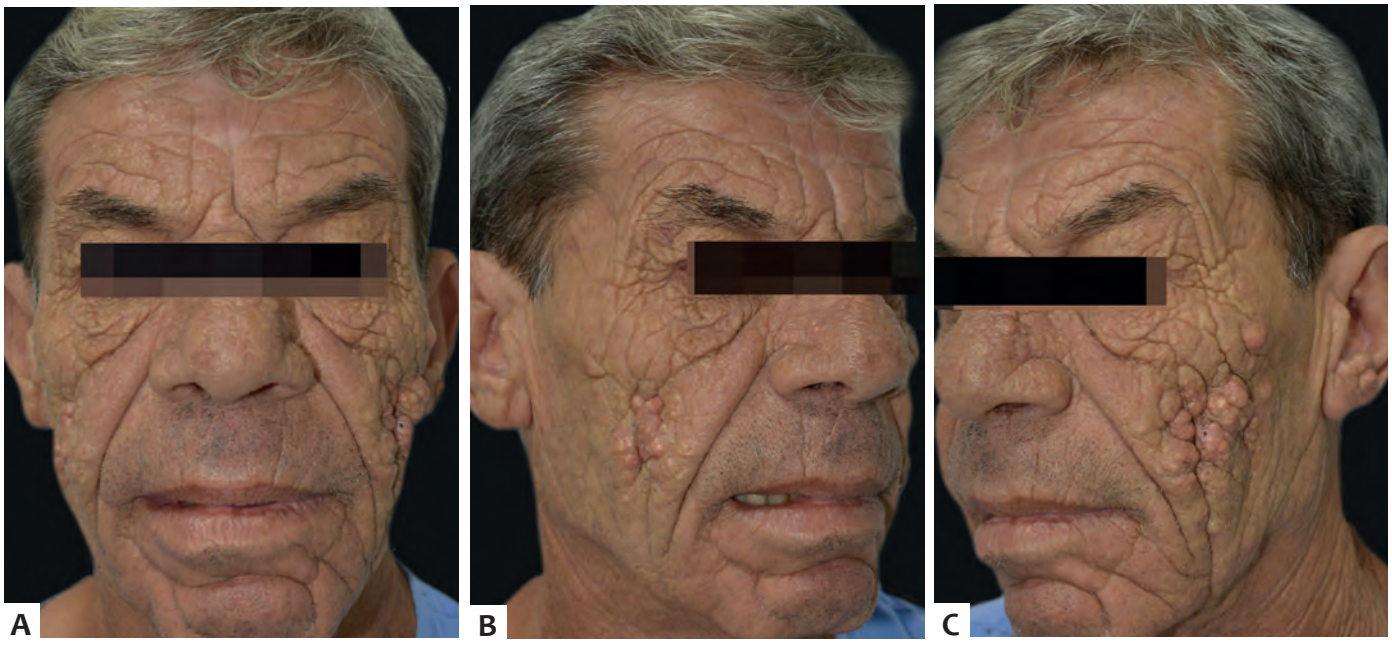

Figure 1: A - Preoperative lesions on the face; **B** - Preoperative lesions in the right hemiface; **C -** Preoperative lesions in the left hemiface

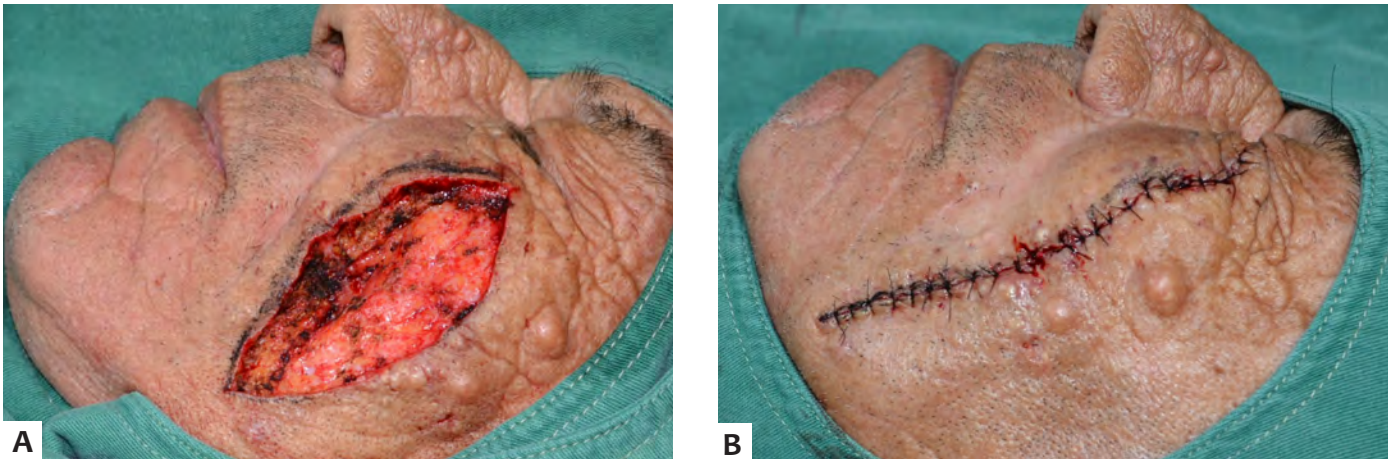

Figure 2: A - Elliptical resection of the lesions in the left hemiface; **B –** Left hemiface in the immediate postoperative period

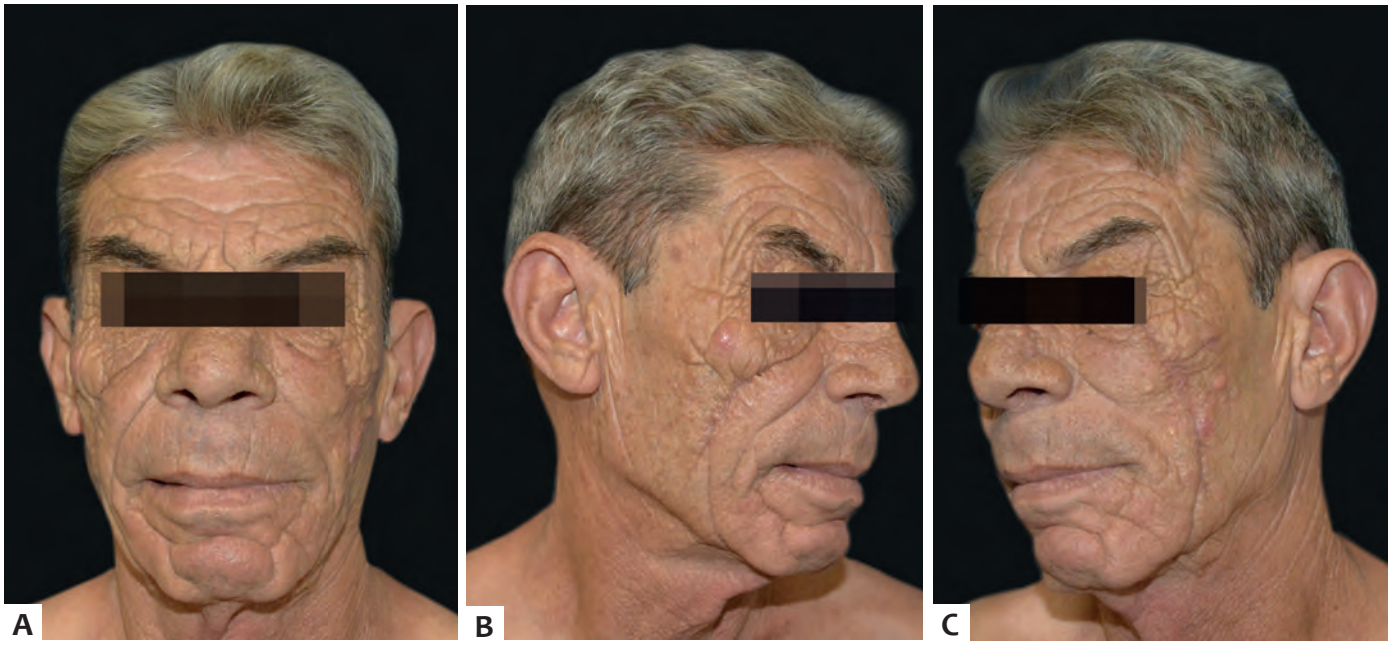

Figure 3: A - Preoperative lesions on the face; **B -** Preoperative lesions in the right hemiface; **C -** Preoperative lesions in the left hemiface

Rai et al. described successful therapy with the use of CO2 laser, associated with manual expression of comedones under local injectable anesthesia. In this case series, patients were followed up for a period ranging from eight months to three years: two of them required a new treatment in within two and three years after the initial one, while recurrence was observed after more than one year following the primary treatment. [1] In a diverse study, 50 patients underwent superpulsed CO2 laser followed by extraction of cystic and comedonic material using gentle pressure with a pair of forceps, without topical or intralesional anesthetics, leading to satisfactory cosmetic outcomes. [16]

Surgical options include dermabrasion, curettage, or surgical excision of comedones and cysts. [2] In the present case, a decision was made for the partial surgical excision of the lesions due to the important extension of the picture, complain of sporadic inflammation of the cysts, and "excess skin", with the achievement of excellent outcome and relevant patient satisfaction. Therefore there are several treatment options for the improvement of the aesthetics and quality of life of patients bearers of Favre-Racouchot syndrome, and the dermatologist physician should be able to choose the modality that best suits his or her patient.

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Atypical and exuberant presentation of sebaceous nevus of Jadassohn

Apresentação atípica e exuberante de nevo sebáceo de Jadassohn

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ABSTRACT

The sebaceous nevus of Jadassohn is a benign neoplasia, usually present at birth. It usually arises as a small yellowish and oval plaque in the scalp and face, with large lesions being uncommon. The authors report a case of an atypical and exuberant sebaceous nevus of Jadassohn, located in the frontal-parietal-occipital region of a male child, associated with alopecia.

