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d- Descrição dos métodos utilizados para avaliação dos resultados.

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

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

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

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Photodynamic therapy (PDT) supplement

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This supplement comprises four articles on PDT in addition to ten others addressing diverse subjects of interest of Surgical & Cosmetic Dermatology.

Regarding PDT, which uses 5-aminolevulinic acid and methyl aminolevulinate (MAL) as photosensitizing agents activated by LED (Light Emitting Diode) lamps, this publication brings two extensive and up-to-date reviews led by the fellow dermatologist physician Dr. Maria Claudia Issa, an Associate Professor of Dermatology at the Universidade Federal Fluminense (UFF, Niteroi - RJ, Brazil). After having been introduced in the dermatologists' armamentarium, this technique was initially used in the treatment of actinic keratoses and field cancerization. Later on, its use was expanded to the treatment of photoaging, acne, hidradenitis suppurativa, scleroderma, psoriasis, warts and leishmaniasis among other dermatoses. These two review articles focus on the outcomes of PDT in photoaging and the diffusion of this technique in Brazil.

The two other articles on PDT describe the technique's most recent advances, namely the replacement of artificial sources of light by the daylight (Daylight PDT) and the association of transepidermal application of drugs (transepidermal drug delivery). These two new approaches facilitate the use of PDT, leading to a significant decrease of the pain phenomenon linked to the exposure to LEDs and an intensification of the MAL's action in the facial skin, respectively.

This supplement offers another ten articles addressing current issues such as the treatment of melasma, surgical solutions for various types of cutaneous and nails disorders, in addition to two different and innovative therapies for alopecia areata.

Ever grateful for our Authors' availability, we wish a pleasant reading and an enjoyable review of our specialty to SBD members.

Dr. Bogdana Victoria Kadunc
Scientific Editor, Surgical & Cosmetic Dermatology

Photodynamic therapy in photoaging: literature review

Terapia fotodinâmica no fotoenvelhecimento: revisão da literatura

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ABSTRACT

Topical photodynamic therapy (TPT) is a well-established therapeutic modality in the treatment of non-melanoma skin cancer. It is based on light-activated chemical reaction in the presence of oxygen. In recent years, this therapy has been used in cosmiatric dermatology, and studies on the mechanisms of TPT action in dermal remodeling of the photodamaged skin have been reported. This review addresses procedures with different light sources and photosensitizers, as well as clinical and collateral effects of this therapy in the treatment of photoaging.

Keywords: photodynamic therapy, photosensitizer, photoaging, rejuvenation, collagen, dermis

RESUMO

A terapia fotodinâmica (TFD) tópica é uma modalidade terapêutica bem estabelecida no tratamento do câncer de pele não melanoma. Baseia-se em reação química ativada por luz, na presença oxigênio. Nos últimos anos, essa terapia vem sendo usada na dermatologia cosmiátrica, e estudos sobre mecanismos de ação da TFD na remodelação dérmica da pele fotodanificada vêm sendo relatados. Nesta revisão serão abordados os procedimentos com diferentes fontes de luz e fotossensibilizantes, bem como os efeitos clínicos e colaterais desta terapia no tratamento do fotoenvelhecimento.

Palavras-chave: *terapia fotodinâmica; fotossensibilizante; fotoenvelhecimento; colágeno; derme*

INTRODUCTION

Aging is a complex and multifactorial process that occurs in all individuals, being influenced by environmental, hormonal, and genetic factors. Photoaging, or extrinsic aging, arises from exposure to environmental factors. UV radiation is one of the main factors involved, being responsible for the increase in matrix metalloproteinase (MMPs) on *in vivo* human skin. MMPs are enzymes responsible for the degradation of protein in the extracellular matrix (ECM), such as collagen type I and III.[1-2] Photodamaged skin manifests itself clinically by changes in texture and pigmentation, wrinkles, flaccidity, telangiectasia and, in some cases, actinic keratosis lesions, and non-melanoma skin cancer.[1-2, 3]

Photodynamic Therapy (PDT) bases itself in a photochemical reaction that causes the selective destruction of a tumor cell. In order for this reaction to take place, a topical photosensitizer placed on the tissue, a light source and oxygen are needed. The main photosensitizers are aminolevulinic-acid (ALA) and methyl aminolevulinate (MAL). MAL is an esterified derivative of ALA, it is more lipophilic and presents greater selectivity to neoplastic cells. The main light source is the Light Emitting Diode (LED), which emits visible blue or red light. The use of MAL - Red Light is recommended for the treatment of deeper lesions, due to the greater skin penetration that the MAL and the red light have on the skin.[4-8] PDT with visible light is recommended in the treatment of actinic keratosis (AK), field cancerization and non-melanoma skin cancer (NMSC): Basal Cell Carcinoma (BCC) and Bowen's Disease.[9-17]

Clinical improvement of the photodamaged skin (texture, pigmentation, wrinkles and flaccidity) after the field cancerization treatment has been described as photodynamic rejuvenation. During a long time, only clinical studies sustained the indication of PDT for photoaging treatment.[8-23] It has only been in the last few years that histological and immunohistochemical studies have described the dermal remodeling induced by PDT in the cutaneous rejuvenation.[20, 23, 24] Among off-label indications, photorejuvenation is more often reported in cosmetic dermatology, however it is worth to note that PDT is being adopted as a form of treatment for other neoplasias, infectious and inflammatory diseases.[25-30]

Photoaging

Cutaneous alterations of aging derive from two distinct processes that come together. The natural aging process that occurs in all organs, in a similar way, is either intrinsic or chronological. Photoaging, or extrinsic aging, happens due to the overlapping of environmental factors such as exposure to UV radiation, smoke, wind, and chemical agents. UVA and UVB rays are involved in the pathogenesis of skin cancer and photoaging. UV radiation causes genetic and molecular changes in the epidermal cells and increases the levels of enzymes responsible for the modulation of ECM.[1-3] Histologically, cellular atypia is observed, with loss of keratinocyte polarity and accentuated irregularity in cell size.[1, 2, 3, 5] On the dermis, histological findings include solar elastosis, thickened and disorganized elastic fibers, and thinly squeezed and flattened collagenous fibers, and increased glycosaminoglycans.[1-3]

For photoaging treatment, surgical procedures are commonly associated with topical and / or oral clinical treatments. Among the procedures are chemical peels, lasers and lights, botulinum toxin and fillers. Photodynamic therapy has become an excellent choice for the treatment of photodamaged skin with actinic keratosis, not only for inducing rejuvenation, but also mainly for treating pre-malignant subclinical lesions not visible to the naked eye.[2, 31-40, 41]

Photodynamic Therapy

In order to perform a topical PDT, a photosensitizing agent, a light source and oxygen are needed. Topical photosensitizers are, in fact, prodrugs, which are transformed into protoporphyrin IX (PpIX) inside the cytoplasm and mitochondria, after penetrating the target cell. The photochemical reaction triggered by PDT leads to cell death through the production of singlet oxygen and other reactive oxygen species (ROS).[1, 2, 4, 5, 6, 7]

The main topical photosensitizers are ALA and MAL. In the United States, 20% ALA (Levulan Kerastick®, DUSA Pharmaceuticals) is presented as a pen containing a solution that is activated at the time of use. It was approved by the FDA in 1999 and associated with blue light for treatment of non-hypertrophic AKs. It is not marketed in Brazil. The time of incubation of ALA in the target tissue ranges from 1 hour to 20 hours, with several protocols described in the literature. Once opened, the product must be fully used and cannot be used in more than one session.[1] MAL is widely marketed in several countries around the world, including Brazil, under the name Metvix® (Galderma Pharmaceutical Industry, Paris, France), being approved for AK, BCC and Bowen's Disease. For these indications, the incubation time of MAL is 3 hours, with two sessions with a one-week interval for BCC and Bowen's Disease, and only one session for AK. It is presented as a lipophilic cream, and after it has been opened, it can be kept in refrigerator for up to 1 week. In the photorejuvenation treatment protocol, the incubation time can be reduced to 1 or 2 hours, with two to four sessions, and intervals varying between 2 and 4 weeks.[2, 20]

Light sources must emit luminous energy in the absorption spectrum of PpIX, which is the target of the treatment. PpIX has maximum light absorption peak at 410 nm, blue light, considered effective because it is very well absorbed by the photosensitizer in the target tissue. On the other hand, this wavelength penetrates superficially, being well indicated for treatment of actinic keratosis, field cancerization. PpIX also absorbs other light lengths, such as red light (630nm), which penetrates more deeply into the skin and is therefore the best choice for the treatment of carcinomas (NMSC). Both are well indicated for treatment of photodamaged skin.[2, 31, 32] Other light sources for the treatment of photoaging include Intense Pulsed Light (IPL) and Lasers (PDL). It is worth to noting that although IPL yields good results in the overall appearance of the skin, including pigmentation and texture, it is less effective than LED for the treatment of actinic keratosis in the long term, and are contraindicated for the treatment of carcinomas.[2, 31-40]

Photodynamic Therapy in the Treatment of Photoaging

The effects of light on the skin involve complex mechanisms. Photoaging is mediated by direct absorption of UV radiation and by indirect mechanisms through ROS-mediated photochemical reactions.[2] UV radiation activates AP-1 and NF-Kappa B transcription factors that regulate genes responsible for the production of enzymes that modulate MEC of the dermis, among them MMP-1, MMP-9, MMP-3 and MMP-10. MMP-1 degrades intact collagen, and MMP-9 cleaves the collagen that was previously cleaved by MMP-1. This degradation sequence is critical for repair of the dermis, since the cleavage of the collagen fractions that have a high molecular weight interrupts the synthesis inhibition of new, type I, collagen.[42, 43, 44] The activation of AP-1 and NF Kappa is also responsible for increased transcription of cytokines such as IL-1 beta, IL-2, IL-6, IL-10, TNF-alpha and TGF-beta. TGF-beta is involved in dermal remodeling not only by stimulating the synthesis of procollagen (types I and III), but also by inhibiting its degrading enzymes.

The inflammatory response that accompanies PDT-mediated tumor destruction, with release of cytokines and growth factors, is of fundamental importance in the dermal remodeling of the photodamaged skin.[45-47] In vitro study for the quantification of MMPs and the expression of mRNA of collagen, showed increased MMP-1 and 3 and reduced expression of type I collagen in culture of fibroblasts (normal skin and scleroderma) treated with ALA and red light.[48] The result of this study suggests an anti-sclerotic effect of PDT in the skin. In contrast, Issa et al[23] reported increased MMP-9, without modification of MMP-1 and 3, and increased type I collagen, three and six months after treatment of photodamaged skin with two sessions of PDT (MAL-Red light), respectively. The authors have concluded that the modification of the dermis caused by MMP-9, initially, allowed the modification of the ECM and its relation with the fibroblasts, which consequently produced new collagen, after six months.

Procedure – PDT for Photoaging

To proceed with of the conventional topic PDT in the treatment of the photodamaged skin we can consider the following steps: 1) Cleaning of the area that will be treated with makeup remover, followed by the application of alcoholic chlorhexidine;

2) Soft skin curettage, prior to the application of the photosensitizer, in order to remove the more superficial layers of the AK lesions; 3) Application of the topic photosensitizer in the entire area that will be treated; 4) Occlusive dressing with a plastic film to increase the penetration of the product, followed by aluminum foil to prevent the activation of PpIX by ambient light during the incubation period of the photosensitizer. For photorejuvenation, the need for occlusion is variable in the literature. The dressing and the excess of the medication are removed with saline solution 0.9% and gauze, before exposure to the light source; 5) Exposure to the light source (Figure 1). Patients and doctor should wear protective eyewear during lighting session. After each session, patients should be instructed to avoid sun exposure for 48 hours, and to use sunscreen after that period.[2] Patients should be aware of the benefits and limitations of the technique as well as being made aware of the possible side-effects.

PDT application protocols for photoaging treatment vary widely in the literature. The number of sessions varies on average from two to three, ranging from 15 to 30 days in between each. Generally, a thin layer, half a tube, 1g. per face is used in each session. A thicker layer (5mm) should be applied over the AK lesions isolatedly. The incubation time of the photosensitizer varies from one to three hours, and each light source will have an adequate parameter. In the case of an LED, the required amount of light is predetermined by the lamp, which switches off automatically at the end of the treatment. When the incubation time is greater than one hour or when the patient has many AK lesions, the side effects are more evident. These include pain, especially during exposure to the light source, and in the initial 24 hours following the procedure; edema and erythema. Desquamation begins on the third or fourth day, and between the seventh and tenth days the facial skin is fully recovered (Figure 2). Cold compresses and soothing and healing creams can be used for approximately 7-10 days. Topical corticosteroids are rarely indicated. Dyschromias are rare and, if they occur, usually temporary. Anti-viral prophylaxis should be done in patients with a history of cold sores. Bacterial infection is rare, but sterile pustules are reported after acne treatment.[1, 2]

Treatment Protocols with Different Light Sources

a. **PDT with Intense Pulsed Light (IPL)**

Ruiz-Rodriguez et al.[40], evaluated 17 patients with different degrees of photodamage and AKs (38 lesions altogether) treated with two sessions of ALA IPL. The ALA incubation time was 4 hours and the interval between sessions was 1 month. Thirty-three of the 38 AK lesions were healed in the three-month follow-up period. The technique was well tolerated, and aesthetic results were excellent in all patients.

Several IPL parameters, in regards to the cut-off filter wavelength, pulse duration, pulse interval and energy density, have been used for photorejuvenation with PDT. Many authors have reported significant improvement of photoaged skin (texture, pigmentation, fine wrinkles and AK) with the combination of ALA and IPL, when compared to the use of IPL alone. MAL is also used with IPL to treat photodamaged skin effectively and safely.

Although both photosensitizers are effective for photorejuvenation with IPL, AK healing should be monitored long term.[8, 35, 36, 39]

b. **PDT with Pulsed Dye Laser (PDL)**

Alexiades-Armenakas et al.[37], in a study using PDT-PDL (585nm), evaluated 2,561 AK lesions on the face, scalp and extremities. They reported a cure rate of 99.9% on the 10th day, and 90.1% for lesions on the face, on the fourth month. The lesions at the extremities showed a lower percentage of response. PDT with PDL is considered to be an adequate form of treatment for the vascular component of the photodamaged skin, since this component has a lower response to PDT visible light.[37, 49]

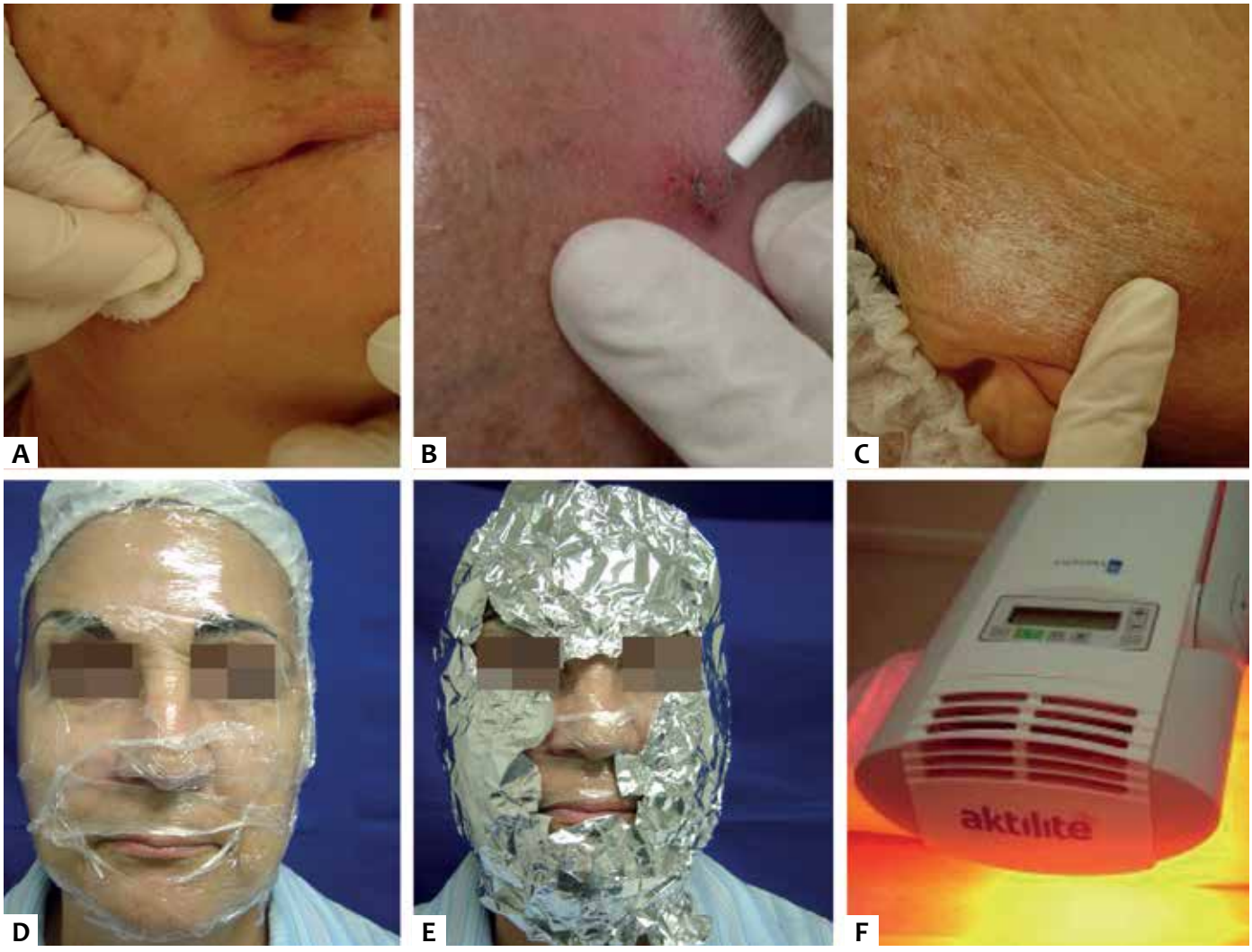

Figure 1: Steps: **A)** cleansing the skin; **B)** surface curettage; **C)** MAL application with glove finger; **D)** occlusive dressing with plastic film and light protection with aluminum foil; **E)** red LED lighting; **F)** Light Source

c. PDT with Blue Light

Even though Blue Light penetrates the skin superficially, many studies confirm the efficacy of PDT with Blue Light in the treatment of aging. These studies report improvement not only with AK lesions, but also in texture and pigmentation of the skin.

Palm et al[31] who treated 18 photoaging patients with photodynamic therapy using MAL Visible Light, and compared the Blue Light with the Red Light, reported that there was no significant difference between the treatments.

The inflammatory reaction after treatment with ALA-Blue Light is usually more intense than with MAL-Red Light, when the photosensitizers have the same incubation time.

d. PDT with Red Light

Sanclemente et al.[32] studied the histopathological changes after treatment with photodynamic therapy in combination with MAL and Red Light, and reported improvement of collagen and elastic tissues, although not statistically significant.

Ferola et al.[1] demonstrated the overall clinical improvement of the skin with whitening, AK improvement, fine wrinkles and flaccidity after three sessions of photodynamic therapy with ALA (2 hours) and Red Light (20 min) with a fifteen-day interval in between sessions. The histology, due to picrosirius staining, observed an improvement in the organization of the collagen fibers in the dermis.

Issa MCA[1] evaluated the therapeutic response of PDT in the treatment of photodamaged skin in 14 women with and without AKs. Two sessions of MAL-Red Light were performed with a 30-day interval between sessions. Three skin biopsies were performed on the face (pre-treatment, after 3 months and after 6 months). The incubation time of the MAL was of 2 hours under occlusion.

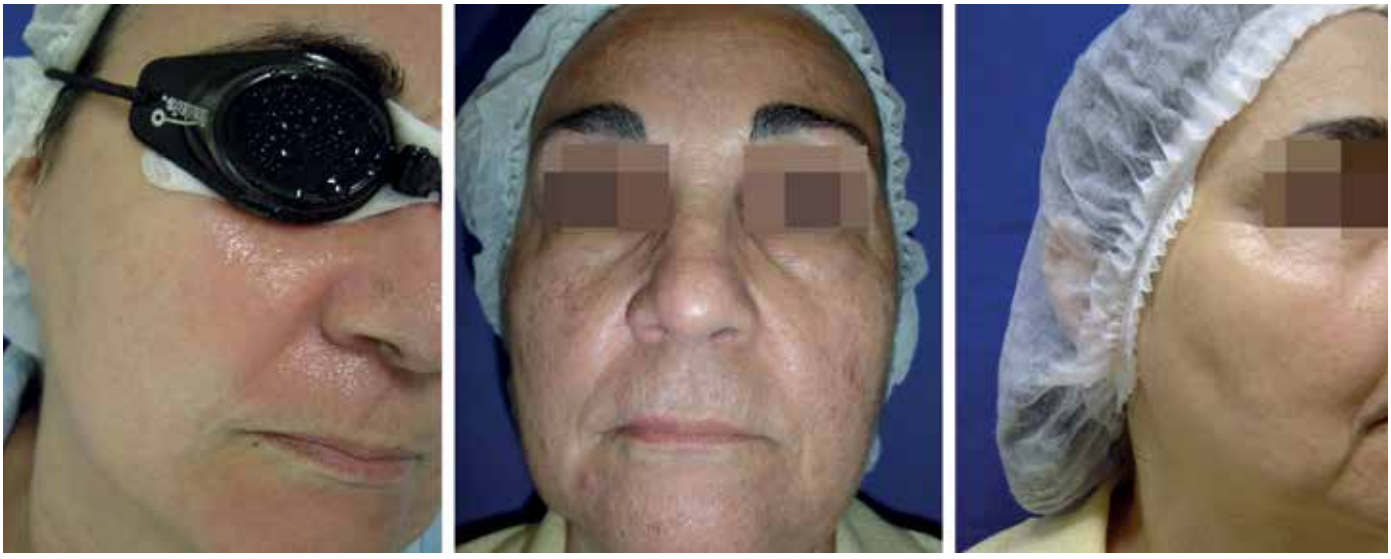

Figure 2: A) Erythema immediately after procedure; **B)** Desquamation after 72 hours; **C)** complete recovery after 8 days

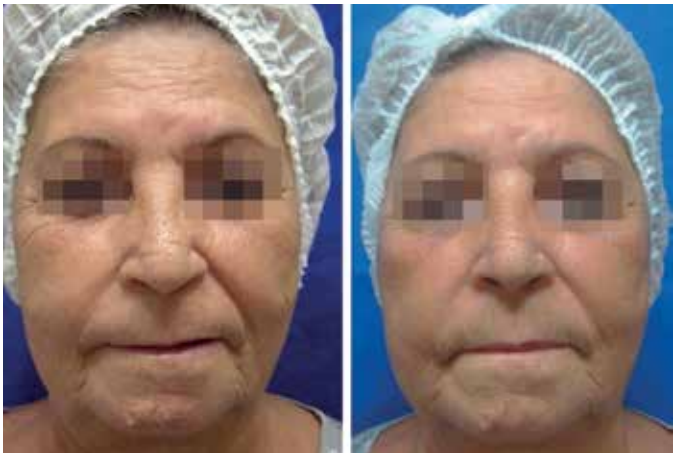

Figure 3: Before and 6 months after treatment with two sessions of conventional MAL-PDT. Improved texture, wrinkles and sulcus

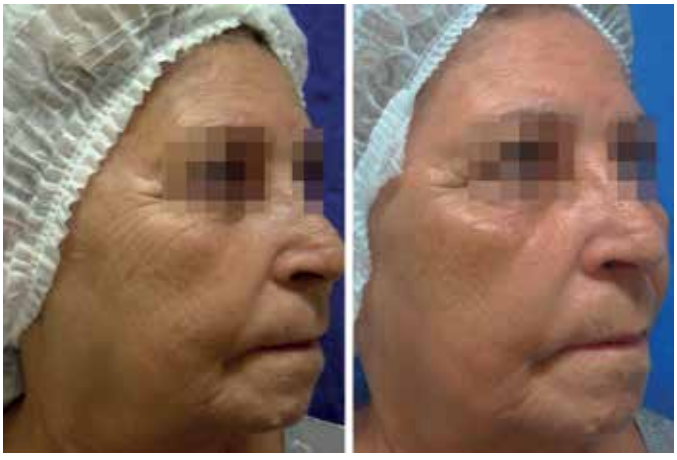

Figure 4: Before and 6 months after treatment with two sessions of conventional MAL-PDT. Improved texture, wrinkles and sagging

The LED used was Aktilite (Photocure, Oslo, Norway) at the dose of 37mJ /cm^2. Clinical results showed improvement in texture, pigmentation and wrinkles after the first session, with progressive improvement after a 3-month and 6-month follow-up. At 6 months, it was observed an improvement in the firmness of the skin, with decrease of sagging, becoming more evident (Figures 3 and 4). The improvement findings were observed for up to a 12-month period. Among the observed side effects there were pain, edema, erythema and desquamation with variable intensity, in most cases of mild to moderate intensity. There were also some cases with greater intensity.

Issa et al.[20] studied the histological and morphometric changes in the patients mentioned above, observing a statistically significant increase in collagen by picrosirius staining three months after treatment. This improvement was maintained after 6 months, when it was noted that, due to orcein staining, elastic fibers also increased, becoming thinner and with better histological organization. Issa et al.[23] also evaluated, through immunohistochemical studies, the substrates involved in dermal remodeling, such as type I and III collagen, ECM-degrading enzymes involved in photoaging, such as MMPs [1, 3, 7, 9, 12], as well as inhibitors of MMPs such as TIMP 1 and 2. The results found included a statistically significant increase of MMP-9 after 3 months and a statistically significant increase in type I collagen after 6 months.

Le Pillouer-Prost and Cartier,[50] in reviewing of the literature, have observed that PDT has a high level of efficacy, improvement of fine wrinkles, tonus, skin roughness, texture and remodeling of the dermis. The best indication is for the patient

who had chronic exposure to the sun and has multiple actinic keratoses.

CONCLUSIONS

The technique called "photodynamic rejuvenation" has been discussed in the literature since 2002.[40] Many authors have described the beneficial clinical effects of this therapy, and studies on the histological and immunohistochemical modifications induced by PDT corroborate the clinical findings in photorejuvenation.[2, 20, 23, 24] The protocols vary in the preparation of the skin, in the incubation time and occlusion of the photosensitizer, in the number and break of sessions, and in the light source and its parameters. Regardless of the protocol used, an overall skin rejuvenation is achieved, with improved texture, pigmentation, wrinkles and sagging, in addition to the cure of actinic keratoses. Patients who have suffered chronic exposure to the sun and have photodamaged skin with actinic keratosis are the most indicated for this therapeutic modality.

REFERENCES

1. Ferolla ACJ. Estudo da pele humana fotoenvelhecida após tratamento com terapia fotodinâmica associada ao ácido 5 delta aminolevulínico tópico: avaliação imunoistoquímica, do colágeno e do tecido elastic [tese]. São Paulo: Faculdade de Medicina da Universidade de São Paulo; 2007.
2. Issa MCA. Estudo Da Remodelação Dérmica Induzida Pela Terapia Fotodinâmica (MAL-TFD) Na Pele Fotodanificada [tese]. Rio de Janeiro: Universidade Federal do Rio de Janeiro; 2008.
3. Gilchrest BA. Skin aging and photoaging: an overview. J Am Acad Dermatol. 1989; 21:610-3.
4. Issa MCA, Patricia-Azulay M. Terapia Fotodinâmica: revisão da literatura e documentação iconográfica. Anais Bras Dermatol. 2010; 85(4): 501-11.
5. Kalka K, Merk H, Mukhtar H. Photodinamic therapy in dermatology. J. Am. Acad. Dermatol. 2000; 42(3): 389-413.
6. Szeimies RM, Calzavara-Pinton P, Karrer S, Ortel B, Landthaler M. Topical photodynamic therapy in dermatology. J Photochem Photobiol. 1996; 36(2): 213-9.
7. Casas A, Fukuda H, Di Venosa G, Batlle A. Photosensitization and mechanism of cytotoxicity induced by the use of ALA derivatives in photodynamic therapy. Br J Cancer. 2001; 85(2):279-84
8. Nestor MS, Gold MH, Kauvar AN, Taub AF, Geronemus RG, Ritvo EC, et al. The use of photodynamic therapy in dermatology: results of a concensus conference. J Drugs Dermatol. 2006; 5:140-54
9. Hurlimann, AF, Panavizzon, RG, Burg, A. Topical photodynamic treatment of skin tumours and dermatoses. Dermatology 1994; 3(3): 327.
10. Szeimies RM, Morton CA, Sidoroff A, Braathen LR. Photodynamic therapy for non-melanoma skin cancer. Acta Derm Venereal. 2005;85(6):483-90.
11. Szeimies RM, Karrer S, Sauerwald A. Photodynamic therapy with topical application of 5-aminolevulinic acid in the treatment of actinic keratoses: an initial clinical study. Dermatology. 1996; 192(3):246-51.
12. Fink-Puches R, Soyer HP, Hofer A, Kerl H, Wolf P. Long-term follow-up and histological changes of superficial nonmelanoma skin cancers treated with topical-aminolevulinic acid photodynamic therapy. Arch Dermatol. 1998; 134(7):821-6.
13. Szeimies R-M, Sassy T, Landthaler M. Penetration potency of topical applied-aminolevulinc acid for photodynamic therapy of basal cell carcinoma. Photochem Photobiol. 1994; 59(1):73-6.
14. Szeimies RM, Karrer S, Radakovic-Fijan S, Tanew A, Calzavara-Pinton PG, Zane C, et al. Photodynamic therapy using topical methyl 5-aminolevulinate compared with cryotherapy for actinic keratosis: a prospective, randomized study. J Am Acad Dermatol. 2002; 47(2):258-62.