Keywords: Hamartoma; Nevus, sebaceous of Jadassohn; Sebaceous glands; Skin neoplasms

RESUMO

O nevo sebáceo de Jadassohn é uma neoplasia benigna geralmente presente ao nascimento. Costuma apresentar-se como pequena placa amarelada e oval no couro cabeludo e face, sendo incomum o encontro de lesões de grandes dimensões. Diante disso, os autores relatam um caso de nevo sebáceo de Jadassohn de apresentação exuberante e atípica, localizado na região fronto-parieto-occipital de uma criança do sexo masculino, associado a alopecia

Palavras-Chave: *Glândulas sebáceas; Hamartoma; Nevo sebáceo de Jadassohn; Neoplasias cutâneas*

INTRODUCTION

Sebaceous nevus, also known as organoid nevus, is a congenital hamartoma that was described in 1895 by Jadassohn, having been named sebaceous nevus of Jadassohn by Robinson in 1932.[1] It occurs in roughly 0.3% of newborns, with proliferative alteration of sebaceous glands, sweat glands and hair follicles. It usually arises as a small dimension orangish-yellow circumscribed lesion located in the scalp and face.[1, 2] There are few reports of cases with multiple or extensive lesions, which is an uncommon form of presentation.[2] In light of this, the authors of the present paper describe the case of a patient bearing sebaceous nevus of Jadassohn with extensive linear presentation in the scalp.

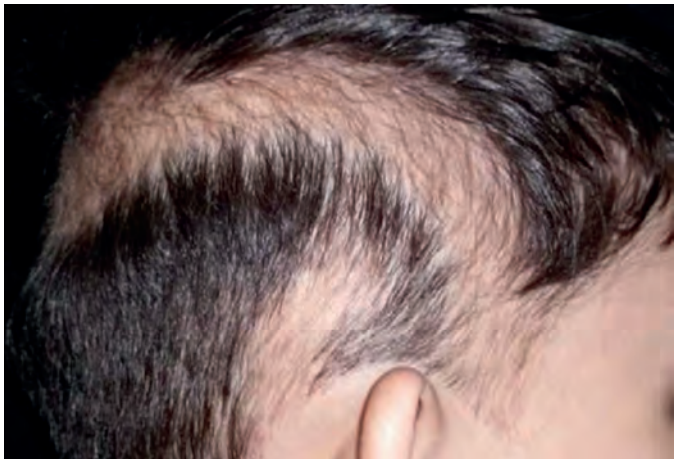

Figure 1: Right temporal-parietal-occipital region with an extensive alopecia band with thin and light colored strands

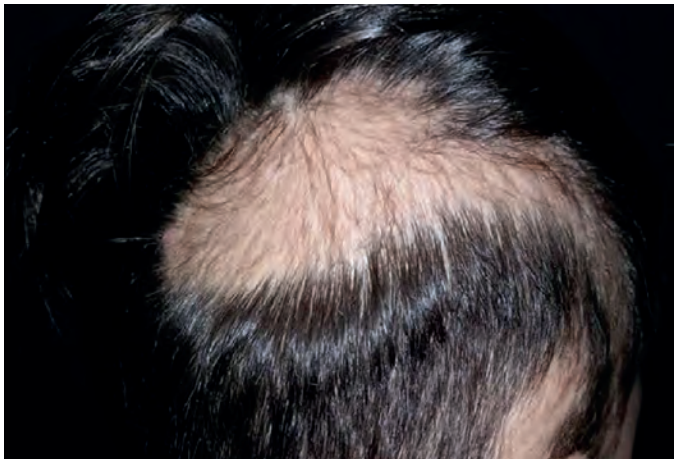

Figure 2: Extension of the alopecia band in the parietal-occipital region

CASE REPORT

A 6-year-old Caucasian male patient with an alopecia plaque located in the scalp since birth was taken to a medical consultation. He denied pruritus, pain or any additional symptom. Dermatological examination evidenced an extensive strip of alopecia with thin, light color strands in the right temporal--parietal-occipital region (Figures 1 and 2); as well as a narrow linear orangish-yellow plaque, with finely wrinkled surface in the temporal region (Figure 3). Punch biopsy was performed, with histology evidencing hyperkeratosis, regular acanthosis, papillomatosis, decreased size and number of hair follicles and sebaceous glands (Figures 4 and 5). In face of the diagnosis of sebaceous nevus, the parents were advised on the lesion's benign nature, and low risk of malignancy reported in the literature by some authors. Concerned with the unsightly aesthetics of the lesion and possible social exclusion of the child, the parents requested a referral to the Plastic Surgery Clinic, which indicated surgical correction with the previous use of expanders, with this therapeutic option being postponed for future analysis.

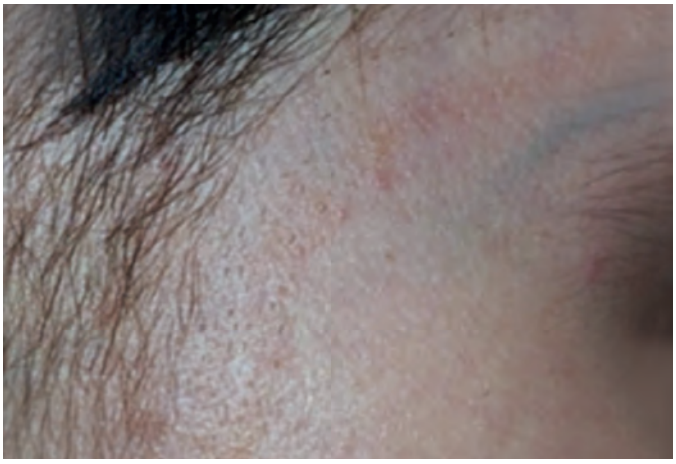

Figure 3: Detail of the temporal region with thin linear plaque, orangish-yellow in color and with finely verrucous surface

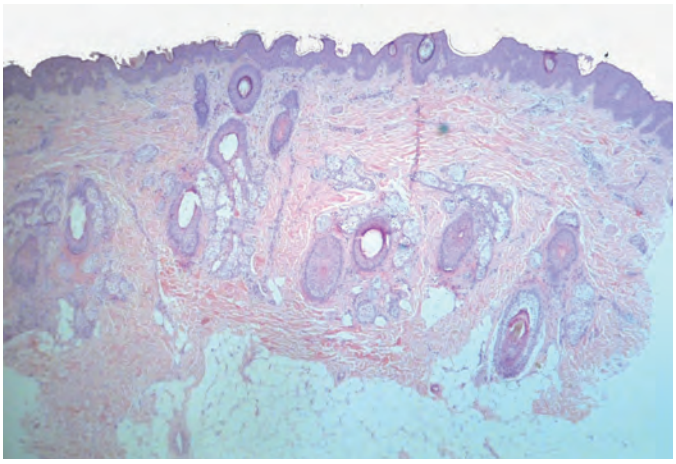

Figure 4: Histology with 40x magnification evidencing hyperkeratosis, regular acanthosis, papillomatosis, decrease in the number and size of the hair follicles

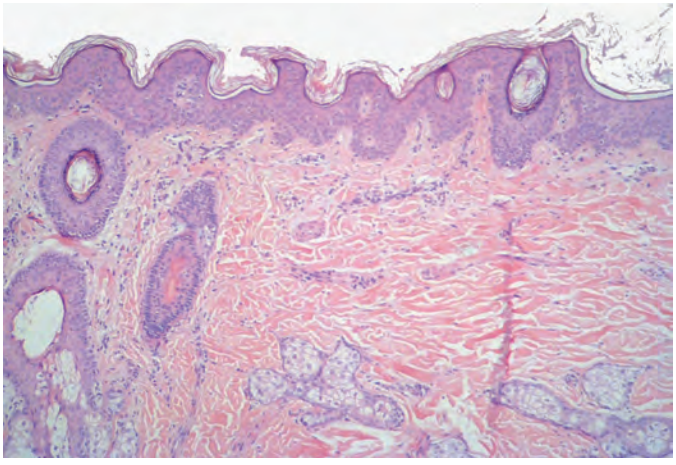

Figure 5: Histology with 100x magnification evidencing hyperkeratosis, papillomatosis, presence of rudimentary hair follicle and sebaceous glands

DISCUSSION

The etiology of sebaceous nevus is still unknown, however studies have shown a probable association of genetic co-mutations, especially those related to HRAS and KRAS genes. [3] The typical initial presentation is round, oval or linear plaques, of small size and orangish-yellow in color, located in the cervical region, and head and scalp – where it causes alopecia.[3] Although the location and morphology of the patient's lesions could point towards this diagnosis, the lesion's dimensions were uncommon, meaning that was a rare form of presentation in the age group. Under puberty's hormonal influence, it is common to observe growth of the lesion, which lends it a more verrucous surface and makes it more evident.[3, 4] Hair follicles are small and rudimentary.[4] Diagnosis is usually clinical; nevertheless biopsy may be necessary, especially in atypical conditions, such as in the studied patient. The histology may vary according to the lesion's lifetime. In the initial lesions it is possible to observe underdeveloped sebaceous glands in smaller numbers, as well as immature hair follicles – with the latter finding being very important for the diagnosis.[4] During puberty, hyperplasia of the epidermis and papillomatosis, superficial and abundant sebaceous glands, as well as ectopic apocrine glands are expected to be found. The histological changes found in the case corroborate the diagnosis in question based on classic findings, such as papillomatosis, decrease in the size and number of sebaceous glands and hair follicles. Depending on the location, sebaceous nevus can only lead to unsightly consequences, although in adult life up to 15% of cases may be related to benign and malignant neoplasms, which is the most common complication. The most frequently associated malignant tumor is basal cell carcinoma, with an incidence below 2%.[5] In cases of rapid growth, ulceration, surface changes and bleeding, there must be suspicion of a possible malignant transformation. In the case reported, despite the lesion's extension, no sign of malignancy was observed. The most frequently associated benign lesions are syringocystadenoma papilliferum and trichoblastoma.[5, 6] The preferential treatment of classic lesions is total thickness surgical excision, with margins of 2 to 3 mm. Prophylactic surgery in children is widely debatable, and some authors advocate clinical follow-up and intervention only in cases of modifications that suggest malignancy. [7] Surgery can be justified for aesthetical reasons – since the facial and scalp locations, the latter with alopecia, can have a significant effect on the physical appearance – or even be aimed at preventing the formation of tumors. Nonetheless, there is no consensus regarding this approach in the literature.[7, 8] The choice will depend on the lesion's location, child's age, surgical risk, among other factors, also requiring meticulous discussion. When the lesions are extensive – such as those in the present case – the use of expanders and subsequent surgery would be an option. [9] In the present case the approach to be taken is still being discussed, since there is prospect of an increase in the lesion at puberty. Other options, such as rotation flaps, Mohs surgery, and CO2 laser ablation are described as alternative therapies in small lesions. Yet, it should be noted that ablative treatments are usually limited to improving the superficial appearance of the lesion, without treating the commonly associated alopecia and do not exclude the need for long-term monitoring of malignancies. [10] When choosing the therapeutic modality, it is recommended that not only the risk of malignization be evaluated, but also the aesthetic, psychosocial and functional harm that an extensive nevus of Jadassohn lesion can inflict during its natural course. [10] It is important to note the frequent occurrence of sebaceous nevus in children and adolescents, as well as to bear in mind that diagnosis should be considered even in atypical and extensive cases. There are few reports in the literature describing exuberant manifestations of organoid nevus, which is a rare form of presentation. The authors of the present paper also emphasize the important role of dermatologic surgery in cases such as the one in question, where aesthetic and functional reconstruction has a positive impact on the patients' quality of life.