15. Salim A, Leman JA, McColl JH, Chapman R, Morton CA. Randomized comparison of photodynamic therapy with topical 5-fluorouracil in Bowen's disease. Br J Dermatol. 2003;148(3): 539-43.
16. Lee PK, Kloser AJ.Current methods for photodynamic therapy in the US: comparison of MAL/PDT and ALA/PDT. J Drugs Dermatol. 2013 Aug;12(8):925-30
17. Babilas P, Karrer S, Sidoroff A, Landthaler M, Szeimies RM. Photodynamic therapy in dermatology: an update. Photodermatol Photoimmunol Photomed. 2005; 21(3):142-9.
18. Bruscino N, Rossi R, Dindelli M, Ghersetich I, Lotti T. Facial skin rejuvenation in a patient treated with photodynamic therapy for actinic keratosis Dermatol Ther. 2010; 23(1):86-9.
19. Park MY, Sohn S, Lee ES, Kim YC. Photorejuvenation induced by 5-aminolevulinic acid photodynamic therapy in patients with actinic keratosis: a histologic analysis. J Am Acad Dermatol. 2010; 62(1):85-95.
20. Issa MC, Piñeiro-Maceira J, Vieira MT, Olej B, Mandarim-de-Lacerda CA, Luiz RR, et al. Photorejuvenation with Topical Methyl Aminolevulinate and Red Light: A Randomized, Prospective, Clinical, Histopathologic, and Morphometric Study. Dermatol Surg. 2010; 36(1):39-48.
21. Shamban AT. Current and new treatments of photodamaged skin. Facial Plast Surg. 2009;25(5):337-46.
22. Bjerring P, Christiansen K, Troilius A, Bekhor P, de Leeuw J. Skin fluorescence controlled photodynamic photorejuvenation. J Lasers Surg Med. 2009; 41(5): 327-36.
23. Almeida Issa MC, Piñeiro-Maceira J, Farias RE, Pureza M, Raggio Luiz R, Manela-Azulay M. Immunohistochemical expression of matrix metalloproteinases in photodamaged skin by photodynamic therapy. Br J Dermatol. 2009;161(3):647-53.
24. Szeimies RM, Torezan L, Niwa A, Valente N, Unger P, Kohl E, et al. Clinical, histopathogical and immunohistochemical assessment of human skin field cancerization before and after photodynamic therapy. Br J Dermatol. 2012 l;16(1):150-9.
25. Morton CA, Szeimies RM, Sidoroff A, Braathen LR. European guidelines for topical photodynamic therapy part 2: emerging indications: field cancerization, photorejuvenation and inflammatory/infective dermatoses. J Eur Acad Dermatol Venereol. 2013; 27(6):672-9.
26. Alster TS, Tanzi EL. Photodynamic therapy with topical aminolevulinic acid and pulsed dye laser irradiation for sebaceous hyperplasia. J Drugs Dermatol. 2003; 2(5):501-4.
27. Calvazara-Pinton P, Arisi M, Sereni E, Ortel B. A critical reappraisal of off-label indications for topical photodynaic therapy with aminovelunic acid and methylaminolevulinate. Rev Recent Clin Trilas 2010; 5 (2):112-6.
28. Bissonnette R, Tremblay J-F, Juzenas P, Boushira M, Lui H. Systemic photodynamic therapy with aminolevulinc acid induces apoptosis in lesional T lymphocytes of psoriatic plaques. J Invest Dermatol. 2002; 119(1):77-83.
29. Szeimies RM, Landthaler M, Karrer S. Non-oncologic indications for ALA-PDT. J Dermatolog Treat. 2002(b); 13(suppl 1):S13-8.
30. Gold MH, Goldman MP. 5-aminolevulinic acid photodynamic therapy: where we have been and where we are going. Dermatol Surg. 2004; 30(8):1077-84.
31. Palm MD, Goldman MP. Safety and efficacy comparison of blue versus red light sources for photodynamic therapy using methyl aminolevulinate in photodamaged skin. J Drugs Dermatol. 2011; 10 (1):53-60.
32. Sanclemente G, Correa LA, Garcia JJ, Barrera M, Villa JF, Garcia HI. Methyl aminolevulinate plus red light vs. placebo plus red light in the treatment of photodamaged facial skin: histopathological findings. Exp Dermatol. 2012;37(4):379-86.
33. Bjerring P, Clement M, Heickendorff L, Lybecker H, Kiernan M. Dermal collagen production following irradiation by dye laser and broadband ligt source. J Cosmetic laser Ther. 2002;4(2):39-43.
34. Karrer S, Bäumler W, Abels C, Hohenleutner U, Landthaler M, Szeimies R-M. Long-pulse dye laser for photodynamic therapy: investigations in vitro and in vivo. Lasers Surg Med.1999; 25(1):51-9.
35. Dover JS, Bhatia AC, Stewart B, Arndt KA. Topical 5-aminolevulinic acid combined with intense pulsed light in the treatment of photoaging. Arch Dermatol. 2005; 141(10):1247-52.
36. Alster TS, Tanzi EL, Welsh EC. Photorejuvenation of facial skin with topical 20% 5-aminolevulinic acid and intense pulsed light treatment: a split-face comparison study. J Drugs Dermatol. 2005; 4(1):35-8.
37. Alexiades-Armenakias MR, Gernemus RG. Laser-mediated photodynamic therapy of actinic keratosis. Arch Dermatol. 2003;139(10):1313-20.
38. Gold MH, Bradshow VL, Boring MM, Bridges TM, Biron JA. Split face comparison of photodynamic therapy with 5-aminolevulinic acid and inense intense intense pulsed light versus intense pulsed light versus intense pulsed light alone for photodadage. Dermatol Surg. 2006;32(6):795-801.
39. Mamur ES, Phelps r, Goldberg DJ. Ultraestructural changes seen after ALA – IPL photorejuvenescimention: a pilot study. J Cosmetic Laser Ther. 2005;7(1):21-4.
40. Ruiz-Rodriguez R, Sanz-Sanchez T, Cordoba S. Photodynamic photorejuvenation. Dermatol Surg. 2002 A;28(8):742-44; discussion 744.
41. Touma DJ, Gilchrest BA. Topical photodynamic therapy: a new tool in cosmetic dermatologic. Semin Cutan Med Surg. 2003;22(2):124-30.
42. Fisher GJ, Kang S, Varani J, Bata-Csorgo Z, Wan Y, Datta S, et al. Mechanisms of photoaging and chronological skin aging. Arch Dermatol. 2002;138(11):1462-70.
43. Kang S, Fisher GJ, Voorhees JJ. Photoaging: pathogenesis, prevention, and treatment. Clin Geriatr Med. 2001; 17(4): 643-659, v-vi.
44. Chung JH, Seo JY, Choi HR, Lee MK, Youn CS, Rhie G, et al. Modulation of skin collagen metabolism in aged and photoaged human skin in vivo. J Invest Dermatol. 2001; 117(5): 1218-1224.
45. Naderi-Hachtroudi L, Peters T, Brenneisen P, Meewes C, Hommel C, Razi-Wolf Z, et al. Induction of manganese superoxide dismutase in human dermal fibroblasts: a UV-B-mediated paracrine mechanism with the release of epidermal interleukin 1 alpha, interleukin 1 beta, and tumor necrosis factor alpha. Arch Dermatol. 2002; 138(11): 1473-1479.
46. Dougherty TJ, Gomer CJ, Henderson BW, Jori G, Kessel D, Korbelik M, et al. Photodynamic therapy. J Natl Cancer Inst. 1998 Jun 17; 90(12):889-905.
47. Brenneisen P, Sies H, Scharffetter-Kochanek K. Ultraviolet-B irradiation and matrix metalloproteinases: from induction via signaling to initial events. Ann N Y Acad Sci. 2002; 973:31-43.
48. Karrer S, Bosserhoff AK, Weiderer P, Landthaler M, Szeimies RM. Influence of 5-aminolevulinic acid and red light on collagen metabolism of human dermal fibroblasts. J Invest Dermatol. 2003 Feb; 120(2): 325-31.
49. Friedmann DP, Goldman MP, Fabi SG, et al. Multiple sequencial light and laser sources to activate aminolevulinic acid in photodamage: A retrospective study. Cosmet Laser Ther. 2015; 17(5): 252-8
50. Le Pilloer-Prost A; Cartier H Photodynaimic Photorejuvenation: A Review. Dermatol Surg 2016;42(1): 21-30.

Photodynamic therapy in Brazil: 10 years of history

Terapia fotodinâmica no Brasil: 10 anos de história

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ABSTRACT

Conventional Photodynamic Therapy (c-PDT), approved in Brazil since 2006 for non-melanoma skin cancer, is a well-established treatment worldwide. The evolution of PDT, in the last 10 years, includes its use in other indications, its association with techniques that promote increased photosensitizer permeation and use of daylight instead of artificial light. This new method, which uses daylight, was approved in Brazil in 2014 for the treatment of actinic keratosis and field cancerization, with the benefit of maintaining c-PDT's efficacy without adverse events.

Keywords: photochemotherapy; light; skin neoplasms; keratosis, actinic

RESUMO

A Terapia Fotodinâmica convencional, aprovada no Brasil desde 2006 para câncer de pele não melanoma, é um tratamento consagrado em todo mundo. A evolução da TFD, nos últimos 10 anos, inclui seu uso em outras indicações, sua associação às técnicas que promovem aumento da permeação do fotossensibilizante e o uso da luz do dia, em substituição à luz artificial. Esta nova modalidade, que utiliza a luz do dia, foi aprovada no Brasil em 2014 para tratamento de ceratose actínica e campo de cancerização, e apresenta a vantagem de manter a eficácia da Terapia Fotodinâmica convencional sem seus efeitos colaterais.

Palavras-chave: *terapia fotodinâmica; luz; câncer da pele; ceratose actínica*

INTRODUCTION

Topical Photodynamic Therapy (PDT) is defined as a photochemical reaction used to cause selective destruction of a tissue through the formation of singlet oxygen and other reactive oxygen species, which accumulate in malignant and pre-malignant cells, producing a cytotoxic effect. In order for this reaction to take place, a photosensitizer on the target tissue, a specific light source to excite the photosensitizer, and the presence of oxygen are needed.[1,2] The most commonly used topical photosensitizers are Aminolevulinic Acid (ALA) and Methyl Aminolevulinate (MAL) (Figure 1). Both are prodrugs, and need to be modified enzymatically within the cell into protoporphyrin IX (PpIX), which is the endogenous photosensitizer. For the procedure, a mild curettage should be performed prior to the application of the photosensitizer (either ALA or MAL), which will remain on the skin under occlusion, before exposure to light (Figure 2). Among light sources used in conventional Photodynamic Therapy (c-PDT), broad-spectrum light emitting diodes (LEDs), Intense Pulsed Light (IPL) and lasers are available.[3-5]

Review articles

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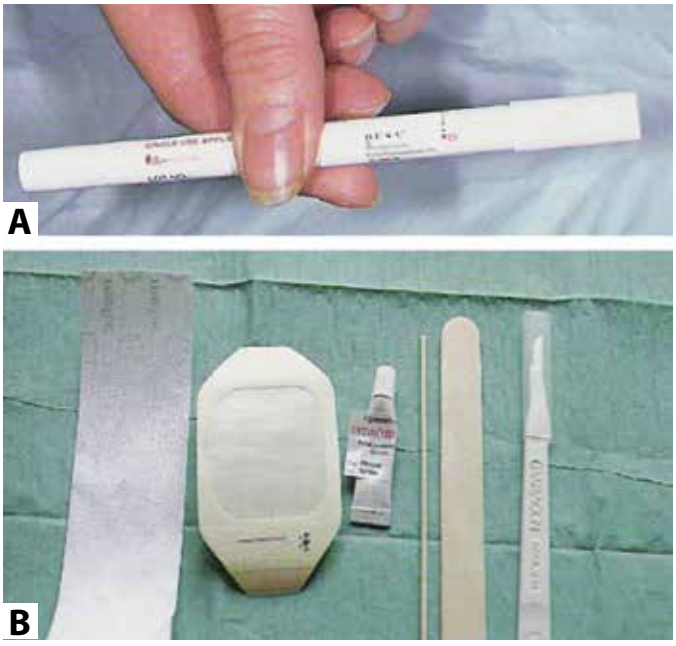

Figure 1: A LEVULAN KERASTICK® DUSA; **B** METVIX® GALDERMA

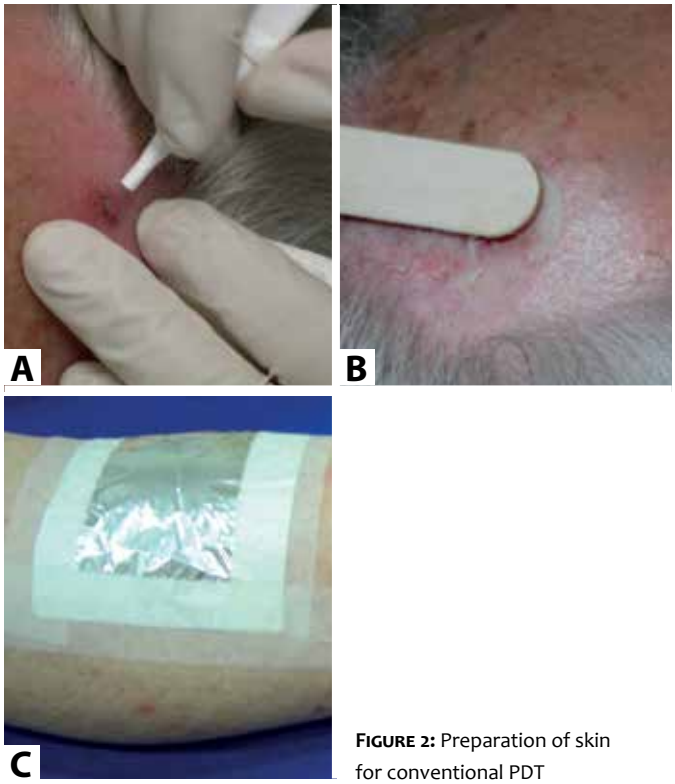

Figure 2: Preparation of skin for conventional PDT

c-PDT has a more precise indication in the treatment of Non-Melanoma Skin Cancer (NMSC), and is approved for Actinic Keratosis (AK), low-risk superficial Basal Cell Carcinoma (BCC), and Bowen's Disease.[6-8] Among the off-label indications, the photoaging treatment that was based on the findings of overall skin quality improvement (wrinkles, texture and pigmentation) during the treatment of the field cancerization.[9-15]

A new technique that uses the fraction of visible light from solar radiation is called Daylight Photodynamic Therapy (DLPDT). Several studies report that DLPDT has the same efficacy as c-PDT in the treatment of AK lesions and field cancerization, but with fewer side effects. This new therapy is not indicated for treatment of carcinomas.[16-23]

More recently, fractional ablative methods (Radiofrequency Ablation, and Erbium Laser or CO_2) and microneedling have been used for Transepidermal Drug Delivery (TED).[24-42] The use of TED has been related for the treatment of different dermatoses, and its combination with PDT in order to increase the penetration of ALA or MAL seems to potentialize the results of c-PDT or even PDT with sunlight.

BACKGROUND

In 1999, the Food and Drug Administration (FDA) approved 5-Aminolaevulinic Acid ALA (Levulan Kerastick®, DUSA Pharmaceuticals, Massachusetts, USA) for multiple actinic keratoses. In 2002, the esterified derivative of ALA, Methyl Aminolevulinate -MAL (Metvix ®, Galderma, Paris, France) was approved in Europe for Actinic Keratoses and Basal Cell Carcinoma. MAL was later approved in the USA in 2004 for actinic keratoses. In 2006, the MAL had its approval widely diffused in the world. At that time, it was approved in Brazil for actinic keratoses and basal cell carcinoma. It was only in 2008 that Levulan arrived in Brazil, having been distributed for a short period. In 2009, MAL was also approved for Bowen's Disease in our country. The innovation of the technique by using daylight for MAL activation was approved in Brazil in 2014 and in Europe in 2015.