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Case Reports

Poroid hidradenoma: a rare adnexa tumor

Hidradenoma poroide: um raro tumor de anexo

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ABSTRACT

The poroid hidradenoma is a rare benign intradermal neoplasm rare that is poorly described in the literature. It usually affects elderly individuals and is characterized as a solitary, painless and well-circumscribed nodule. The diagnosis is confirmed by the histological characteristics of the hidradenomas and poromas. The treatment corresponds to complete surgical excision, thus avoiding recurrence and malignancy. The authors report a case of a 64 year-old patient, with a single, well-delimited and asymptomatic nodular lesion that had emerged 5 months before.

Keywords: Neoplasms, Adnexal and skin appendage; Poroma; Sweat gland neoplasms

RESUMO

O hidradenoma poroide é uma neoplasia intradérmica benigna rara e pouco descrita na literatura. Afeta geralmente indivíduos idosos e caracteriza-se como nódulo solitário, indolor e bem circunscrito. O diagnóstico é firmado por características histológicas de hidradenomas e poromas. O tratamento é realizado através de excisão cirúrgica completa, evitando assim recidiva e malignização. Relatamos caso de uma paciente, 64 anos, com lesão nodular única, bem delimitada e assintomática há 5 meses.

***Palavras-chave**: Neoplasias das glândulas sudoríparas; Neoplasias de anexos e de apêndices cutâneos; Poroma*

INTRODUCTION

Poroid hidradenoma is a rare benign neoplasm that was first described in 1990 by Abenoza and Ackerman.[1] It usually emerges as an asymptomatic, solitary nodule, commonly found in elderly women.[2] It has eccrine differentiation, with structural characteristics of hidradenomas and cytological characteristics of poromas.[3] Since it is a rare, little described condition in the literature, the present case report expands the differential diagnosis of cutaneous nodules, offering a widened base of comparison for the dermatologist physician.

CASE REPORT

A 64-year-old female patient, without relevant personal history, sought care for a nodular, erythematous, asymptomatic lesion in her left hand, with five months of development and slow growth. At the clinical examination, a single, nodular, well-delimited lesion, with 1 cm in its largest diameter, could be observed on the dorsum of the left hand (Figure 1). The hypotheses of poroma, myxoid cyst, amelanotic melanoma and pyogenic granuloma were hypothesized. After exeresis, the anatomopathological examination evidenced a cystic structure in the dermis, containing homogeneous eosinophilic material and a wall that was sometimes atrophic, with segments containing proliferation of small poroid cells, and larger cuticular cells around lumens (Figures 2, 3, 4 and 5), confirming the diagnosis of poroid hidradenoma. Four months after surgery, the patient remained asymptomatic and without recurrence.

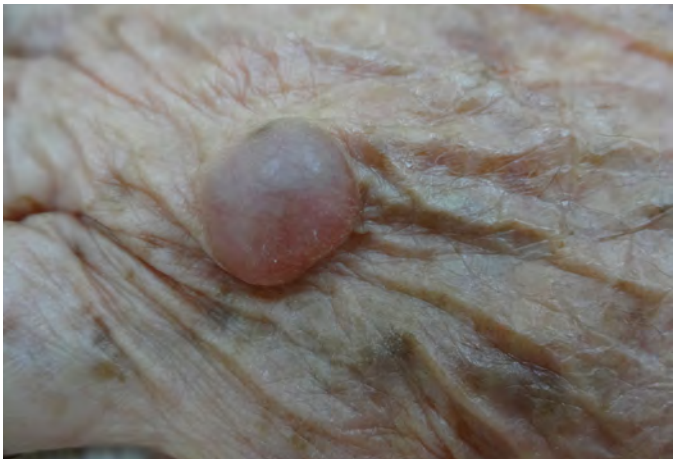

Figure 1: Solitary, nodular, well-delimited lesion on the dorsum of the left hand, measuring 1cm in its largest diameter

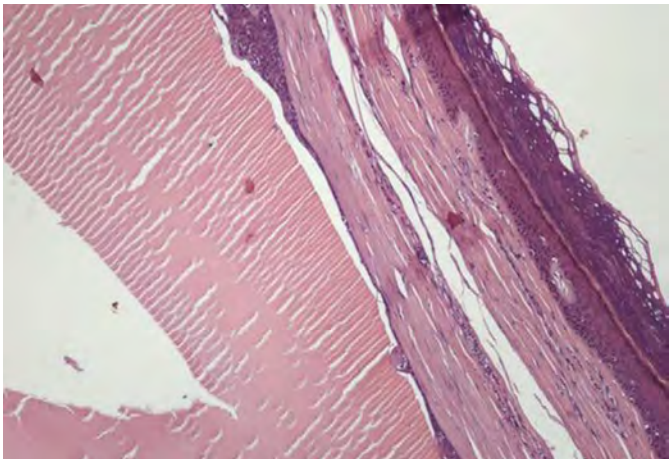

Figure 4: Superficial location of the cyst with atrophic wall

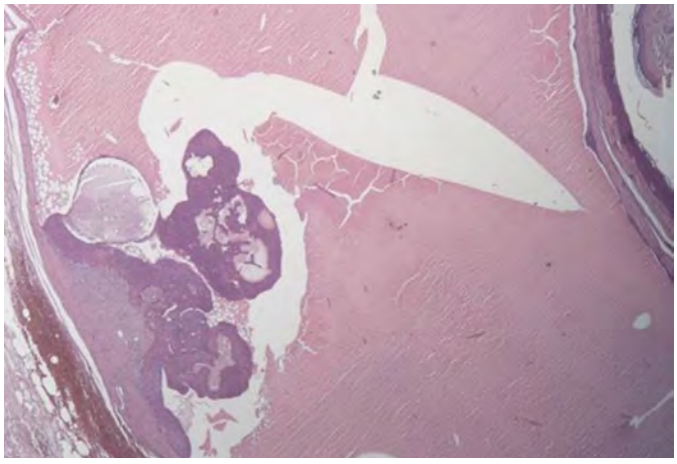

Figure 2: Non-keratinized cystic structure in the dermis

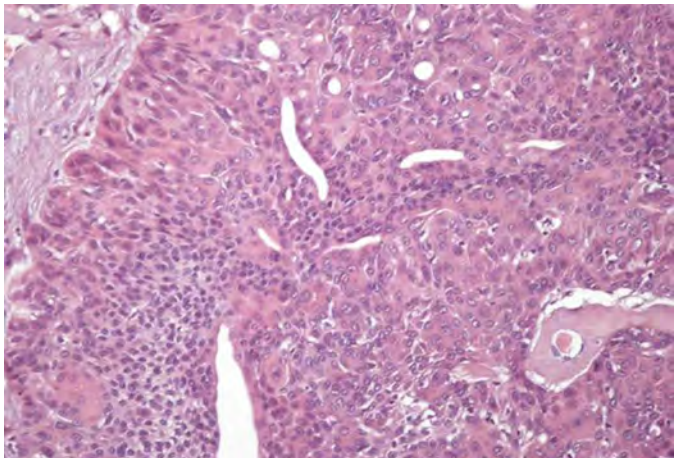

Figure 5: Poroid cells in detail

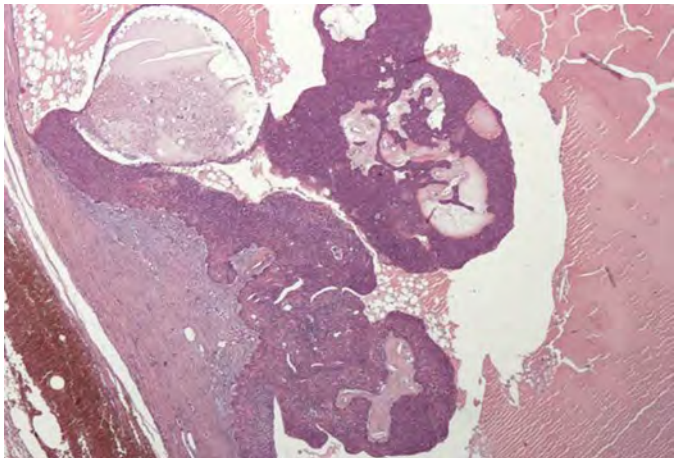

Figure 3: Wall with proliferation of poroid cells

DISCUSSION

Poroid hidradenoma belongs to the poromas group, which also includes hidroacanthoma simplex, eccrine poroma and the dermal duct tumor. [4, 5] It is a rare benign neoplasm of the sweat gland, corresponding to 5% of all hidradenomas.[2, 6] The risk of malignant transformation is less than 1%.[3, 7]

It mainly affects women in their seventh decade of life and has preference for the head, neck and extremities.[3, 5] It is characterized by a solitary, asymptomatic nodule or papule, reddish in color and well circumscribed, generally ranging from 1cm to 2cm in diameter. [4] Its components are entirely confined in the dermis, without connection to the epidermis. [2] Approximately 25% may have a bluish hue due to the presence of cystic content.[3, 7] Diagnosis is based on structural histological features of hidradenoma (presence of solid and cystic areas), combined with cytological characteristics of poromas (poroid and cuticular cells with ductal differentiation). In tumors with cystic forma-

tion, aspiration with a fine needle can be an additional method to diagnosis and, therefore, to surgical planning.[3, 6] Differential diagnosis is carried out with other poromas, including apocrine hidradenomas and other neoplastic formations, such as fibromas, fibrolipomas, dermatofibromas, hemangiomas, in addition to malignant eccrine poroma and pyogenic granuloma.[7, 8] Surgery is the definitive treatment for this neoplasm, with complete excision of the lesion aimed at avoiding recurrence. Radical excision is recommended – with total removal of skin and subcutaneous cellular tissue up until the superficial fascia – due to the fact it originates from dermal tissue.[7]

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Similarities between a post-traumatic pseudolipoma and a liposarcoma: a case report

Semelhanças entre um pseudolipoma pós-traumático e um lipossarcoma: relato de caso

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ABSTRACT

The post-traumatic pseudolipoma (PTPL) is a unencapsulated proliferation of mature adipose tissue that develops after a local trauma. We report a case of a male child, who presented with a tumor on the left forearm which appeared weeks after a local blunt trauma. We perform a biopsy of the lesion and the diagnosis of post-traumatic pseudolipoma was established. This case exposes an example that PTPL can simulate liposarcoma clinically. In addition, both disorders are rarely reported in dermatological journals, which cause a poor knowledge about its clinical resemblances and differences by dermatologists.

Keywords: Forearm injuries; Lipoma; Liposarcoma; Neoplasms, post-traumatic

RESUMO

O Pseudolipoma pós-traumatico (PLPT) é uma proliferação de adipócitos maduros, não encapsulada, que se desenvolve após trauma local. Relatamos o caso de uma criança do sexo masculino, que exibiu uma tumoração no antebraço esquerdo, semanas após trauma contuso. Procedeu-se à biópsia da lesão e foi estabelecido o diagnóstico de PLPT. O caso relatado expõe as similaridades clínicas do PLPT com lipossarcoma, que também possui associação com trauma local prévio, pode se apresentar como tumoração de consistência amolecida e frequentemente se localiza no membro superior. Ambas as afecções são pouco relatadas nos periódicos dermatológicos, o que causa desconhecimento de suas características pelos dermatologistas.

Palavras-Chave: *Lipoma; Lipossarcoma; Neoplasias pós-traumáticas; Traumatismos do antebraço*

INTRODUCTION

Post-traumatic pseudolipoma (PTPL) is a focal proliferation of non-encapsulated mature adipose tissue that develops after local trauma. Despite its good prognosis, pseudolipoma can cause focal motor or sensory deficits by compression to adjacent muscular and nerve structures. A PTPL can sometimes simulate a liposarcoma due to its location and clinical appearance. The authors of the present paper report a case of a child who developed PTPL that is still growing, which led to the suspicion of liposarcoma.

Case Reports

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CASE REPORT

A 13-year-old male patient complained of a progressively growing tumor in the anterior region of the left forearm. The lesion emerged 2 years before, some weeks after an episode of blunt trauma at the site. The patient reported that after the trauma, a hematoma developed at the site, having been treated with hot compresses that caused a 2nd degree burn in the forearm. Regarding his personal history, he denied comorbidities or use of medications. At the physical examination, a tumor of 10 cm in diameter located on the anterior aspect of the left forearm, poorly delimited, with soft consistency, no inflammatory signs or pain to palpation was observed, associated with an atrophic scar on the overlying skin (Figure 1). No sensory or motor deficits were detected in the affected limb. On-site ultrasound showed focal proliferation of subcutaneous tissue. A biopsy of the lesion was performed, whose histology suggested abundant subcutaneous adipose tissue with mature adipocytes, without atypia (Figures 2 and 3). The diagnosis of post-traumatic pseudolipoma was then established. After learning about the benign nature of the lesion, the patient and his father chose not to undergo any treatment, with clinical follow-up of the lesion being carried out on a quarterly basis.

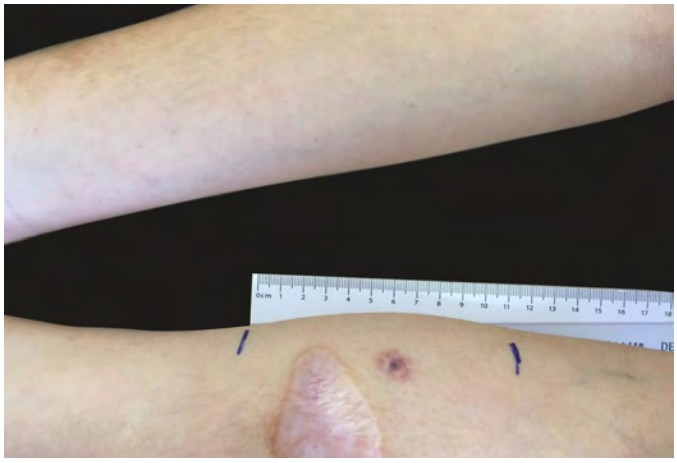

Figure 1: Tumor with 10 cm in diameter and atrophic scar at the site of the trauma that originated the pseudolipoma

DISCUSSION

PTPL was first described in 1932 by Adair et al. and is defined as a non-encapsulated proliferation of adipose tissue that develops after acute or chronic trauma. It is markedly more common in middle-aged women (3.8 : 1) (mean age = 46 years) and typically occurs in the lower limbs, specifically the thighs and glutei. [1]

The pathogenesis of PTPL has not yet been clarified, and two pathogenic mechanisms have been proposed. The earliest of these mechanisms was proposed by Broke and McGregor in 1969, who suggested that the pseudolipoma would arise after an herniation of adipose tissue through traumatic lesions in the Scarpa's fascia. [2] However, this hypothesis was not confirmed by other studies. Other authors have suggested that the development of the neoplasia is due to the maturation of pre-adipocytes stimulated by cytokines and inflammatory mediators released during the trauma, accumulated hematoma or lesioned adipocytes. [3]

Clinically, PTPL differs from lipoma due to the absence of a capsule and for developing from weeks to months after an event of local trauma. Its development is benign, chronic and without complications, however there are reports of motor and / or sensory deficits due to the compressive effect of the lesion on adjacent nerve or muscle structures. In these cases, surgical treatment is mandatory, which can be performed by liposuction (in the case of larger lesions) or surgical excision (in the case of smaller lesions). [4]

Regarding the lesion's location, occurrence of PTPL in the upper limbs is rare. In 2009, Galea et al. reviewed 124 cases, reporting that the occurrence of this neoplasia in the upper

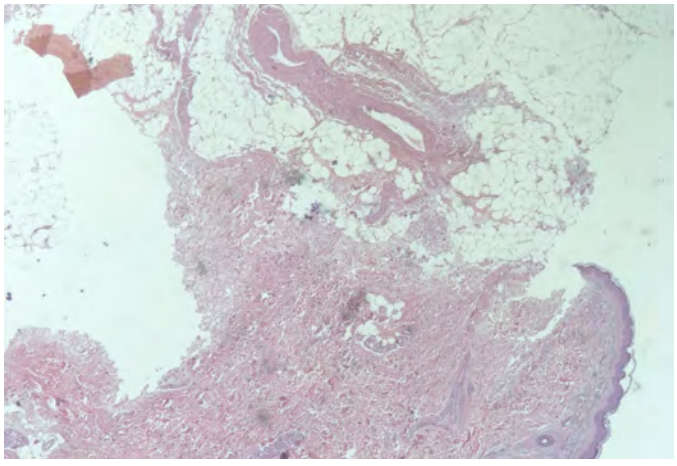

Figure 2: Epidermis and dermis without changes. (Hematoxylin & eosin, 20x)

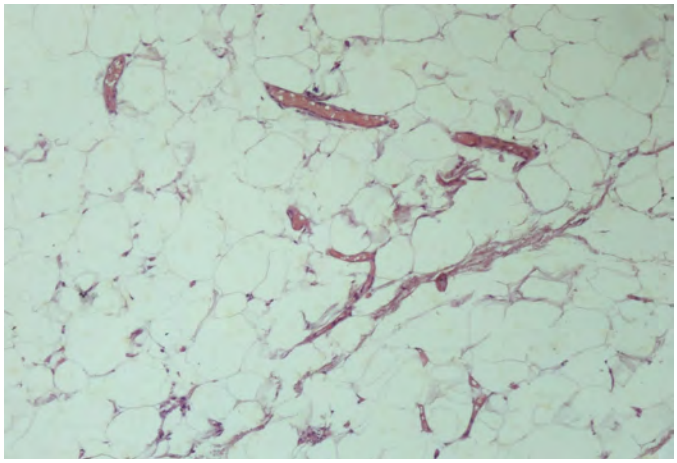

Figure 3: Abundant subcutaneous, mature adipose tissue without atypia. (Hematoxylin & eosin, 100x)

limbs is uncommon. On the other hand, 74.4% of the cases studied in that series were located in the lower limbs.

In 2015, Jacolino and Wingerden reviewed 15 PTPL cases specifically located in the upper limbs – with only 5 located in the forearm, as in the present case. This topographic finding has importance in the differential diagnosis of PTPL with liposarcoma, which also has an association with previous local trauma, may clinically arise as a tumor of softened consistency and is frequently located in the upper limb. The diagnostic suspicion of liposarcoma can be raised based on magnetic resonance imaging, however has to be confirmed by biopsy of the lesion. [4, 5] In the present case, the progressive growth of the lesion and its location induced the hypothesis of liposarcoma, however the histological examination discarded this possibility.

Finally, there is a shortage of PTPL cases reported in the dermatological literature, which explains the limited knowledge of this condition by dermatologist physicians. The vast majority of reports and case series on the subject have been published on journals that are predominantly from other surgical specialties. In addition, the case reported in the present paper is an uncommon occurrence in the literature due to the following facts: it affects a male child, has a history of progressive growth and is located in the upper limb – all of which emphasized its clinical similarity with liposarcoma of the extremities.

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Case Reports

Porokeratoma: a new clinical entity?

Poroqueratoma: uma nova entidade clínica?

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ABSTRACT

Porokeratoma is an entity defined as an acanthoma with porokeratosis characteristics. It has a distinct histological pattern from that of the cornoid lamella and has clinical differences regarding the typical porokeratosis. The condition has been described only recently and there are few cases reported in the literature. The authors report the case of a 46 year-old male patient with an exophytic nodular lesion located in the intergluteal region. Histological examinations evidenced multiple cornoid lamellae, with those located on the periphery being better defined. Based on the clinical and histological appearance, the lesion was diagnosed as a porokeratoma.

Keywords: Acanthoma; Keratosis; Porokeratosis

RESUMO

O poroqueratoma é entidade definida como acantoma com características de poroceratose. Apresenta padrão histopatológico distinto de lamela cornóide e diferenças clínicas em relação à poroceratose típica. Trata-se de uma afecção recentemente descrita, com poucos casos relatados na literatura. Apresentamos caso de paciente do sexo masculino, 46 anos, com lesão nodular exofítica, localizada na região interglútea. O exame histopatológico evidenciou múltiplas lamelas cornóides, sendo as periféricas as mais bem definidas. Devido à apresentação clínica e histopatológica, o diagnóstico foi de poroqueratoma.

Palavras-Chave: *Acantoma; Ceratose; Poroceratose*

INTRODUCTION

Porokeratomas is a dermatological condition that was first described in 2007 by Walsh *et al.*[1], who defined it as an acanthoma with porokeratosis characteristics. Porokeratoma and porokeratosis share the cornoid lamella histological feature, which is a disorder of the epidermis' maturation. [1, 2, 3] Porokeratosis has several variants: porokeratosis of Mibelli, disseminated superficial actinic porokeratosis, disseminated palmoplantar porokeratosis, linear porokeratosis and porokeratosis punctata.[1]

Porokeratoma has a distinct cornoid lamella pattern, in addition to clinical and epidemiological differences. For this reason it has recently been deemed a new clinical entity. This case report offers an extension of the knowledge about this little known condition for the dermatologist physician.