Conventional Photodynamic Therapy in the Treatment of Non-Melanoma Skin Cancer

AK presents molecular and genetic alterations similar to Squamous Cell Carcinoma (SCC) lesions, and some authors consider it a carcinoma *in situ*. Others consider it a premalignant lesion, with an annual transformation rate into SCC of between 0.25% and 16% within 10 to 25 years.[43,44] Among the treatments used for AK are cryosurgery, electrocoagulation, topical medications, surgical excision, and PDT. In general, the use of topical PDT for treatment of AK has a cure rate between 73% and 100%. PDT has similar or superior efficacy when to compared to conventional treatments, as well as being a quick and easy-to-apply method with a short recovery time and excellent cosmetic result.[45-47] In a study conducted by Freeman et al[48], MAL-PDT was statistically more effective than a single freeze-thaw cycle with liquid nitrogen spray.

Dragieva et al[49] evaluated the efficacy of PDT with MAL in transplant patients. The double-blind study with 2 sessions of MAL-PDT or placebo, with a 1-week interval, was performed in 17 patients with a total number of 129 AK lesions. The study concluded that treatment with MAL-PDT is safe and effective in treating AK in transplanted patients and may reduce the risk of transformation to invasive Squamous Cell Carcinoma.

Basal Cell Carcinoma (BCC) is the most common cutaneous malignant tumor (70%) in adulthood. Its treatment should be chosen according to the clinical type, histology, size and location of the tumor. Among the therapeutic options are surgical excision (gold standard), electrocoagulation and curettage, cryotherapy, immunomodulators, cytotoxic agents and radiotherapy. Although a better result is described with MAL, possibly due to the greater lipophilicity, greater selectivity and penetration capacity,[50] the clinical and histopathological characteristics, and aggressive nature of the tumor are important factors for the correct indication of PDT. Statistical data based on multicenter, multi-patient, five-year follow-up studies reveal that PDT with MAL-Red Light achieves a cure rate of approximately 95% in the treatment of superficial BCC, and 73% to 94% for nodular BCC at the evaluation after 3 months. The recurrence rate for superficial BCC is approximately 22%, similar to conventional treatments, such as cryotherapy with a recurrence rate of around 19%. For nodular BCC, in the long term, the rate of recurrence is close to 14%, higher when compared to a recurrence of only 4% of the surgery.[46,51]

With regard to Bowen's disease, comparative studies between MAL-PDT, cryotherapy and 5-fluorouracil (5-FU) showed superior cosmetic outcome with MAL-PDT, and, after 24 months, cure rates of 68% for MAL-PDT, 60% for Cryotherapy, and 59% for 5-FU. c-PDT is well indicated for the treatment of large-diameter lesions located in the lower limbs, which present great difficulty in cicatrization after surgical procedure or cryotherapy.[51]

Conventional Photodynamic Therapy: Off-Label Indications

Exposure to ultraviolet radiation is the leading cause of skin disorders such as sunburn, photodamage, and skin cancer. The visible signs of photodamaged skin are characterized by wrinkles, rough skin texture, altered pigmentation, telangiectasias and, in some cases, AK and carcinomas (BCC and SCC).[14, 15, 52] Light-based technologies (LEDs, LIP and Laser) in an isolated way, without photosensitizer, act on the pigmentary and vascular alterations, in addition to inducing the synthesis of collagen in the photodamaged skin. However, only PDT, in combination with the light and photosensitizer, also treats AK.[11, 53, 54]

In addition to the clinical improvement of photodamaged skin, which is widely reported in the literature, some authors have described histological and immunohistochemical modifications induced by c-PDT, such as: better organization of elastic fibers, increased density of collagen fibers, increased metalloproteinases.[14, 15, 55]

Other off-label indications include the treatment of inflammatory acne, viral warts, leishmaniasis, necrobiosis lipoidica, granuloma annulare, mycosis fungoides, and extramammary Paget's disease.[24, 25] For all these indications, the mechanisms of action are poorly understood and results are varied. Therefore, PDT should not be considered as the first choice treatment, and should be indicated in specific cases.

Transepidermal Application of Medicine Associated with Conventional Photodynamic Therapy

TED is a new therapeutic modality in Dermatology used to increase the penetration of drugs through the more superficial layers of the skin. In the literature, old techniques with poorly understood mechanisms are cited with the objective of transposing this cutaneous barrier at different depths, including iontophoresis, electroporation and photomechanical waves.[37-42] The use of ultrasound (U/S) for transepidermal administration of different molecules, such as insulin, mannitol, glucose, heparin, morphine, caffeine and lidocaine,[56] both *in vitro* and *in vivo* have been described in the literature.[57, 58] More recent studies on TED report the use of ablative methods for drug permeation in the treatment of various dermatological diseases, such as actinic keratosis, hypertrophic scars, stretch marks and alopecia areata.[59, 60]

By the means of fractional ablative methods (ablative radiofrequency, Erbium laser and CO_2) and microneedling (Figure 3), micro-perforations permeate drugs applied topically to the surface of the skin, surpassing its main cutaneous barrier, the stratum corneum.[24-31] Fukui et al[25] reported the association of fractional CO_2 Laser to c-PDT for the treatment of non-melanoma skin cancer, extra-mammary Paget's disease and parakeratosis. Kassuga and Issa[61] reported the clinical effects of isolated c-PDT compared to the combination of PDT with the fractional ablative radiofrequency (RF) treatment. They revealed that, even by reducing the incubation time of the photosensitizer (MAL) from 3 hours to 1 hour, this combination was more effective in reducing the number of AK lesions in the forearms than the PDT alone. In addition to improved AK, there was improvement in texture and pigmentation of all treated areas, with better rejuvenation of the side treated by RF associated with PDT.

The microneedling technique used for TED in combination with PDT has also been reported. Available in the market, there are some derma roller brands for microneedling that are rolled on the cutaneous skin, as well as motorized pens with disposable needles for stamp-type microneedling. Torezan et al [36] compared c-PDT with PDT in combination with the use of microneedles. There was no evidence of an increase in the efficacy of PDT associated with microneedles in relation to the number of AKs. However, this association improved the overall quality of the skin, reduced hyperpigmentation and sagging, and reduced deep wrinkles.

Daylight Photodynamic Therapy

Daylight PDT has been studied in Europe and Australia in recent years and was approved in Brazil in 2014, with the aim to reduce side effects and preparation time of c-PDT, while maintaining its effectiveness in the treatment of AK and field cancerization. There are no studies indicating the use of DLPDT for carcinomas.[18-23]

For daylight PDT to be performed, all exposed skin should be covered with pure chemical sunscreen without physical blockers. In this manner, only visible light action will be allowed on the skin while maintaining protection against ultraviolet radiation.[18] After approximately 15 minutes, curettage is performed with a dermal curette. In case of discreet bleeding, gauze compression should be performed prior to the application

of the MAL photosensitizer, which should not be occluded. The patient should be exposed to daylight within 30 minutes. This exposure should be performed for a period of 2 hours (Figure 4). For the whole face treatment, the amount of 1g of MAL (half a tube) is sufficient in each session.

Daytime PDT should not be performed on rainy day or on days with dark clouds that may disrupt light. However, it can be performed in other climatic conditions, such as with the presence of clear clouds. In cold-weather countries, the temperature should be adequate for patient comfort and should not be less than 10ºC so that there is no interference in the production of PpIX during the sun exposure period. Similar efficacies were achieved despite cloudy or sunny weather in studies evaluating the treatment of actinic keratoses in different countries with different latitudes and altitudes, including Brazil.[18-20] In Brazil, the average luminance emitted in all months of the year and in all regions from North to South was similar to the brightness of the Australian studies, which gives us the information that DLPDT will have the same effectiveness throughout the national territory.

Daytime PDT provides excellent patient tolerability, with reports typically describing minimal pain or total absence of pain during the procedure. This can be explained by the fact that, in c-PDT, there is a large formation of PpIX during the occlusion of MAL in the treated area for 3 hours before exposure to LEDs, with subsequent great excitation of PpIX and free radical production. In contrast, in Daytime PDT, the MAL incubation time is at most 30 minutes, without occlusion, before exposure to daylight. In this manner, PpIX excitation and degradation occurs during light exposure, with gradual production of the photochemical response in this period and consequent reduction of the intensity of the inflammatory response (pain, erythema and edema).[19-22]

Transepidermal Drug Application in combination with Daylight Photodynamic Therapy

The clinical response of AK and the field cancerization of DLPDT is similar to the clinical response to the c-PDT with artificial light.[20,21] However, the improvement of other aspects of photodamaged skin, such as wrinkles, pigmentation and sagging, appear to be less evident when compared to that of c-PDT. This fact is probably due to the lower inflammatory response induced by the visible light of the solar radiation spectrum on Protoporphyrin IX, formed simultaneously with the period of daylight exposure.

Based on studies about TED in combination with c-PDT,[36,61] the authors of the present study believe that TED in combination with Daylight PDT can also bring benefits to the overall photodamaged skin treatment, with improvement not only to actinic keratosis but also to texture, wrinkles and skin pigmentation. Pilot cases, performed by us, show this new therapeutic possibility, combining Daylight PDT with TED techniques in overall skin rejuvenation (refer to article #10 published in this journal).

Conclusion

Topical PDT is a very useful tool for dermatology around the world, and has been approved in Brazil since 2006 for the treatment of non-melanoma skin cancer. In this period, the technique has undergone innovations and new indications that are based on international and national studies. Currently, a new PDT modality that uses daylight is also approved in our country, bringing benefits, such as the treatment of large areas, in a practical and effective way, with short recovery time and without side-effects. The combination of techniques to increase the permeation of the photosensitizer is a very recent subject and seems to complement the benefits of day-to-day c-PDT and PDT.

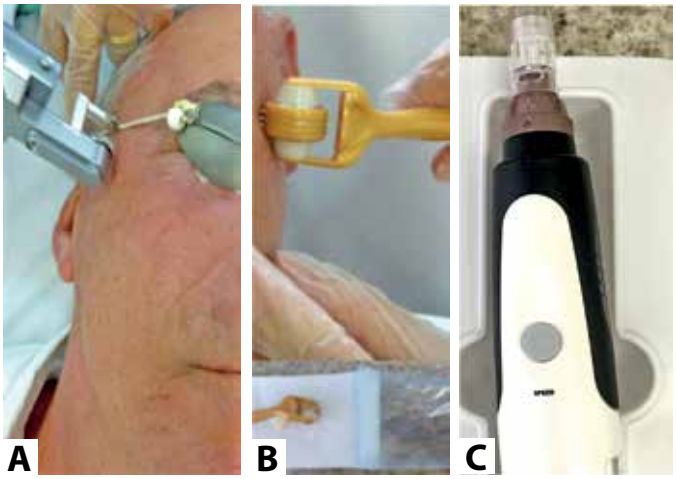

Figure 3: Methods for transepidermal drug application (MAL); **A** Fractional CO2 Laser; **B** Microneedling with derma roller; **C** Microneedling with pen

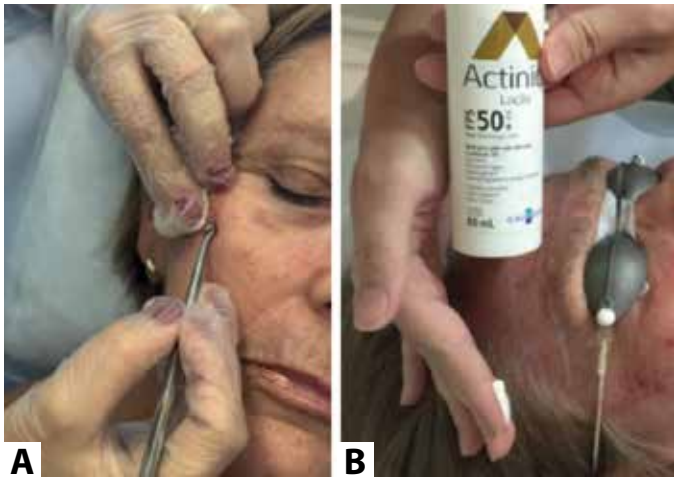

Figure 4: Skin preparation for Daylight Photodynamic Therapy: **A** Superficial lesion curettage (actinic keratosis); **B** Application of pure chemical sunscreen

REFERENCES

1. Kalka K, Merk H, Mukhtar H. Photodynamic Therapy In Dermatology. J Am Dermatol 2000; 42 (3): 389-413.
2. Allison RR, Mota HC, Sibata CH. Clinical PD/PDT in North America. Photodiagnosis Photodyn Ther. 2004;1(4):263-77.
3. Kurwa HA, Barlow RJ. The role of photodynamic therapy in dermatology. Clin Exp Dermatol.1999; 24(3): 143-8.
4. Morton CA. Photodynamic therapy for nonmelanoma skin cancer—and more?. Arch Dermatol. 2004;140(1):116-20.
5. Issa MCA, Manela-Azulay M. Terapia fotodinâmica: revisão da literatura e documentação iconográfica. An Bras Dermatol. 2010;85(4):501-11.
6. Varma S, Wilson H, Kurwa HA, Gambles B, Charman C, Pearse AD, et.al. Bowen's disease, solar keratoses and superficial basal cell carcinomas treated by photodynamic therapy using a large field incoherent light source. Br J Dermatol. 2001; 144(3): 567–74.
7. Peng Q, Soler AM, Warloe T, Nesland JM, Giercksky KE. Selective distribution of porphyrins in skin thick basal cell carcinoma after topical application of methyl 5-aminolevulinate. J Photoche Photobiol B: Biol. 2001; 62(3): 140–5.
8. Soler AM, Warloe T, Berner A, Giercksky KE. A follow-up study of recurrence and cosmesis in completely responding superficial and nodular basal cell carcinomas treated with methyl-5-aminolevulinate-based photodynamic therapy alone and with prior curettage. Br J Dermatol. 2001; 145(3): 467–71.
9. Raulin C, Greve B, Grema H. IPL technology: A review. Lasers Surg Med. 2003;32(2):78-87.
10. Avram DK, Goldman MP. Effectiveness and safety of ALA-IPL in treating actinic keratoses and photodamage. J Drugs Dermatol. 2004; 3(1 Suppl):S36-39.
11. Nestor MS. Combination therapy in clinical and cosmetic dermatology: the marriage of device and drug. J Drugs Dermatol. 2004; 3(5 Suppl):S4-11
12. Touma DJ, Gilchrest BA. Topical photodynamic therapy: a new tool in cosmetic dermatology. Semin Cutan Med Surg. 2003; 22(2):124-130.
13. Gold MH, Bradshaw VL, Boring MM, Bridges TM, Biron JA. Split-face comparison of photodynamic therapy with 5-aminolevulinic acid and intense pulsed light versus intense pulsed light alone for photodamage. Dermatol Surg. 2006; 32(6):795-801; discussion 801-793.
14. Almeida Issa MC, Piñeiro-Maceira J, Farias RE, Pureza M, Raggio Luiz R, Manela-Azulay M. Immunohistochemical expression of matrix metalloproteinases in photodamaged skin by photodynamic therapy. Br J Dermatol. 2009; 161 (3): 647-53.
15. Issa MCA, Pineiro-Maceira J, Vieira MTC, Olej B, Mandarim-de-Lacerda CA, Luiz RR, et al. Photorejuvenation with Topical Methyl Aminolevulinate and Red Light: A Randomized, Prospective, Clinical, Histopathologic, and Morphometric Study. Dermatol Surg. 2010;36(1):39-48.
16. Braathen LR. Daylight Photodynamic Therapy in Private Practice in Switzerland: Gain Without Pain. Acta Derm Venereol. 2012; 92(6):652-3.
17. Wiegell SR1, Wulf HC, Szeimies RM, Basset-Seguin N, Bissonnette R, Gerritsen MJ, et al. Daylight photodynamic therapy for actinic keratosis: an international consensus: International Society for Photodynamic Therapy in Dermatology. J Eur Acad Dermatol Venereol. 2012; 26(6): 673–9.
18. Morton CA, Wulf HC, Szeimies RM. Practical approach to the use of daylight photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: a European consensus. J Eur Acad Dermatol Venereol. 2015;29(9):1718-23.
19. Rubel DM, Spelman L, Murrell DF, See JA, Hewitt D, Foley P, et al. Daylight PDT with methyl aminolevulinate cream as a convenient, similarly effective, nearly painless alternative to conventional PDT in actinic keratosis treatment: a randomized controlled trial. Br J Dermatol. 2014; 171(5): 1164–71.
20. Lacour J. Results of 2 randomised, controlled, phase III studies with Daylight- PDT in Australia and Europe. Euro-PDT 14th Annual Congress; April 4th–5th, 2014; Nice, France.
21. Wiegell SR, Haedersdal M, Philipsen PA, Eriksen P, Enk CD, Wulf HC. Continuous activation of PpIX by daylight is as effective as and less painful than conventional photodynamic therapy for actinic keratoses – a randomized, controlled study. Br J Dermatol 2008; 158(4): 740–6.
22. Wiegell SR, Haedersdal M, Eriksen P, Wulf HC. Photodynamic therapy of actinic keratoses with 8% and 16% methyl aminolaevulinate and home-based daylight exposure: a double-blinded randomized clinical trial. Br J Dermatol 2009; 160(6):1308–14.
23. Wiegell SR1, Fabricius S, Stender IM, Berne B, Kroon S, Andersen BL, et al. A randomized, multicenter study of directed daylight exposure times of 1½ vs. 2½ h in daylight-mediated photodynamic therapy with methyl aminolaevulinate in patients with multiple thin actinic keratoses of the face and scalp. Br J Dermatol 2011; 164(5):1083–90.
24. Yoo KH, Kim BJ, Kim MN. Enhanced efficacy of photodynamic therapy with methyl 5-aminolevulinic acid in recalcitrant periungual warts after ablative carbon dioxide fractional laser: a pilot study. Dermatol Surg 2009; 35(12):1927-32.
25. Fukui T, Watanabe D, Tamada Y, Matsumoto Y. Photodynamic therapy following carbon dioxide laser enhances efficacy in the treatment of extramammary Paget's disease. Acta Derm Venereol 2009;89(2):150-4.
26. Letada PR, Shumaker PR, Uebrlhoer NS. Demonstration of protoporphiryn IX (PpIX) localized to ares of palmar skin injected with 5 aminolevulinic acid (ALA) and pre-treated with a fractionated CO2 laser prior to topically applied ALA. Photodiagnosis Photodyn Ther. 2010;7(2):120-2.
27. Haedersdal M, Sakamoto FH, Farinelli WA, Doukas AG, Tam J, Anderson RR. Fractional CO2 laser-assisted drug delivery. Laser Surg Med. 2010;42(2):113-22.
28. Shen SC, Lee WR, Fang YP, Hu CH, Fang JY. In vitro percutaneous absorption and in vivo protoporphiryn IX accumulation in skin and tumors after topical 5-aminolevulinic acidapplication with enhancement using an Erbium:YAG laser. J Pharm Sci. 2006; 95(4):929-38.
29. Stumpp OF, Welch AJ, Milner TE, Neev J. Enhacement of transepidermal skin clearing agent delivery using a 980 nm diode laser. Lasers Surg Med. 2005;37(4):278-85.
30. Fang JY, Lee WR, Shen SC, Fang YP, Hu CH. Enhancement of topical 5-aminolevulinic acid delivery by Erbium:YAG laser and microdermoabrasion: a comparison of iontophoresis and electroporation. Br J Dermatol. 2004 ;151(1): 132-40.
31. Wang KF, Fang JY, Hu CH, Lee WR. Erbium:YAG laser pretreatment accelerates the response of Bowen´s disease treated by topical 5-flouracil. Dermatol Surg. 2004; 30(3): 441-5.
32. McAllister DV, Allen MG, Prausnitz MR. Microfabricated microneedles for gene and drug delivery. Annu Rev Biomed Eng. 2000; 2: 289-313.
33. Henry S, McAllister DV, Allen MG, Prausnitz MR. Microfabricated microneedles: a novel approach to transdermal drug delivery. J Pharm Sci. 1998; 87(8): 922-5.

34. Donnelly RF, Morrow DI, McCarron PA, Woolfson AD, Morrissey A, Juzenas P, et al. Microneedle-mediated intradermal delivery of 5-aminolevulinic acid: potential for enhanced topical photodynamic therapy. J Control Release. 2008;129(3):154-62.
35. Mikolajewska P1, Donnelly RF, Garland MJ, Morrow DI, Singh TR, Iani V, et al. Microneedle pre-treatment of human skin improves 5-aminolevulininc acid (ALA)- and 5-aminolevulinic acid methyl ester (MAL)-induced PpIX production for topical photodynamic therapy without increase in pain or erythema. Pharm Res. 2010;27(10):2213-20.
36. Torezan L, Chaves Y, Niwa A, Sanches JA Jr, Festa-Neto C, Szeimies RM. A pilot split-face study comparing conventional methyl aminolevulinate-photodynamic therapy (PDT) with microneedling-assisted PDT on actinically damaged skin. Dermatol Surg. 2013;39(8):1197-201.
37. Curdy C, Kalia YN, Guy RH. Non-invasive assessment of the effects of iontophoresis on human skin in vivo. J Pharm Pharmacol. 2001;53:769-77.
38. Li GL, van der Geest R, Chanet L, van Zanten E, Danhof M, Bouwstra JA. In vitro iontophoresis of R-apomorphine across human stratum corneum. Structure–transport relationship of penetration enhancement. J Control Release. 2002;84(1-2): 49-57.
39. Prausnitz MR. A practical assessment of transdermal drug delivery by skin electroporation. Adv Drug Delivery Rev. 1999;35(1): 61-76.
40. Vanbever R, Preat V. In vivo efficacy and safety of electroporation. Adv Drug Deliv Rev. 1999; 35(1):77-88.
41. Lee S, Kollias N, McAuliffe DJ, Flotte TJ, Doukas AG. Topical drug delivery in humans with a single photomechanical wave. Pharm Res. 1999; 16(11): 1717-21.
42. Lee S, McAuliffe DJ, Kollias N, Flotte TJ, Doukas AG. Permeabilization and recovery of the stratum corneum in vivo: the synergy of photomechanical waves and sodium lauryl sulfate. Lasers Surg Med. 2001;29(2): 145-50.
43. Malvehy, J. A new vision of actinic keratosis beyond visible clinical lesions. J Eur Acad Dermatol Venereol. 2015;29 Suppl 1:3-8.
44. Erlendsson AM, Egekvist H, Lorentzen HF, Philipsen PA., Stausbøl-Grøn B., Stender IM, et al. Actinic keratosis: a cross-sectional study of disease characteristics and treatment patterns in Danish dermatology clinics. International Journal of Dermatology, 55(3): 309–16.
45. Goldman M, Atkin D. ALA/PDT in the treatment of actinic keratosis: spot versus confluent therapy. J Gosmet Laser Ther. 2003;5(2):107–110.
46. Braathen LR, Szeimies RM, Basset-Seguin N, Bissonnette R, Foley P, Pariser D, et al. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: An international consensus. J Am Acad Dermatol. 2007;56(1):125–43.
47. Fink-Puches R, Soyer HP, Hofer A, Kerl H, Wolf P. Long-term follow-up and histological changes of superficial nonmelanoma skin cancers treated with topical delta-aminolevulinic acid photodynamic therapy. Arch Dermatol. 1998; 134(7):821-6.
48. Freeman M, Vinciullo C, Francis D, Spelman L, Nguyen R, Fergin P, et al. A comparison of photodynamic therapy using topical methyl aminolevulinate (Metvix) with single cycle cryotherapy in patients with actinic keratosis: a prospective, randomized study. J Dermatolog Treat. 2003 ;14(2):99-106.
49. Dragieva G, Prinz BM, Hafner J, Dummer R, Burg G, Binswanger U, et al. A randomized controlled clinical trial of topical photodynamic therapy with methyl aminolaevulinate in the treatment of actinic keratoses in transplant recipients. Br J Dermatol. 2004;151(1):196-200.
50. Szeimies RM. Methyl aminolevulinate-photodynamic therapy for basal cell carcinoma. Dermatol Clin. 2007; 25(1):89-94.
51. Lehmann P. Methyl aminolaevulinate-photodynamic therapy: a review of clinical trials in the treatment of actinic keratoses and nonmelanoma skin cancer. Br J Dermatol. 2007; 156(5):793-801.
52. Cesarini JP, Michel L, Maurette JM, Adhoute H, Bejot M. Immediate effects of UV radiation on the skin: modification by an antioxidant complex containing carotenoids. Photodermatol Photoimmunol Photomed. 2003;19(4):182-9.
53. Ruiz-Rodriguez R, Sanz-Sanchez T, Cordoba S. Photodynamic photorejuvenation. Dermatol Surg. 2002; 28(8):742-744; discussion 744.
54. Alster TS, Tanzi EL, Welsh EC. Photorejuvenation of facial skin with topical 20% 5-aminolevulinic acid and intense pulsed light treatment: a split-face comparison study. J Drugs Dermatol. 2005; 4(1):35-38.
55. Szeimies RM, Torezan L, Niwa A, Valente N, Unger P, Kohl E, et al. Clinical, histopathological and immunohistochemical assessment of human skin field cancerization before and after photodynamic therapy. Br J Dermatol. 2012;167(1):150-9.
56. Lavon I, Kost J. Ultrasound and transdermal drug delivery. Drug Discov Today 2004;9(15):670-6.
57. Tachibana K, Tachibana S. Transdermal delivery of insulin by ultrasonic vibration. J Pharm Pharmacol 1991;43(4):270-1.
58. Sintov AC, Krymberk I, Daniel D, Hannan T, Sohn Z, Levin G. Radiofrequency-driven skin microchanneling as a new way for elletrically assisted transdermal delivery of hydrophilic drugs. J Control Release 2003; 89 (2):311-20.
59. Issa MCA, Kassuga LEBP, Chevrand NS, Pires, MTF. Topical delivery of triamcinolone via skin pretreated with ablative radiofrequency: a new method in hypertrophic scar treatment. Int J Dermatol. 2012. 52(3): 367-70.
60. Issa MC, Pires M, Silveira P, Xavier de Brito E, Sasajima C. Transepidermal drug delivery: a new treatment option for areata alopecia? J Cosmet Laser Ther. 2015;17(1):37-40.
61. Kassuga LEBP, Issa MCA, Chevrand NS. Aplicação transepidérmica de medicamento associado a terapia fotodinâmica no tratamento de ceratoses actínicas. Surg Cosmet Dermatol. 2012; 4 (1): 89-92.

Transepidermal drug delivery in daylight photodynamic therapy in the treatment of photodamaged skin: a pilot study

Aplicação transepidérmica de medicamento na terapia fotodinâmica com a luz do dia para o tratamento da pele fotodanificada: estudo piloto

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ABSTRACT

Introduction: Daylight photodynamic therapy (PDT) is a recent therapeutic modality for actinic keratoses and field cancerization. The association of techniques to PDT for transepidermal delivery of the photosensitizer is a new option for the treatment of photodamaged skin with actinic keratosis.

Objective: To evaluate the clinical efficacy and the adverse events of photodamaged skin treatment through the transepidermal drug delivery and daylight-PDT.

Methods: Seven patients with phototype II and III, aged 60-73 years, with photodamaged skin, with and without actinic keratoses, were submitted to the association of methods (CO_2 laser, micro-abrasion or microneedling) and daylight-PDT. Two sessions were performed with two weeks intervals. MAL was applied after micro-abrasion and after CO_2 laser, but before the micro-needling. All patients were exposed to daylight for a period of 2 hours. Clinical evaluations were performed before, 15 days and three months after treatment.

Results: CO_2 laser associated with daylight-PDT was more effective in overall improvement of the skin (texture, pigmentation and wrinkles). Microneedling associated with daylight-PDT was effective in improving texture and pigmentation. Micro-abrasion proved to be effective when combined with microneedling. Excellent improvement of actinic keratosis lesions was achieved with all associations of techniques. Adverse events were transient and more intense with the association of CO_2 Laser.

Conclusion: Association of TDD with daylight-PDT was effective in the treatment of photodamaged skin and safe in all protocols.

Keywords: photodynamic therapy, photosensitizer, light, actinic keratosis, photoaging.

RESUMO

***Introdução**: A Terapia Fotodinâmica com a luz do dia é uma modalidade terapêutica recente para ceratoses actínicas e campo de cancerização. A associação de técnicas `a TFD para aplicação transepidérmica do fotossensibilizante é uma nova opção para tratamento da pele fotodanificada com ceratose actínica.*

***Objetivo**: Avaliar a eficácia clínica e os efeitos colaterias do tratamento da pele fotodanificada através da aplicação transepidérmica de medicamentos e TFD com luz do dia.*

***Métodos**: Sete pacientes fototipos II e III, 60-73 anos, com pele fotodanificada, com e sem ceratoses actínicas foram submetidos à associação de métodos (laser de CO_2, micro-abrasão ou microagulhamento) e TFD com a luz do dia. Foram realizadas duas sessões com intervalo de duas semanas. O MAL foi aplicado após a micro-abrasão e após o laser de CO_2, entretanto antes do micro-agulhamento. Todos os pacientes foram expostos à luz do dia por um período de 2 horas. Avaliações clinicas foram realizadas antes, 15 dias e três meses após tratamento.*

***Resultados**: O Laser de CO_2 associado à DLPDT foi mais eficaz na melhora global da pele (textura, pigmentação e rugas). O micro- agulhamento associado à DLPDT foi eficaz na melhora da textura e da pigmentação. A micro-abrasão se mostrou eficaz quando associada ao microagulhamento. Excelente melhora das lesões de ceratose actínica foi alcançada com todas as associações de técnicas. Os efeitos colaterais foram transitórios e mais intensos com a associação de Laser de CO_2.*

***Conclusões**: A associação de TED à DLPDT foi eficaz no tratamento da pele fotodanificada e segura em todas os protocolos.*

Palavras-chave: *terapia fotodinâmica; fotossensibilizante; luz; ceratose actínica; fotoenvelhecimento*

INTRODUCTION

Chronic exposure to sunlight increases the incidence of nonmelanoma skin cancer, to be included of actinic keratosis (AK), basal cellular carcinoma and spinocellular carcinoma. It is also responsible for the photoaging of the skin, observed clinically by the presence of wrinkles, erythema, coarseness, telangiectasia and irregular pigmentation.[1] Among treatment options for photodamaged skin with AK, conventional photodynamic therapy (c-PDT) stands out due to its high efficacy and excellent cosmetic results. Some factors, such as side-effects (pain, erythema and edema), the incubation time of the methyl aminolevulinate (MAL) lasting 3 hours under an occlusive dressing and the need of an artificial lamp for the lighting, may be limiting for patients and doctors.[2, 3]

Over the last few years, studies have reported the efficacy of a new technique, which follows the same principle of c-PDT, but uses daylight as a source of light (fraction of visible sunlight). Daylight Photodynamic Therapy (DLPDT) is well tolerated by the patient. Pain is either absent or discrete during the lighting, and cutaneous reaction in the period following the procedure, such as erythema and edema, are minimal.[4-11]

The treatment protocols of the conventional form and with the sunlight differ in several aspects (Table 1). With c-PDT, the MAL must be applied to the previously curetted skin, and maintained under occlusion for a period of 3 hours. After this incubation period, the skin is exposed to a source of artificial light (red LED) for approximately 10 minutes, which is equivalent to a dose of 37J/cm^2. With the DLPDT, the MAL is applied without occlusion over the previously curetted area and with the chemical sunscreen. The patient must be exposed to daylight, in up to 30 minutes after the procedure, and remain under it for a period of 2 hours. DLPDT minimizes the disadvantages of c-PDT, and maintains its efficacy in the treatment of actinic keratosis and cutaneous field cancerization.[4-11]

Regardless of the type of light that is being used, artificial or daylight, the penetration of the photosensitizer through the stratum corneum layer in the area of the skin that is to receive treatment remains a limiting factor of the technique. Inasmuch, a new possibility for the PDT is the association of techniques that may augment the penetration of the photosensitizer. This new therapeutic modality is called transepidermal drug delivery (TED). Among the most recently described techniques for performing TED are microneedling[12-14] and the fractional ablative methods, such as fractional ablative radiofrequency and the CO_2 and Erbium lasers.[15-19] Microneedling acts by "pushing" the medication through the perforations caused during its application on the cutaneous surface. The fractional ablative methods promote the production of pathways within the epidermis all the way to the papillary dermis, depending on the parameters being used, which permeate the substances applied topically. Microdermabrasion collaborates with simple curettage in order to remove the topmost layers of the epidermis.