CASE REPORT

A 46-year-old male patient sought care due to the recurrence of an exophytic nodular lesion in the intergluteal region (Figure 1). The lesion had been excised 5 years before, when no specimen was sent to histological analysis. The patient denied comorbidities or use of drugs. The examination revealed a verrucous solitary lesion with 1cm in diameter, hyperkeratotic center and elevated crest in the periphery. The patient had hypochromia in the intergluteal sulcus, secondary to intertrigo. There were no other skin or mucosal changes. The hypotheses of irritated seborrheic keratosis, pyogenic granuloma and verrucous squamous cell carcinoma were raised. After the incisional biopsy of the lesion, the histological analysis evidenced epidermis with regular acanthosis, orthokeratosis and parakeratosis, exhibiting multiple cornoid lamellae – the peripheral being more well defined. In the dermis, it was possible to observe a focal lymphocytic infiltrate and the presence of an elevated adipose tissue band (Figures 2, 3 and 4).

Based on the clinical and histological appearance, porokeratoma was diagnosed, with the complete excision of the lesion having been performed with free margins.

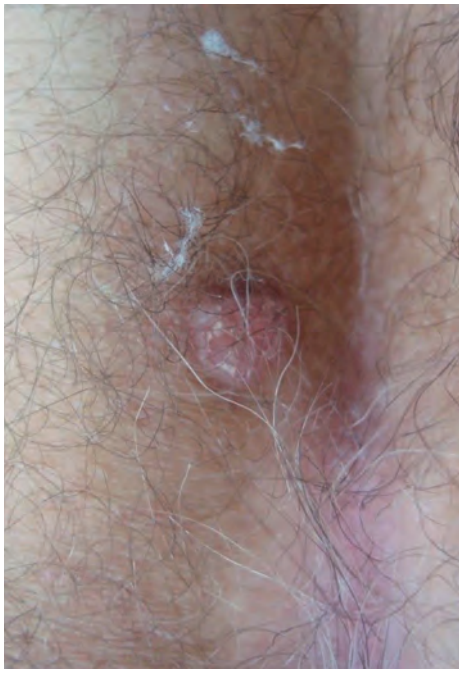

Figure 1: PIsolated, verrucous papule with elevated crest on the periphery

DISCUSSION

Porokeratoma is a type of verrucous acanthoma that was recently described (in 2007) by Walsh et al., as a lesion with characteristics of porokeratosis, however with a diverse distribution pattern of the cornoid lamellae. [2, 3]

Porokeratosis comprises a group of acquired or genetic skin diseases that clinically arise as hyperkeratotic or squamous annular plaques with a raised peripheral crest that expands centrifugally.[4] It also has association with immunosuppression and a positive family history[1, 2, 3,] in addition to potential for malignancy.[4]

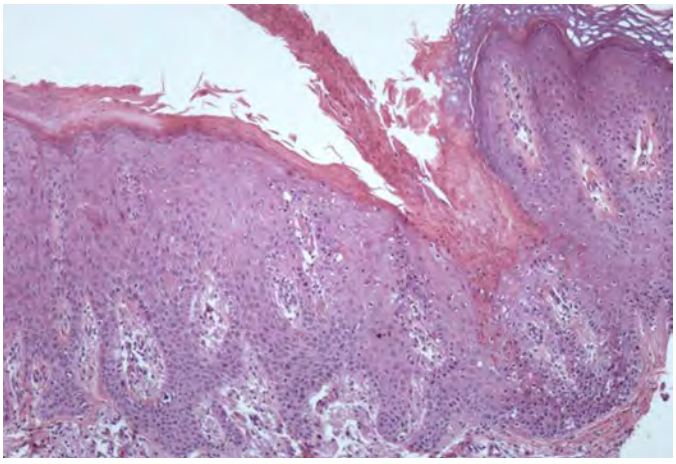

Figure 3: Central depression with choroid lamella on the periphery

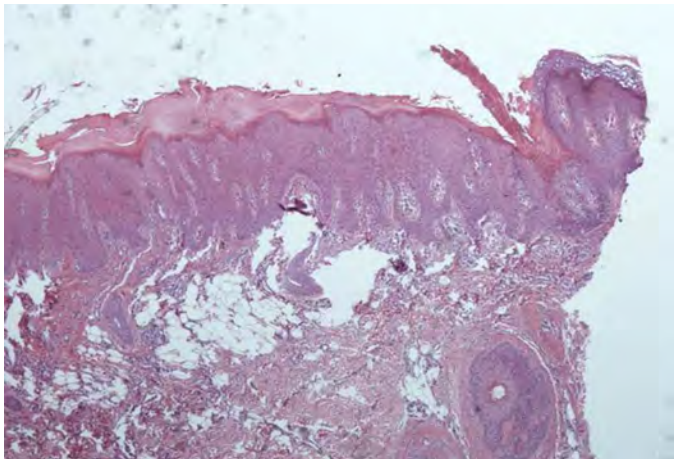

Figure 2: Epidermis with regular acanthosis, orthokeratosis and parakeratosis, showing a choroid lamella on the well-defined periphery. Presence of elevated adipose tissue band

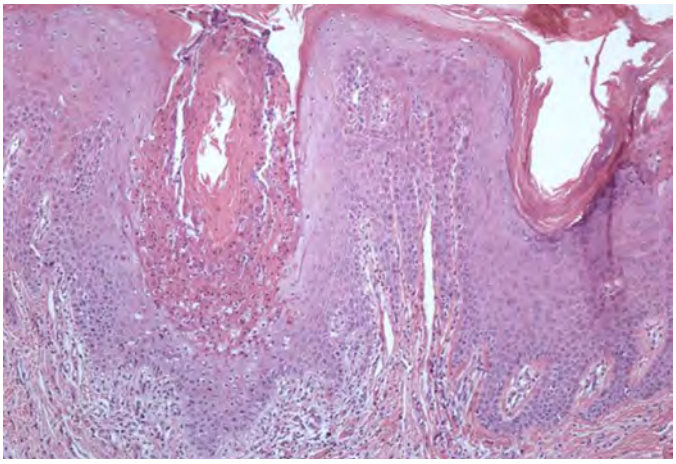

Figure 4: Dyskeratosis and absence of granular layer

Porokeratoma has an average development of 2 years and occurs in patients with no prior personal or family history of porokeratosis.[1,2] There is no association with immunosuppressive conditions[3] and there are reports of cases suggesting correlation with ankylosing spondylitis.[2,3] It is mainly found in the limbs, as well as in the head, neck, thorax, buttocks and intergluteal region. It clinically arises as a solitary plaque, papule or hyperkeratotic nodule, and may present verrucous appearance.[1,2,3] It is generally mistaken with squamous cell carcinoma, seborrheic or actinic keratosis, verruca vulgaris and nodular prurigo.[1,2]

It may microscopically present orthokeratosis, acanthosis, occasional papillomatosis, in addition to dyskeratosis congenita, loss of the granular layer and cornoid lamella. It is an epidermal maturation specific disorder that is related to the vertical column of parakeratotic cells, which extends from the invagination of the epidermis to the adjacent skin. These findings are similar to those found in porokeratosis, however the cornoid lamellae's distribution pattern is diverse: whereas in porokeratoma the multiple and wide cornoid lamellae are distributed throughout the lesion, in porokeratosis they are arranged along the borders, with central atrophy.[1,4]

Since porokeratoma and porokeratosis share histological similarities, with the latter being subject to malignization, the literature does not exclude the possibility of malignant transformation of porokeratoma. Although there are no cases described, it is suggested that the porokeratoma be completely excised with free surgical margins. In this manner, patients should be followed up on an outpatient basis, especially those who are immunocompromised.[2,3] Due to the diverse clinical, histological and epidemiological characteristics, it is believed that porokeratoma is a new clinical entity.

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Exuberant facial cutaneous angiosarcoma

Angiossarcoma cutâneo exuberante na face

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ABSTRACT

Angiosarcoma is a rare and aggressive vascular neoplasia that can occur anywhere in the skin integument, especially in the face and scalp. It has a branched character, and can clinically arise as a macula, papule, plaque or nodule of erythematous hue, with imprecise limits and expansive growth, and diagnosis based on the clinical-pathological correlation. In the present study, the authors report the case of a patient with exuberant cutaneous angiosarcoma on the face, where surgical resection was performed as the first therapeutic option.

Keywords*:* Dermatology; Hemangiosarcoma; Sarcoma;Vascular neoplasms

RESUMO

O angiossarcoma é neoplasia vascular rara e agressiva, que pode ocorrer em qualquer região do tegumento cutâneo, principalmente na face e no couro cabeludo. De caráter ramificado, clinicamente pode apresentar-se como mácula, pápula, placa ou nódulo de coloração eritematosa, limites imprecisos e crescimento expansivo, sendo o diagnóstico baseado na correlação clínico-patológica. No presente estudo, relata-se o caso de paciente com quadro exuberante de angiossarcoma cutâneo na face tendo sido realizada ressecção cirúrgica como primeira opção terapêutica

Palavras-Chave: *Dermatologia; Hemangiossarcoma; Neoplasias vasculares; Sarcoma*

INTRODUCTION

Angiosarcoma is a rare vascular neoplasm originating in epithelial cells. It accounts for 1%-2% of soft tissue sarcomas and less than 1% of the malignancies affecting the head and neck region.[1-3] It can occur in any body region, however commonly affects the face and scalp of individuals of over 60 years of age. Its incidence is more frequent in men and slightly more common in the Caucasian race.

It is an aggressive neoplasia characterized by high rates of local recurrence and early metastasis. It may clinically arise as a macula, papule, plaque or nodule of erythematous hue, poor delimitation and expansive growth, with diagnosis based on clinicopathological correlation. The primary tumor's size, resection outcome, histological differentiation, and presence or absence of metastases are important prognostic factors. Its diagnosis is established by the correlation between the clinical picture and anatomopathological findings. [3]

Case Reports

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CASE REPORT

A 78-year-old male patient sought care at the Dermatology Department of the Hospital Celso Pierro, Pontifícia Universidade Católica de Campinas (PUC-Camp / Campinas, SP, Brazil) describing the emergence of a spot on the face ten months before. The dermatological examination evidenced an infiltrated, poorly delimited erythematous-violet plaque, approximately 12cm long, extending from the left temporal and malar regions to the left retroauricular region, with absence of palpable regional lymph nodes (Figure 1).