Several studies have reported the association of fractional ablative methods with a method for potentializing the efficacy of the c-PDT.[20-24] Also, it is mentioned that this clinical response, potentialized by the association of TED with c-PDT may be attained even with a time reduction in the incubation of MAL to one hour.[15] The association of TED with DLPDT however, is still rarely mentioned in the medical literature. The efficacy in the association of the CO_2 laser with the DLPDT in the treatment of actinic keratosis in transplanted patients was recently reported by Togsverd-Bo et al in 2015.[25]

Based on recent data found in the medical literature, we have proposed this pilot study, which seeks to clinically evaluate the modifications induced by this association (TED + DLPDT), by comparing different protocols and techniques.

METHODOLOGY

CLINICAL TRIAL STUDY DESIGN

A non-randomized prospective pilot study was done with 7 patients from both genders, phototypes II and III, aged between 60 and 73 years old, presenting photodamaged skin on the face and chest (degrees III and IV on the Glogau scale), with and without actinic keratosis. Patients who were smokers, pregnant, diagnosed with photosensitivity, malignant neoplasm, collagenosis, local or systemic infections, immunodepression or were making use of photosensitive substances. All patients were photographed and signed a consent and clarification form in order to take part in the study. The procedures took place at the researcher's private clinic, which allowed for the usage of her own CO_2 laser (I-Pixel CO_2 – Alma Lasers, Caesarea, Is-

Table 1: Differences between conventional PDT and PDT with daylight

	c-PDT	DLPDT
PREPARATION	Curettage	Curettage + Chemical sunscreen
INCUBATION OF PHOTOSENSITIZER (MAL)	3 hours under occlusion	Maximum of 30 minutes without occlusion
LIGHT SOURCE	Artificial (Light-Emitting Diode / LED)	Daylight (Fraction of Visible Sunlight)
EXPOSURE TIME TO LIGHT SOURCE	Approximately 10 minutes	2 hours

rael), her crystal peeling device (by the company Pan Electronic, Rio de Janeiro, Brazil), and donated the derma rollers (Doctor-roller-2,5mm, Moohan Enterprise Ltd, Gwangju, South Korea). The MAL was donated by Galderma Pharmaceutical Industry (*Galderma Indústria Farmacêutica*). The patients had no financial expenditures but their transportation costs. The researchers involved received no remuneration.

The treatment was comprised of undergoing one or two MAL-TFD sessions with daylight, two weeks apart, in combination with the transepidermal application techniques of MAL (aluminum oxide crystal microdermabrasion – crystal peeling; microneedling; and fractional CO_2 ablative laser). In some cases, cosmeceuticals, such as vitamin C and depigmenting agents (Skinceuticals, L'Oréal, Paris, France) were combined with the MAL for drug delivery. After each session, the patients were told to apply a wound healing cream that contained dexpanthenol (3x/day for 7 days) and SPF50 sunscreen (Actinica® Galderma, Paris, France). Prophylaxis was carried out using an antiviral (acyclovir) at its full dosage for five days in all patients who underwent laser and microneedling procedures. Applying the sunscreen was the first step of the protocol, even before all other procedures, except for those cases in which microdermabrasion with crystal peeling was used.

The photosensitizer used was the 16% MAL cream (Metvix®, GALDERMA, Paris, France) in the amount of 1 gram per session (face or cleft) in all patients. However, the order it was applied varied according to the method of TED that was used. Thus, the MAL was applied after the microdermabrasion and after the CO_2 laser, however it was always applied before the microneedling. It was only in one patient that two TED techniques were used in the same area in one single session. In this case, the MAL was applied after the microdermabrasion and before the microneedling. In every situation, however, the MAL was applied after the sunscreen.

All patients were exposed to daylight within 30 minutes of the MAL application, remaining exposed for 2 hours (open and well-lit space) before returning to the clinic for the skin cleansing with 0.9% Saline, reapplication of sunscreen and clinical evaluation of the immediate effects.

TECHNIQUES FOR TRANSEPIDERMAL APPLICATION OF DRUGS

1. Aluminum Oxide Crystal Microdermabrasion (Crystal Peeling):

Before the simple curettage and the application of MAL, many scrubs in different directions were performed (vertical, horizontal and oblique) until a homogeneous erythema in the entire area was reached.

2. Microneedling:

The derma roller with 2.5mm needles was used immediately after the application of the MAL photosensitizer. Several scrubs in different directions were performed (like an asterisk), without causing bleeding.

3. Fractional Ablative CO_2 Laser:

It was applied after the curettage of the lesions, and immediately before the application of MAL, with the following parameters: 60 watts of power, fluence of 20 mJ/pixel, spacing of 3 mm in between the pixels, with one single scrub of the whole area, using a roller tip.

CLINICAL EVALUATION

The patients had follow-ups for a period of 3 months in order to evaluate the cure rate of the actinic keratoses and the overall degree of improvement of the skin (texture, wrinkles and pigmentation). Evaluations took place before the procedures first began, 15 days after the first session and 3 months after the treatment.

Texture (coarseness), color (pigmentation) and wrinkles analysis were conducted by the means of qualitative parameters, using the Glogau Aging Scale. The degree of improvement was evaluated in accordance to the quartile scale proposed by Alster et al[26], which considers improvement as minimal (<25%); moderate (25%-50%); significant (51%-75%), and excellent (>75%).

The evaluation concerning the improvement in the actinic keratosis lesions was done with quantitative parameters (lesion count), and also qualitative in accordance to thickness levels (grades 1, 2 and 3). The side effects (pain, erythema and edema) were evaluated by an intensity scale varying from absent, mild, moderate and intense, in the periods immediately following the procedure and two hours after having been exposed to sunlight.

CLINICAL CASES

Case 1:

ID: Male, 70 years old, phototype III (Table 2).

Actinic Keratosis: 3 AK lesions, grade II (2 on the right side, one being hyperchromatic; and 1 on the left side).

Aging Grade: Glogau Type III.

Procedure: face: Two sessions of MAL-DLPDT in combination with the fractional CO_2 ablative laser on the right hemiface and microneedling on the lift hemiface (Figure 1).

Post Immediate: Side treated with the CO_2 laser (right): moderate pain; moderate erythema; mild edema. Side treated with the microneedling (left): mild pain; mild erythema; absence of edema (Table 3).

After 2 hours: Side treated with the CO_2 laser (right): mild pain; moderate erythema; mild edema. Side treated with the microneedling (left): absence of pain; mild erythema; absence of edema (Figure 2). (Table 3).

After 15 days: Side treated with the CO_2 laser (right): showed moderate improvement in texture; showed no improvement in wrinkles and pigmentation; and 50% clinical cure of the actinic keratosis lesions. Side treated with the microneedling (left): showed minimum improvement in texture; absence of improvement in wrinkles and pigmentation; and 100% clinical cure of actinic keratosis (Table 4).

Results after 3 months: On the side treated with the CO_2 laser (right), there was significant improvement in texture, minimum improvement in wrinkles and pigmentation (Figure 3). The cure rate of the AK was 50%, without improvement of the hyperchromatic lesion. On the side treated with micronee-

Table 2: Demographic data and classification of lesions						
PATIENT	**AGE**	**GENDER**	**PLACE**	**PHOTOTYPE**	**ACTINIC KERATOSIS NUMBER / AREA**	**GRADE / AREA**
1	70	M	FACE	III	3 (2D e 1E)	II (*)
2	73	M	FACE	III	6 (6D)	I- 3 Lesions II- 3 Lesions
3	73	F	FACE	II	0	0
4	60	F	FACE	III	2 (1D e 1E)	II
5	70	F	CHEST	II	8 (5D e 3E)	II
6	72	F	FACE	III	5 (5D)	II
7	54	F	FACE	III	15 (9D e 6E)	II

Legenda: *: 1 lesão hipercrômica. D: direita. E: esquerda.

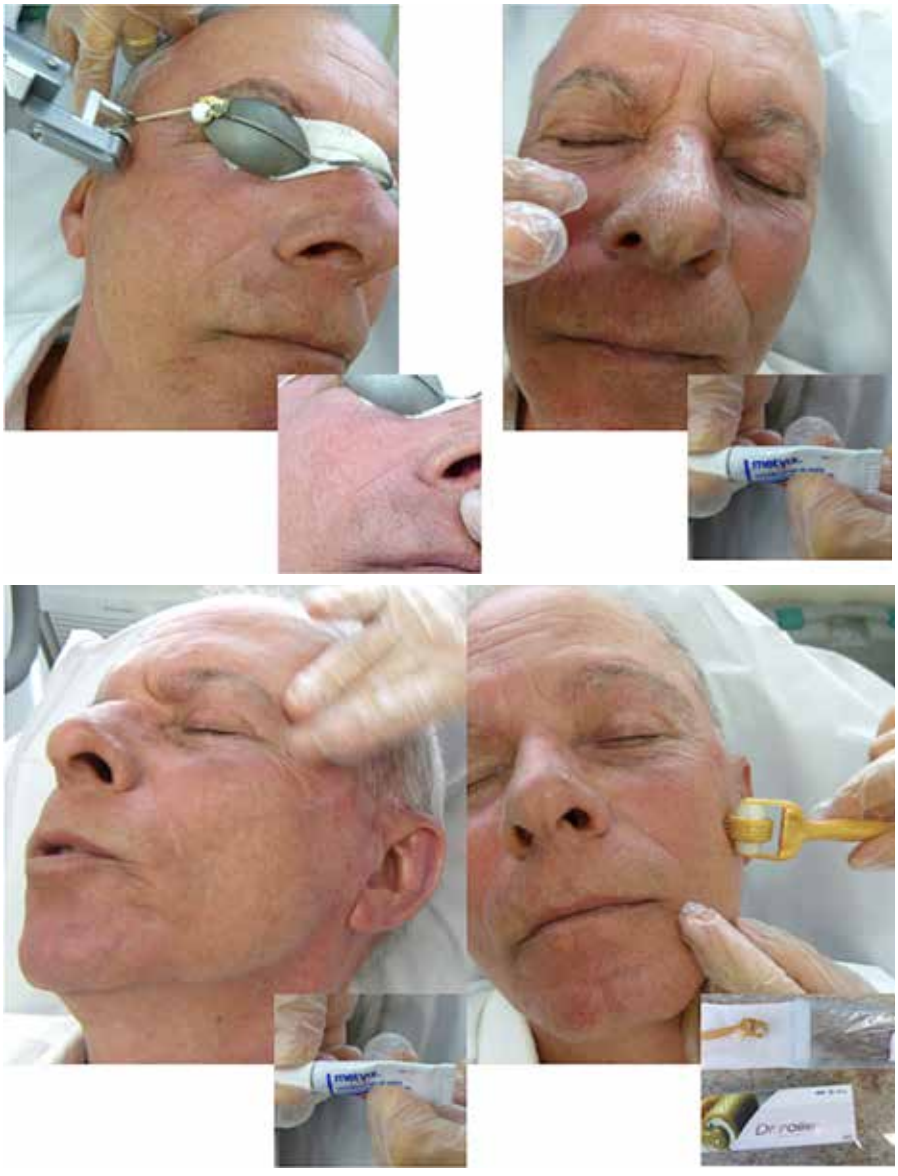


Figure 1: Case 1 - Procedure: Right side with CO_2 laser before the application of MAL. Left side, application of MAL before microneedling

Table 3: Clinical evaluations after Session 1

c	Gender	AGE	Treated Area	PROCEDURE USED IN THE FIRST SESSION		15 DAYS AFTER THE FIRST SESSION							
				RIGHT SIDE	LEFT SIDE	RIGHT SIDE				LEFT SIDE			
						Texture	Wrinkles	Pigmentation	Actinic Keratosis	Texture	Wrinkles	Pigmentation	Actinic Keratosis
1	M	70	FACE	CO2 + MAL	Derma Roller	Moderate + MAL	Absence of improvement	Absence of improvement	50% Clinical Cure	Minimal	Absence of improvement	Absence of improvement	100% Clinical Cure
2	M	73	FACE	Derma Roller + MAL	Derma Roller + MAL with depigmenting agent and vitamin C	Minimal	Minimal	Minimal	33,4% Clinical Cure 66,6% Improvement in the grade	Minimal	Minimal	Moderate	Not applicable
3	F	73	FACE	CO2 + MAL	CO2 + MAL with depigmenting agent and vitamin C	Moderate	Minimal	Minimal	Not applicable	Minimal	Minimal	Moderate	Not applicable
4	F	60	FACE	CO2 + MAL	CO2 + MAL	Minimal	Absence of improvement	Not applicable	100% Clinical Cure	Minimal	Absence of improvement	Not applicable	100% Clinical Cure
5	F	70	COLO	CO2 + MAL	CO2 + MAL	Moderate	Minimal	Moderate	60% Clinical Cure 40% Improvement in the grade	Moderate	Minimal	Moderate	100% Clinical Cure
6	F	72	FACE	Crystal + MAL	Crystal + MAL	Moderate	Minimal	Minimal	80% Cure	Moderate	Minimal	Minimal	Not applicable
7	F	54	FACE	Crystal + MAL + Derma Roller	Crystal + MAL + Derma Roller	Moderate	Minimal	Not applicable	77.7% Cure	Moderate	Minimal	Not applicable	66,6%% Cure

Key - *: Improvement evaluation according to Tina Alster's grading scale, which considers minimal improvement (<25%); moderate (25% - 50%); significant (51% - 75%); and excellent (>75%).