A cutaneous biopsy was performed, with the histological examination revealing vessels with discrete anastomosis patterns and prominence of endothelial elements, alongside a diagnosis compatible with cutaneous angiosarcoma. For tumor staging, CT scans of the skull, neck, thorax and abdomen were requested, and whose nonspecific findings did not suggest signs of metastasis.

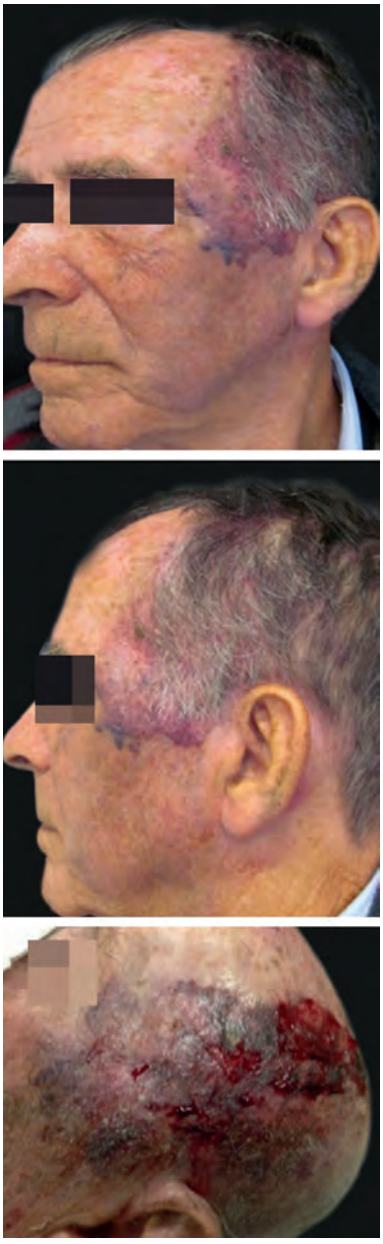

Figure 1: Infiltrated erythematous-violaceous, poorly delimited plaque with approximately 12cm, extending from the left temporal and malar regions to the left retroauricular region, with no palpable lymph nodes

With the assistance of the oncology and head and neck surgery teams, the lesion was resected, associated with the total excision of the left auricular pavilion (Figure 2). The reconstruction of this organ was performed by means of a Converse-type galeal-cutaneous flap of the scalp. Converse proposed to perform an axial skin flap, based on the superficial temporal artery, which uses the frontal region's integument, advancing it towards the nasal region. This flap's pedicle includes a segment of the scalp that, after the integration period, is returned to its original position, with the remaining bloody area being repaired with a free skin graft. In the present case, the technique was adapted, meaning that the scalp pedicle was used to repair a primary defect of the scalp itself and of the auricular region. After three weeks, a new surgical procedure was carried out, when the flap's pedicle was divided, and the excess skin returned to the original site. [4] (Figure 3).

The procedure was performed without intercurrences, and the material sent for anatomopathological analysis, which showed surgical margins free of neoplasia. Adjuvant radiotherapy was started, with the patient loosing clinical and hospital follo-

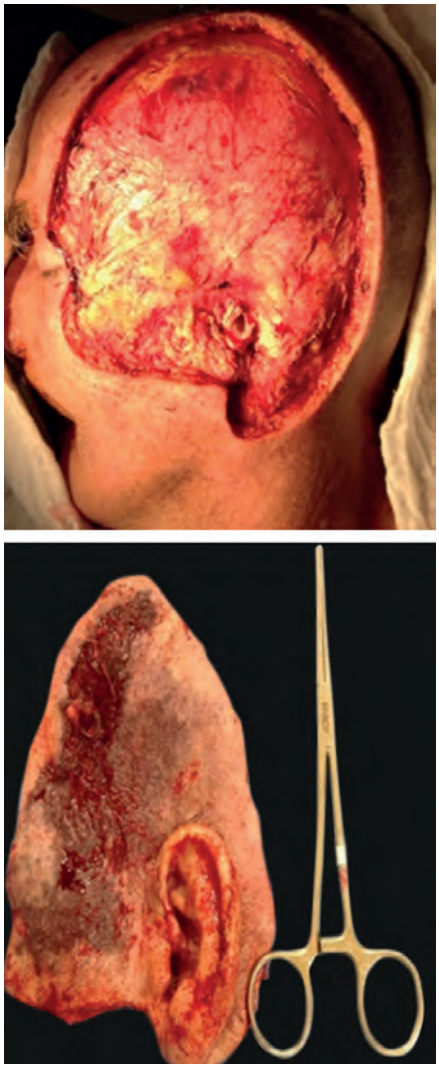

Figure 2: Resection of the lesion associated with the exeresis of the auricular pavilion

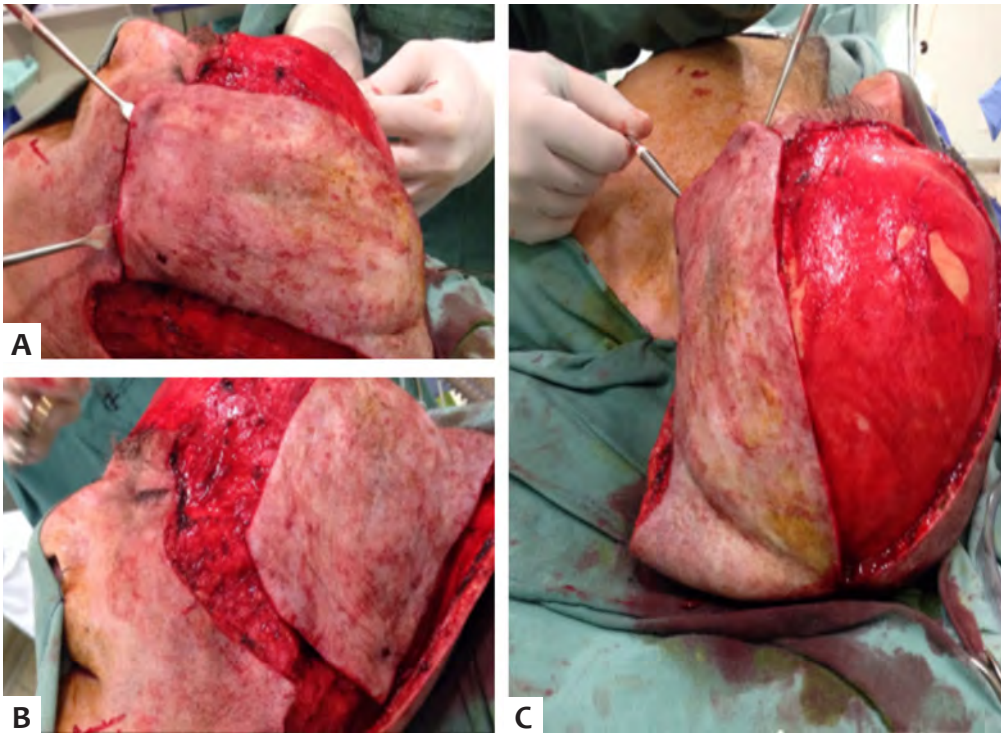

Figure 3: A - Flap transferred to the temporary defect (lateral view). **B -** Oblique view. **C -** Posterior view

w-up after seven sessions. One year after the surgical procedure, the hospital's social assistance team learned of the patient's death, with absence of known cause.

DISCUSSION

Skin cancer is responsible for 25% of malignant tumors reported in Brazil, with 70% of cases corresponding to basal cell carcinomas (BCC), 25% to squamous cell carcinomas (SCC), and 4% to cutaneous melanomas; 1% of the total is linked to less common types, among which is angiosarcoma.[1, 2, 5]

Most cases of cutaneous angiosarcoma occur in the head and neck, the most common sites being the scalp and upper half of the face.[3] Although the etiologic factor is still unknown, it is believed that exposure to sunlight and history of local trauma are risk factors.[3, 6]

The dermatologist physician is crucial for the diagnosis of this disease, and the treatments should be conducted according to the extent, histological features and location of the lesion.[7] Due to the rarity of this vascular neoplasia, there is no consensus on the therapeutic actions to be taken. In the case reported on this paper, surgical resection and adjuvant radiotherapy were performed, with an uncertain development resulting from the facts that the patient lost hospital follow-up and the cause of the death has not been identified.

The disease's prognosis is adverse and local recurrence is common, which makes constant and regular follow-up of paramount importance. Based on the rarity and aggressiveness linked to skin sarcomas, the present paper emphasizes the importance of the dermatologist physician and his or her responsibility in the early diagnosis and vigilant follow-up of these patients.[8, 9]

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Squamous cell carcinoma in the foot: an atypical presentation

Carcinoma espinocelular no pé: apresentação atípica

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ABSTRACT

Squamous cell carcinoma is the second more frequent non-melanoma skin cancer. It is linked to the sunlight exposure and the clinical presentation in the foot is atypical, and rarely develops metastasis. The authors report a case of a patient with an exuberant clinical picture of squamous cell carcinoma in the foot, with long development and absence of metastasis. Surgical treatment was successfully performed.

Keywords: Foot; Melanoma, amelanotic; Neoplasms, squamous cell

RESUMO

O carcinoma espinocelular é a segunda forma de câncer de pele não melanoma. Está relacionado à fotoexposição, e a apresentação clínica no pé é atípica, com pouca capacidade de desenvolver metástase. Relata-se o caso de paciente com quadro clínico exuberante de carcinoma espinocelular no pé, com longo tempo de evolução e ausência de metástase. Foi realizado tratamento cirúrgico com sucesso.

Palavras-Chave: *Neoplasias de células escamosas; Pé; Melanoma amelanótico*

INTRODUCTION

Non-melanoma skin cancer is the most common malignant neoplasm in Brazil, with the highest incidence tumor in both genders. Around 80% of non-melanoma skin cancers are basal cell carcinomas (BCC) while 20% are squamous cell carcinomas (SCC).[1] Squamous cell carcinomas predominantly affect photoexposed areas, and rarely occurs in the feet.[2-4] Surgery is the recommended treatment.[5,6]

The authors of the present paper describe the case of a 47-year-old male patient who bore a tumor lesion in the left foot for 30 years. The lesion was exuberant in appearance and had an atypical location, and absence of metastasis. Surgical excision was carried out, with therapeutic success, and preserved motion and sensitiveness.

CASE REPORT

A 47-year-old male patient, bricklayer by profession, complained of a painful tumor lesion that had emerged 30 years before in his left foot. The patient sough care at the Dermatology Department, Hospital Celso Piero, Pontifícia Universidade Católica de Campinas (PUC-Campinas), Campinas (SP), Brazil. The dermatological examination evidenced a vegetative, verrucous tumor, erythematous-infiltrated well-delimited borders, measuring 5 x 4 x 1.5cm. The lesion was painful and located in the distal portion of the left plantar region, close to the fourth and fifth metatarsals bones (Figure 1). A radiograph of the limb showed no bone involvement. The following diagnostic hypotheses were raised: SCC, amelanotic melanoma, and verrucous carcinoma. An incisional biopsy was performed for elucidation. The anatomopathological analysis evidenced features of cutaneous viral papilloma. Due to clinical-histological incongruity,

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the authors of the present paper chose to perform a minimal margin excision under tumescent anesthesia, with subsequent approximation of the borders and closure by secondary intention (Figures 2 and 3). The final histological analysis, however, confirmed the presence of a well-differentiated SCC with compromised margins, with a negative result for human papillomavirus (HPV) screening using the *in situ* hybridization technique. Computerized tomography scans of the skull, chest and abdomen were performed, with negative results for metastasis. The patient was then referred to the Orthopedics Clinic, where he underwent surgical enlargement with a safety margin of 1cm. The new analysis confirmed the SCC diagnosis, demonstrating that the margins were free of involvement. The patient cursed with preserved motion and sensitiveness for five months (Figure 4). One year after surgery, the scar presented a great aesthetic outcome, with only a moderate degree of hyperkeratosis, which does not imply functional limitation to the limb (Figure 5).

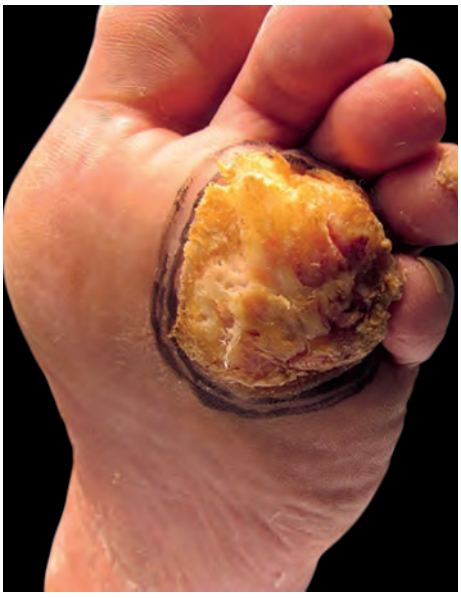

Figure 1: Vegetative tumor with verrucous surface, erythematous-infiltrated and well delimited borders, located in the distal portion of the left plantar region, close to the fourth and fifth metatarsal bones, 5 x 4 x 1.5 cm in size, painful to palpation

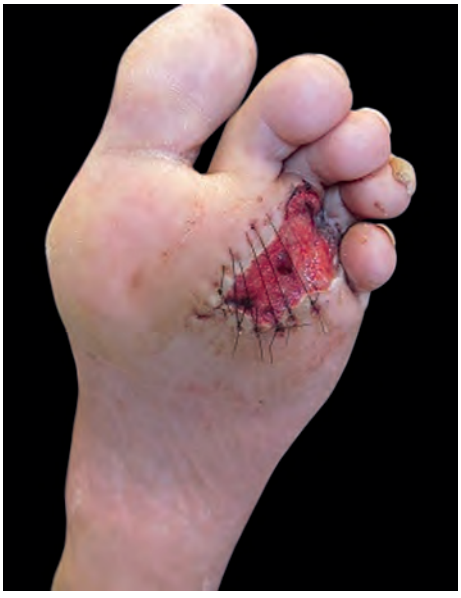

Figure 2: Approximation of the edges and closure by secondary intention

DISCUSSION

Non-melanoma skin cancer is the most common malignant neoplasm in Brazil, with the highest incidence among tumors in both genders.[1] Roughly 80% of the cases derive from the epidermis' basal layer's non-keratinized cells, resulting in BCC, while 20% result in SCC, which derives from the atypi-

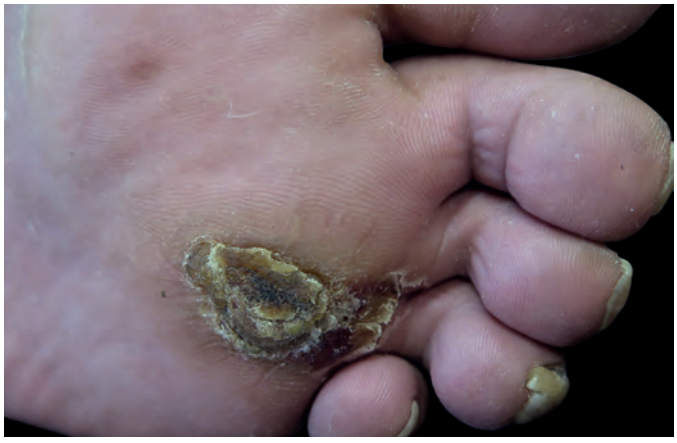

Figure 3: Patient four months after surgery

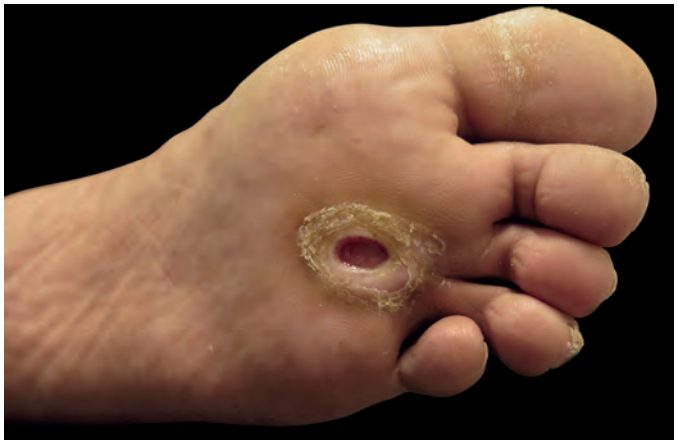

Figure 4: Patient five months after new approach for surgical enlargement with safety margin of 1cm, developing with preserved motion and sensitiveness

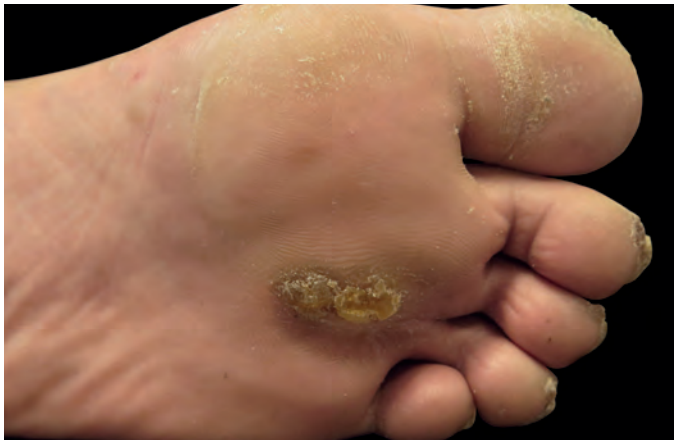

Figure 5: One year after surgery: surgical scar with optimal aesthetic outcome and absence of functional impairment of the limb

cal proliferation of the suprabasal keratinocytes.[1] Squamous cell carcinoma preferably affects body sites with exposure to the sunlight and male individuals of over 50 years of age.[2] It is associated with immunosuppression, chronic ulceration, exposure to arsenic agents and human papillomavirus. It is often originated from previous skin lesions, such as actinic keratosis, leukoplasia and radiodermitis.[7, 8] Squamous cell carcinomas located in the plantar region is infrequent and may arise from lichen planus, deep mycosis, chronic lichen simplex, plantar wart or, more rarely, metastasis.[3, 4] It can emerge with several clinical aspects, such as ulcers, nodulations or vegetating lesions, with exophytic growth of difficult cicatrization.[9] Diagnostic elucidation requires anatomopathological study and imaging (radiography, magnetic resonance imaging) aimed at determining the tumor's extension and allowing surgical planning. Surgery is the treatment of choice, and healing of the operative wound by secondary intention is an appropriate alternative that allows the dermatological surgeon to achieve excellent cosmetic outcomes. It is a simple, practical, efficacious, and cost-effective method that is well accepted by patients, allowing wound bed examination for early recognition of tumor recurrences.[8, 9]

Mohs micrographic surgery has a high cure rate for high-risk primary lesions; curettage, electrocoagulation, or excisional surgery, with a 0.5 to 1cm safety margin, can, however, eliminate about 90% of tumors – especially those with less than 1cm.[5, 6] Metastatic SCC of the foot is very rare, and the cure rate, during a 5-year follow-up period, for patients with large tumors is 70% regardless of the treatment performed.[6] The cumulative risk of developing a second SCC in the first three years is 18%, and that of having another non-melanoma carcinoma in five years reaches almost 50% of those involved. As a result, every patient diagnosed with SCC must be followed-up at intervals ranging from six months to one year, depending on the histological type and number of previous tumors.[10]

CONCLUSION

Squamous cell carcinoma in the foot is rare. It can be primary or of metastatic origin, and surgical excision is the treatment of choice. The authors of the present report described an atypical presentation of a frequent cancer, with many years of development. The authors also emphasize the importance of the recognition of wounds in not-photoexposed areas for the early diagnosis, ensuring the best prognosis of these patients.

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Cutaneous metastasis of follicular thyroid carcinoma mimicking pyogenic granuloma

Metástase cutânea de carcinoma folicular de tireóide mimetizando granuloma piogênico

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ABSTRACT

Follicular thyroid carcinoma is a well-differentiated tumor, and is considered the second most common subtype of thyroid cancer. Its metastasis usually arises hematogenously – mainly to the lungs and bones – and is considered rare when it occurs cutaneously. The authors report a case of a patient with follicular thyroid carcinoma for 5 years who noticed an erythematous, friable exophytic nodular lesion measuring 1cm on the scalp with 7 months of development, simulating a pyogenic granuloma. Biopsy analysis revealed an adenocarcinoma with glandular differentiation and colloid material in the lumen. The immunohistochemical profile was positive for CK-7 and thyroglobulin, favoring the diagnosis of cutaneous metastasis of primary thyroid neoplasia.