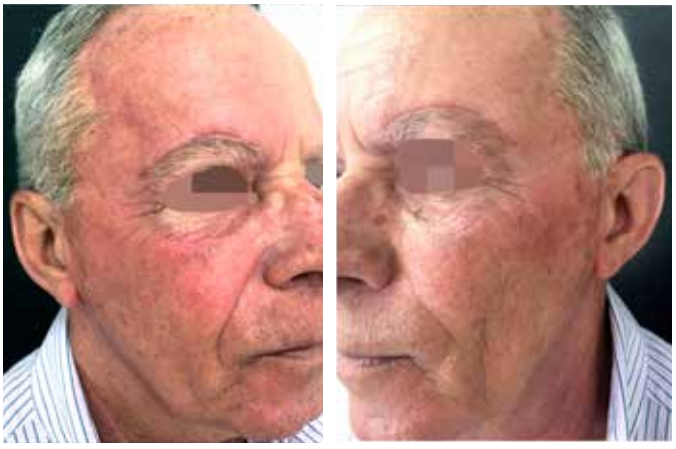


Figure 2: Case 1 - Comparison of erythema 2 hours after it was exposed to the light. Right side (CO2 laser + DLPDT) and left side (microneedling + DLPDT)

dling (left), there was moderate improvement in texture. There was no improvement in wrinkles nor in pigmentation. The AK lesion was cured (Table 5).

Case 2:

ID: Male, 73 years old, phototype III (Table 2).

Actinic Keratosis: 6 AK lesions on the right hemiface (3 grade II and 3 grade III).

Aging Grade: Glogau Type III.

Procedure: face: Two sessions of MAL-DLPDT in combination with microneedling on both hemifaces. On the right hemiface, MAL was used isolatedly, and on the left hemiface, MAL was combined with a depigmenting agent and vitamin C.

Post immediate: Moderate pain; mild erythema; absence of edema on either side. (Table 3).

After two hours: Absence of pain; mild erythema; absence of edema on either side. (Table 3).

After 15 days: On the side treated with a combination of microneedling and MAL (right), there was minimum improvement in texture, wrinkles and pigmentation; 33.4% clini-

Table 4: Clinical Evaluations after Session 2

C	Gender	age	Treated area	Procedure used in the second		3 MONTHS AFTER THE SECOND SESSION OF TED + DLPDT							
				Right side	Left side	Right side			Left side				
						Textura	Wrinkles	Pigmentation	Actinic Keratosis	Texture	Wrinkles	Pigmentation	Actinic Keratosis
1	M	70	Face	Co2 + Mal	Derma Roller + Mal	51-75%	1-25%	1-25%	50% Clinical cure	26-50%	Absence of improvement	Absence of improvement	100% Clinical cure
2	M	73	Face	Derma Roller + Mal	Derma Roller + Mal with depigmenting agent and vitamin C	51-75%	1-25%	1-25%	83,3% Clinical cure 16,7% Improvement in the grade	51-75%	1-25%	26-50%	Not applicable
3	F	73	Face	Co2 + Mal	Co2 + Mal with depigmenting agent and vitamin C	51-75%	51-75%	26-50%	Not applicable	51-75%	51-75%	51-75%	Not applicable
4	F	60	Face	Co2 + Mal	Co2 + Mal	26-50%	1-25%	Not applicable	100% Clinical cure	26-50%	1-25%	Not applicable	100% Clinical cure
5	F	70	Chest	Co2 + Mal	Co2 + Mal	51-75%	26-50 %	26-50%	80% Cure + 20% Improvement	51-75%	26-50%	26-50%	100% Clinical cure
6	F	72	Face	Not applicable	Not applicable	26-50%	1-25%	1-25%	100% Clinical Cure	26-50%	1-25%	1-25%	Not applicable
7	F	54	Face	Not applicable	Not applicable	51-75%	51-75%	Not applicable	88,8% Cure + 11,2% Improvement	51-75%	51-75%	Not applicable	100%

Obs: Cases 6 and 7 – The evaluation of patients took place 3 months after one single treatment session.

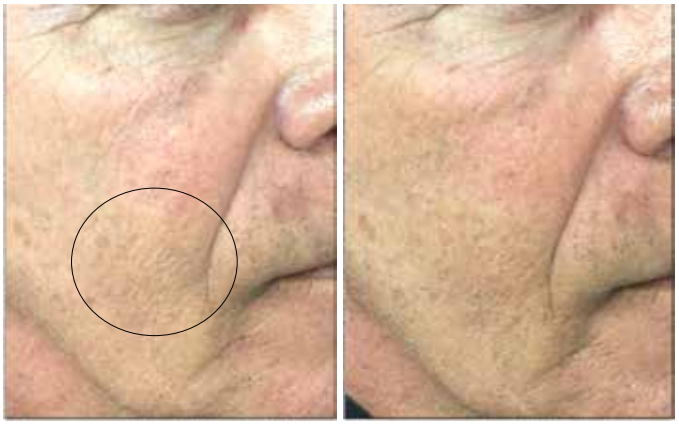


Figure 3: Case 1 - Improvement of fine wrinkles after 2 sessions of DLPDT combined with CO_2 laser

cal cure and 66.6% improvement in the actinic keratosis grade. On the side treated with a combination of microneedling and MAL + depigmenting agents with vitamin C (left), there was minimum improvement in texture and wrinkles, and moderate improvement in pigmentation. (Table 4).

Results after 3 months: On the side treated with a combination of microneedling and MAL (right), there was significant improvement in texture, and minimum improvement in wrinkles and pigmentation. The cure rate of the AK was 83.3%, with 16.7% being reduced from grade III to grade II (Figure 4). On the side treated with a combination of microneedling and MAL + depigmenting agents with vitamin C (left), (Figure 5), there was significant improvement in texture; minimum improvement in wrinkles; moderate improvement in pigmentation (Table 5).

Case 3:

ID: Female, 73 years old, phototype III (Table 2).

Actinic Keratosis: absent.

Aging Grade: Glogau Type III.

Procedure: face: Two sessions of MAL-DLPDT in combination with the fractional CO2 ablative laser on both hemifaces. On the right hemiface, the MAL was applied isolatedly, on the left hemiface the MAL was combined with a depigmenting agent + vitamin C.

Post immediate: Intense pain and erythema and moderate edema on either side. (Table 3).

After 2 hours: Absence of pain; mild edema; moderate erythema on either side. (Table 3).

After 15 days: On the side treated with a combination

Table 5: Clinical evaluation of side-effects

Pacient	PROCEDURE USED		IMMEDIATE POST-PROCEDURE						2 hours after					
	FIRST SESSION													
	Right side	Left Side	Right side			Left Side			Right side			Left Side		
			Pain	Erythema	Edema	Pain	Erythema	Edema	Pain	Erythema	Edema	Pain	Erythema	Edema
1	CO_2 + MAL	Derma Roller + MAL	Moderate	Moderate	Mild	Mild	Mild	Absent	Mild	Moderate	Mild	Absent	Mild	Absent
2	Derma Roller + MAL	Derma Roller + MAL with depigmenting agent and vitamin C	Moderate	Mild	Absent	Moderate	Mild	Absent	Absent	Mild	Absent	Absent	Mild	Absent
3	CO_2 + MAL	CO_2 + MAL with depigmenting agent and vitamin C	Intense	Intense	Moderate	intensa	Intense	moderado	Absent	Moderate	Mild	Absent	Moderate	Mild
4	CO_2 + MAL	CO_2 + MAL	Moderate	Mild	Mild	Moderate	Mild	Mild	Mild	Moderate	Mild	Mild	Moderate	Mild
5	CO_2 + MAL	CO_2 + MAL	Moderate	Mild	Mild	Moderate	Mild	Mild	Mild	Moderate	Mild	Mild	Moderate	Mild
6	Crystal peeling + MAL		Mild	Mild	Mild	Mild	Mild	Absent	Mild	Mild	Absent	Mild	Mild	Absent
7	Crystal peeling + MAL + Derma Roller		Moderate	Intense	Moderate	Moderate	Intense	Moderate	Moderate	Intense	Moderate	Moderate	Intense	Moderate

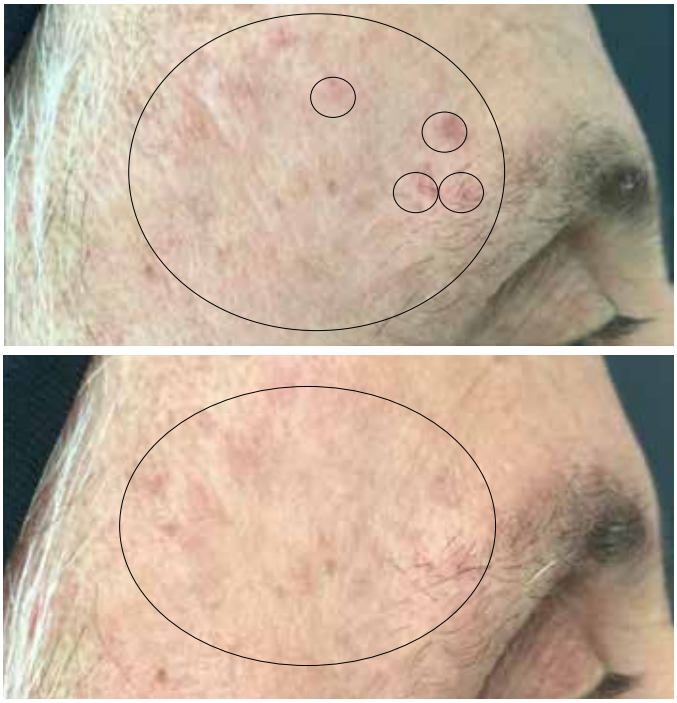


Figure 4: Case 2 - Improvement of actinic keratosis after 2 sessions of microneedling combined with DLPDT

of CO_2 and MAL (right), there was moderate improvement in texture; and minimum improvement in wrinkles and pigmentation. On the side treated with a combination of CO_2 and MAL + depigmenting agent + vitamin C (left), there was moderate improvement in texture; minimum improvement in wrinkles and pigmentation. (Table 4).

Results after 3 months: On the side treated with a combination of CO_2 and MAL (right), there was significant improvement in texture and in wrinkles, with moderate improvement in pigmentation.

On the side treated with a combination of CO_2 and MAL + depigmenting agent + vitamin C (left), (Figure 6), there was significant improvement in texture, wrinkles and pigmentation. (Table 5).

Case 4:

ID: Female, 60 years old, phototype III (Table 2).

Actinic Keratosis: 2 AK lesions, grade II (1 on the right side and 1 on the left side).

Aging Grade: Glogau Type IV.

Procedure: face: Two sessions of MAL-DLPDT in combination with the fractional CO_2 ablative laser on both hemifaces.

Post immediate: Moderate pain; mild erythema; mild edema, on both sides. (Table 3).

After 2 hours: Mild pain; moderate erythema; mild edema, on both sides. (Table 3).

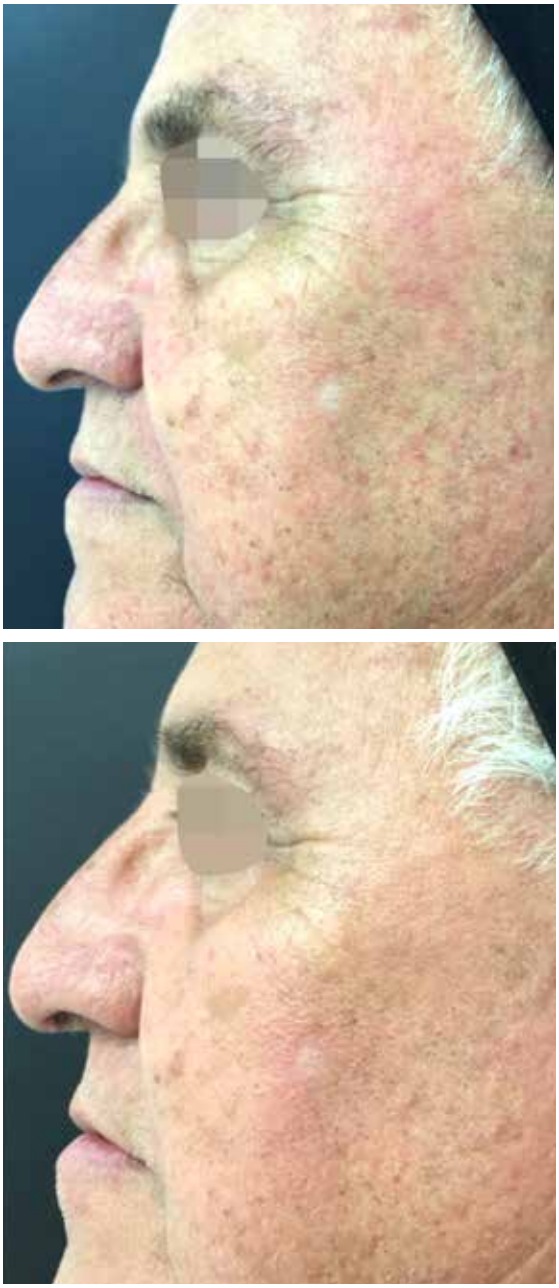


Figure 5: Case 2 - Improvement of texture and pigmentation after 2 sessions of microneedling combined with DLPDT (MAL + depigmenting agent and vitamin C)

Figure 6: Case 3 - Improvement of texture, wrinkles and pigmentation after 2 sessions of CO2 laser combined with DLPDT (MAL + depigmenting agent and vitamin C)

After 15 days: There was minimum improvement in texture; there was no improvement in wrinkles nor in pigmentation; and 100% clinical cure of the actinic keratosis on both sides (Table 4).

Results after 3 months: Moderate improvement in texture, minimum improvement in wrinkles. The cure rate of the AK was 100% on both sides (Table 5).

Case 5:

ID: Female, 70 years old, phototype II (Table 2).

Actinic Keratosis: 8 AK lesions, grade II (5 on the right side and 3 on the left side).

Aging Grade: Glogau Type III.

Procedure: cleft: Two sessions of MAL-DLPDT in combination with the fractional CO_2 ablative laser on both sides of the cleft (divided by an imaginary line between the sternum furcula and the xiphoid process).

Post immediate: Moderate pain; mild erythema; mild edema on both sides. (Table 3).

After 2 hours: Mild pain; moderate erythema; mild edema on both sides. (Table 3).