Keywords: Dermatology; Granuloma, Pyogenic; Neoplasms; Neoplasm metastasis

RESUMO

O carcinoma folicular de tireóide é um tumor bem diferenciado, considerado o segundo subtipo mais comum de câncer de tireóide. Sua metástase geralmente ocorre por via hematogênica, principalmente para pulmões e ossos, porém é rara quando cutânea. Relatamos caso de paciente com carcinoma folicular de tireóide há 5 anos que percebeu lesão nodular exofítica de 1cm, eritematosa, friável no couro cabeludo com 7 meses de evolução, simulando granuloma piogênico. A biópsia revelou adenocarcinoma com diferenciação glandular e material coloide no lúmen. O perfil imuno-histoquímico foi positivo para CK-7 e tireoglobulina, favorecendo o diagnóstico de metástase cutânea de neoplasia primária da tireóide.

Palavras-Chave: *Dermatologia; Granuloma piogênico; Neoplasias; Metástase neoplásica*

INTRODUCTION

Follicular thyroid carcinoma is a well-differentiated tumor and deemed as the second most common subtype of thyroid cancer, followed by papillary carcinoma. Its metastasis usually occurs hematogenously, mainly to the lungs and bones, and the diagnosis is confirmed by the histology and immunohistochemical study of the suspected lesions. [1]

Cutaneous metastases of follicular thyroid carcinoma are considered a rare event, and their occurrence signals an advanced degree of the disease. [2] They arise as erythematous lesions, purpuric plaques or slow-growing nodules, which may ulcerate, in a patient with a history of follicular thyroid carcinoma, usually with already present bone and / or visceral metastasis. In most cases, the lesions are located in the scalp, followed by the face and neck, due to the intense vascularization of the dermis in these body sites. [3]

Due to the clinical similarity – especially when the lesion emerges in a nodular, erythematous and friable form, the differential diagnosis with pyogenic granuloma should be considered.

The authors of the present paper report a case of cutaneous metastasis of follicular thyroid carcinoma on the scalp that clinically simulated a pyogenic granuloma lesion.

CASE REPORT

A 53-year-old female patient was diagnosed with follicular thyroid carcinoma 5 years before, having undergone total thyroidectomy and radioiodine therapy. However, she had bone marrow aplasia following that procedure, and new sessions were contraindicated. In the presence of bone, liver and pulmonary metastases, the patient noticed an exophytic nodular, erythematous, friable lesion measuring roughly 1cm, located on the scalp, that had been developing for 7 months (Figure 1), simulating a pyogenic granuloma. The biopsy evidenced an adenocarcinoma with glandular differentiation and colloid material in the lumen (Figures 2 and 3). The immunohistochemical profile was positive for CK-7 (Figure 4) and thyroglobulin (Figure 5), favoring the diagnosis of cutaneous metastasis of primary thyroid neoplasia.

DISCUSSION

Cutaneous metastases occur in 2% to 9% of patients with malignant diseases. [2] Primary tumors that most frequently metastasize to the skin are those of the breast (in women), and those of the lungs (in men). [4] Even though it occurs more frequently than in papillary thyroid carcinoma, [3] cutaneous metastasis of follicular thyroid carcinoma is considered a rare event. [2] The most commonly affected site is the scalp, [2] and it may also occur in a thyroidectomy's scar and in the sacral region's skin. [5] It should be suspected in the presence of erythematous nodular lesions or slow-growing purpuric plaques – usually asymptomatic – in patients with advanced degree of the disease. [3] Diagnosis is confirmed by histology and immunohistochemistry study. [3] When well-differentiated, cutaneous metastasis maintains the morphological characteristics of the primary tumor. [5]

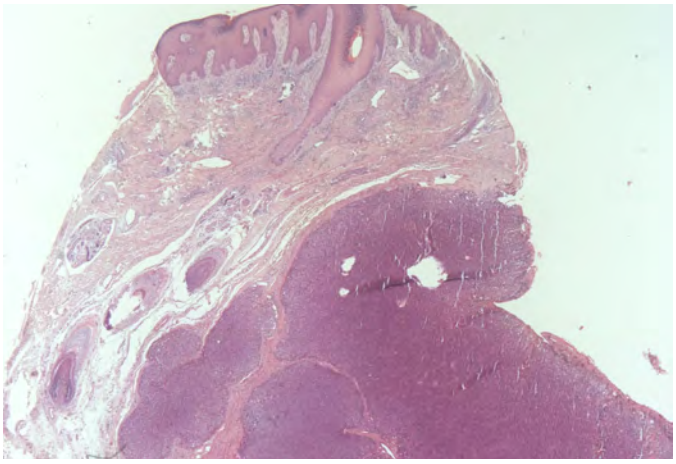

Figure 2: Hematoxylin & eosin (40X): adenocarcinoma with glandular differentiation

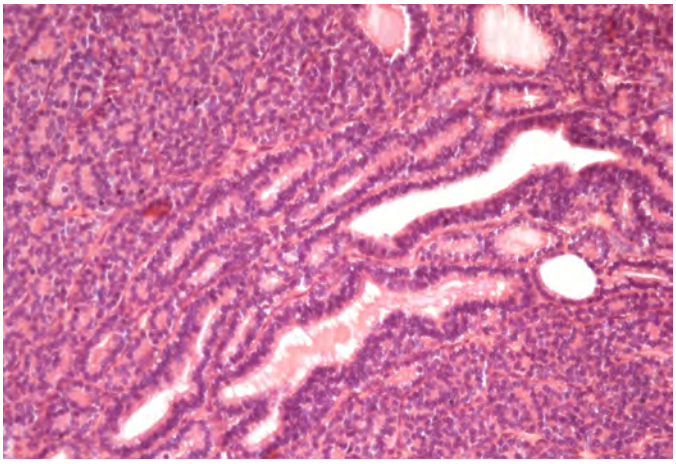

Figure 3: Hematoxylin & eosin (100X): colloid material in the lumen

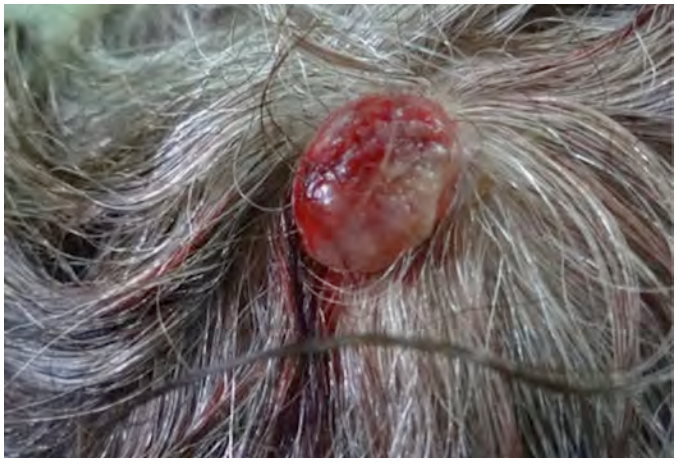

Figure 1: Exophytic and friable nodular lesion on the scalp

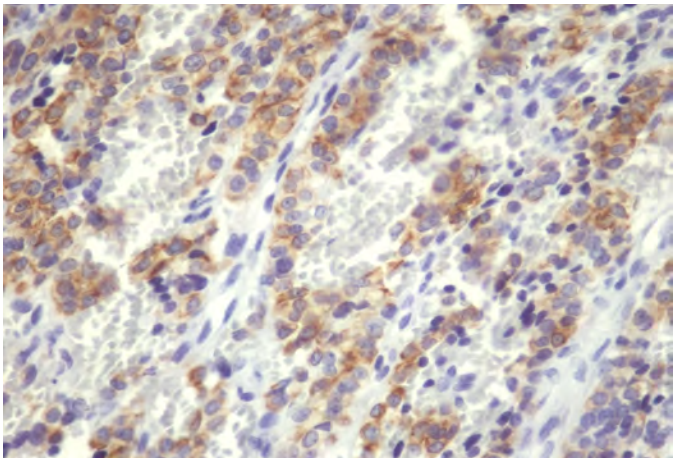

Figura 4: CK 7 (400X): positive

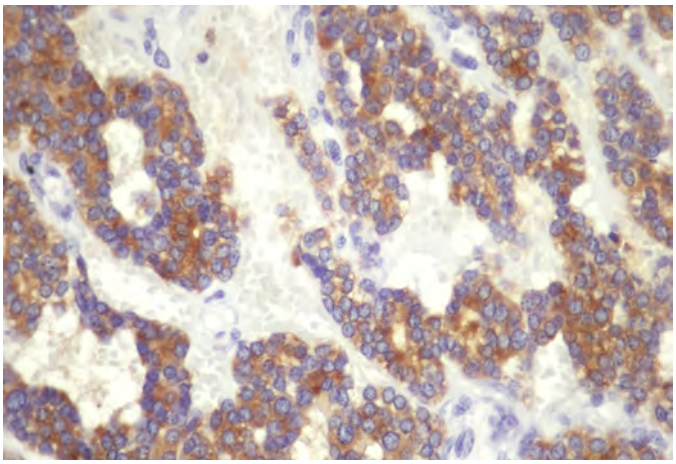

Figure 5: Thyroglobulin (400x): positive

Therapy is based on the treatment of the primary disease, with total thyroidectomy and radioiodine therapy. In advanced cases, the prognosis is limited, with around 19 months of survival after the detection of the cutaneous metastasis. [2-3]

In turn, pyogenic granuloma is a common vascular proliferative tumor found in children, but also in adults, especially on the face, hands, lips, or oral mucosa. [6] It arises as a rapidly growing nodule or papule, usually solitary, red in color, sometimes with a discrete scaly collar, easily bleeding.

The simulation of pyogenic granuloma has already been described in basal cell carcinoma of the finger, [7] in cutaneous metastasis of basal carcinoma of the anal canal, [4] in hepatocellular carcinoma, [8] and in amelanotic melanoma [9] – the authors of the present paper nevertheless did not find reports of cutaneous metastasis of follicular thyroid carcinoma in the form of pyogenic granuloma.

Renal carcinoma metastasis is the one that most resembles a pyogenic granuloma, [4] with Guadalupe et al. reporting in 2006 a case of an 80-year-old patient with an exophytic nodular lesion on the scalp, measuring roughly 1cm, purpuric-red in color, friable, on a smooth and shiny base, with 18 months of development. [10] The biopsy of the lesion was carried out with the diagnostic hypothesis of pyogenic granuloma, with the histology evidencing renal cell metastasis.

In light of the present case, the authors conclude that it is relevant to consider the differential diagnosis of cutaneous metastasis in lesions suggestive of pyogenic granuloma, which should always undergo histology, due to the possibility of simulation of pyogenic granuloma, among which metastases of malignant neoplasms stand out.

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