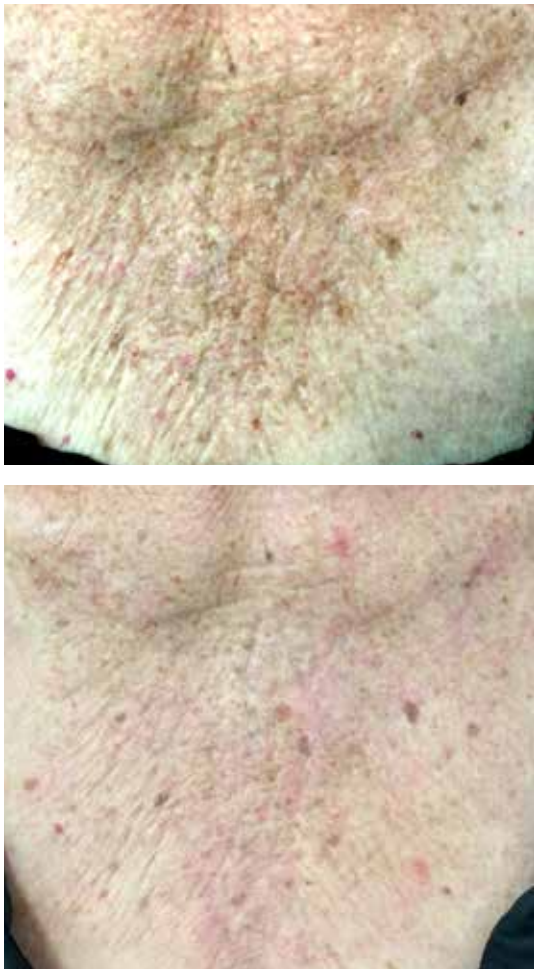
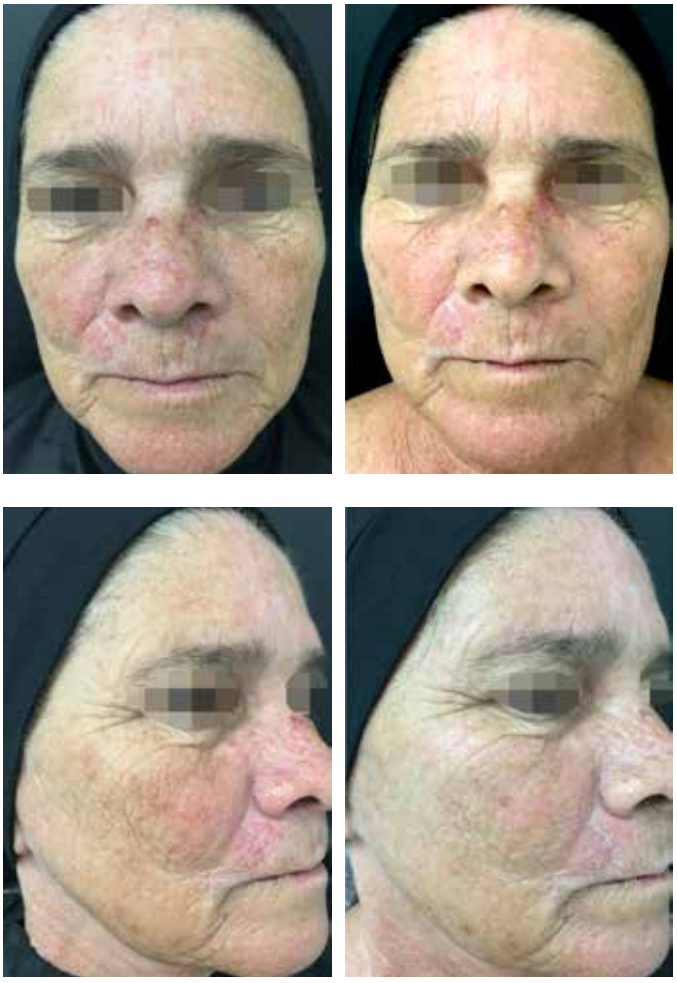


Figure 7: Case 5 - Improvement of texture, wrinkles, pigmentation, and actinic keratosis after 2 sessions of CO_2 laser + DLPDT



Figures 8 e 9: Case 7 - Overall improvement of texture, pigmentation, wrinkles, and actinic keratosis, after the combination of microdermabrasion and microneedling with DLPDT

After 15 days: On the right side, there was moderate improvement in texture and pigmentation, and minimum improvement in wrinkles; with 60% clinical cure and 40% improvement actinic keratosis grading. On the left side, there was moderate improvement in texture and pigmentation; and minimum improvement in wrinkles; with 100% clinical cure of actinic keratosis (Table 4).

Results after 3 months: Significant improvement in texture, moderate improvement in wrinkles and pigmentation on both sides (Figure 7). The cure rate of AK was 80%, with 20% improvement in the reduction grading of the keratosis (from II to I) on the right side. On the left side, the cure rate was 100% (Table 5).

Case 6:

ID: Female, 72 years old, phototype III (Table 2).

Actinic Keratosis: 5 AK lesions, grade II, right side.

Aging Grade: Glogau Type III.

Procedure: face: One single session of MAL-DLPDT in combination with microdermabrasion (crystal peeling) on both hemifaces.

Post Immediate: Mild pain and erythema; absence of edema on either side. (Table 3).

After 2 hours: Mild pain and erythema; absence of edema on either side. (Table 3).

After 15 days: There was moderate improvement in texture, and minimal improvement in wrinkles and pigmentation on both sides.

On the right side, there was 80% clinical cure and 20% improvement in the actinic keratosis grading. (Table 4).

Results after 3 months: Moderate improvement in texture, minimal improvement in wrinkles and pigmentation. The cure rate of the AK was of 100% (Table 5).

Case 7:

ID: Female, 54 years old, phototype III (Table 2).

Actinic Keratosis: 15 AK lesions, grade II (9 on the right side and 6 on the left side).

Aging Grade: Glogau Type III.

Procedure: face: One single session of MAL-DLPDT in combination with microdermabrasion (crystal peeling) +

microneedling on both hemifaces.

Post Immediate: Moderate pain and edema; intense erythema on both sides. (Table 3).

After 2 hours: Moderate pain and edema; intense erythema on both sides. (Table 3).

After 15 days: For both hemifaces, there was moderate improvement in texture; and minimal improvement in wrinkles. On the right side, there was 77.7% clinical cure and 22.3% improvement in the actinic keratosis grading. On the left side, there was 66.6% clinical cure and 33.4% improvement in the actinic keratosis grading (Table 4).

Results after 3 months: Significant improvement in texture and in wrinkles on both sides (Figures 8 and 9). The cure rate of the AK was 88.8% on the right side, with an improvement in the actinic keratosis grading (from II to I) in 11.2%. On the left side, the cure rate of the keratosis was 100% (Table 5).

RESULTS

The CO_2 Laser in combination with DLPDT was more effective in the overall improvement of the skin, mainly in the improvement of wrinkles, when compared to microneedling. Microneedling in combination with DLPDT has proven to be effective in the improvement of texture and pigmentation, mainly when combined with cosmeceutical depigmenting agents. The combination of two TED (microdermabrasion with microneedling) techniques with DLPDT was more effective in the improvement of texture, pigmentation and wrinkles when compared to the use of techniques isolatedly. Excellent improvement in the actinic keratosis lesions was attained with techniques that were combined with TED and DLPDT.

Among all possible side-effects, pain, erythema and edema were observed in most patients. However, these side-effects were observed with greater intensity (moderato to intense) with protocols in which the CO_2 Laser was used. Side effects were mild to moderate when using microdermabrasion or microneedling. The case in which two techniques were combined, microdermabrasion and microneedling to DLPDT, erythema, edema and pain were more intense.

DISCUSSION

Several studies have already shown an increase in effectiveness of conventional PDT in the treatment of actinic keratosis and field cancerization, in combination with methods to increase the permeation of the photosensitizer.[22-24] However, there is a lack of studies regarding the combination of TED with PDT while using daylight. This pilot study is the first of its kind to be conducted in Brazil with the goal to evaluate TED technique with DLPDT.

In the international medical literature, Togsverd-Bo et al[25] have compared the efficacy of isolated DLPDT with DLPDT in combination with the fractional CO_2 ablative laser in the treatment of actinic keratosis with transplanted patients. In our study, we have evaluated the combination of DLPDT with the CO_2 laser and, also, with microneedling and microdermabrasion in the treatment of photodamaged skin with and without actinic keratosis in immunocompetent patients. Togsverd-Bo et al[25] have reported erythema and edema to be more intense in the areas treated with DLPDT when combined with the laser after the procedure, with no long-term change in pigmentation. In our cases, we have also observed a mild increase of erythema and edema immediately after the laser treatment and, also, after daylight exposure, which were transitory, not leading to postinflammatory pigmentation. We have also observed the overall improvement of the skin (texture, fine wrinkles and pigmentation) in varying intensity, according to the other techniques (laser and non-laser) in combination with DLPDT. The clinical response was more evident when combined with the CO_2 laser, and also when we combined the DLPDT to the microdermabrasion with microneedling. The response in pigmentation was slightly better when we combined depigmenting agents and vitamin C to the MAL, either before the microneedling or after the CO_2 laser.

CONCLUSION

Based on the methodology that was used, it is possible to state that the combination of methods such as the CO_2 laser, microdermabrasion and microneedling with DLPDT has proven to be effective in the treatment of photodamaged skin, with improvement of actinic keratosis, texture, pigmentation and wrinkles. The combination of TED and DLPDT was safe in all protocols that it was used.

REFERENCES

1. Issa MCA, Manela-Azulay M. Terapia fotodinâmica: revisão da literatura e documentação iconográfica. An Bras Dermatol. 2010;85 (4):501-511.
2. Kalka K, Merk H, Mukhtar,H. Photodynamic Therapy In Dermatology. J Am Dermatol 2000; 42 (3): 389-413.
3. Morton CA. Photodynamic therapy for nonmelanoma skin cancer. Arch Dermatol. 2004;140(1): 116-120.
4. Braathen LR. Daylight Photodynamic Therapy in Private Practice in Switzerland: Gain Without Pain. Acta Derm Venereol. 2012; 92(6):652-3.
5. Morton CA, Wulf HC, Szeimies RM. Practical approach to the use of daylight photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: a European consensus. J Eur Acad Dermatol Venereol. 2015;29 (9):1718-23.
6. Wiegell SR, Wulf HC, Szeimies RM, Basset-Seguin N, Bissonnette R, Gerritsen MJ, et al. Daylight photodynamic therapy for actinic keratosis: an international consensus: International Society for Photodynamic Therapy in Dermatology. J Eur Acad Dermatol Venereol. 2012; 26(6): 673–9.

7. Rubel DM, Spelman L, Murrell DF, See JA, Hewitt D, Foley P, et al. Daylight PDT with methyl aminolevulinate cream as a convenient, similarly effective, nearly painless alternative to conventional PDT in actinic keratosis treatment: a randomized controlled trial. Br J Dermatol 2014; 171(5): 1164–1171.
8. Lacour J. Results of 2 randomised, controlled, phase III studies with Daylight- PDT in Australia and Europe. Euro-PDT 14th Annual Congress; April 4th–5th, 2014; Nice, France.
9. Wiegell SR, Haedersdal M, Philipsen PA, Eriksen P, Enk CD, Wulf HC. Continuous activation of PpIX by daylight is as effective as and less painful than conventional photodynamic therapy for actinic keratoses – a randomized, controlled study. Br J Dermatol. 2008; 158(4): 740–6.
10. Wiegell SR, Haedersdal M, Eriksen P, Wulf HC. Photodynamic therapy of actinic keratoses with 8% and 16% methyl aminolaevulinate and home-based daylight exposure: a double-blinded randomized clinical trial. Br J Dermatol. 2009; 160(6):1308–14.
11. Wiegell SR, Fabricius S, Stender IM, Berne B, Kroon S, Andersen BL, et al. A randomized, multicenter study of directed daylight exposure times of 1½ vs. 2½ h in daylight-mediated photodynamic therapy with methyl aminolaevulinate in patients with multiple thin actinic keratoses of the face and scalp. Br J Dermatol. 2011; 164(5):1083–90.
12. Donelly RF, Morrow DI, McCarron PA, Woolfson AD, Morrissey A, Juzenas P, et al . Microneedle-mediated intradermal delivery of 5-aminolevulinic acid: potential for enhanced topical photodynamic therapy. J Control Release. 2008;129 (3):154-62.
13. Mikolajewska P, Donnelly RF, Garland MJ, Morrow DI, Singh TR, Iani V, et al. Microneedle pre-treatment of human skin improves 5-aminolevulininc acid (ALA)- and 5-aminolevulinic acid methyl ester (MAL)-induced PpIX production for topical photodynamic therapy without increase in pain or erythema. Pharm Res. 2010;27(10):2213-20.
14. Torezan L, Chaves Y, Niwa A, Sanches JA Jr, Festa-Neto C, Szeimies RM. A pilot split-face study comparing conventional methyl aminolevulinate-photodynamic therapy (PDT) with microneedling-assisted PDT on actinically damaged skin. Dermatol Surg. 2013;39(8):1197-201.
15. Kassuga LEBP, Issa MCA, Chevrand NS. Transepidermal application of medication combined with photodynamic therapy in the treatment of actinic keratosis. Surg Cosmet Dermatol. 2011;3 (4):89-92.
16. Letada PR, Shumaker PR, Uebrlhoer NS. Demonstration of protoporphiryn IX (PpIX) localized to area of palmar skin injected with 5 aminolevulinic acid (ALA) and pre-treated with a fractionated CO2 laser prior to topically applied ALA. Photodiagnosis Photodyn Ther. 2010; 7(2):120-2.
17. Haerdersdal M, Sakamoto FH, FarinelliWA, Doukas AG, Tam J, Anderson RR. Fractional CO2 laser-assisted drug delivery. Laser Surg Med. 2010; 42(2):113-22.
18. Shen SC, Lee WR, Fang YP, Hu CH, Fang JY. In vitro percutaneous absorption and in vivo protoporphiryn IX accumulation in skin and tumors after topical 5-aminolevulinic acid application with enhancement using an Erbium:YAG laser. J Pharm Sci.2006; 95(4):929-38.
19. Fang JY, Shen SC, Lee WR, Fang YP, Hu CH. Enhancement of topical 5-aminolevulinic acid delivery by Erbium:YAG laser and microdermoabrasion: a comparison of iontophoresis and electroporation. Br J Dermatol. 2004 Jul; 151(1):132-40.
20. Yoo KH, Kim BJ, Kim MN. Enhanced efficacy of photodynamic therapy with methyl 5-aminolevulinic acid in recalcitrant periungual warts after ablative carbon dioxide fractional laser: a pilot study. Dermatol Surg 2009; 35(12):1927-32.
21. Fukui T, Watanabe D, Tamada Y, Matsumoto Y. Photodynamic therapy following carbon dioxide laser enhances efficacy in the treatment of extramammary Paget's disease. Acta Derm Venereol 2009;89(2):150-4.
22. Song HS, Jung SE, Jang YH, Kang HY, Lee E, Kim YC. Fractional carbon dioxide laser-assisted photodynamic therapy for patients with actinic keratosis. Photodermatol. Photoimmunol. Photomed 2015; 31(6): 296–301.
23. Jang YH, Lee DJ, Shin J, Kang HY, Lee ES, Kim YC. Photodynamic therapy with ablative carbon dioxide fractional laser in treatment of actinic keratosis. Ann Dermatol Vol. 2013; 25(4): 417-22.
24. Togsverd-Bo K, Haak CS, Thaysen-Petersen D, Wulf HC, Anderson RR, Hædesdal M. Intensified photodynamic therapy of actinic keratoses with fractional CO2 laser: a randomized clinical trial. Br J Dermatol. 2012; 166(6): 1262–9.
25. Togsverd-Bo K, Lei U, Erlendsson AM, Taudorf EH, Philipsen PA, Wulf HC, et al. Combination of ablative fractional laser and daylight-mediated photodynamic therapy for actinic keratosis in organ transplant recipients - a randomized controlled trial. Br J Dermatol 2015; 172 (2): 467-74.
26. Alster TS, Tanzi EL, Welsh EC. Photorejuvenation of facial skin with topical 20% of 5- aminolevulinic acid and intense pulsed light treatment: a split face comparison study. J Drugs Dermatol 2005;4(1):35-8.

Original Articles

Oral use of lingonberry (Vaccinium vitis idaea L.) as an alternative for the treatment of melasma in adult women

Uso oral de lingonberry (Vaccinium vitis idaea L.) como alternativa do tratamento de melasma em mulheres adultas

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ABSTRACT

Introduction: Melasma is a chronic hyperpigmentation of the skin, characterized by irregular brownish spots distributed in areas exposed to the sun, common in Brazilian women. Due to facial involvement, it impacts on appearance, causing psychosocial and emotional discomfort, thus affecting patients' quality of life.

Objective: A double-blind, longitudinal, comparative and monocentric clinical study was conducted comparing the quality of life and the pigmentation intensity of melasma in women before and 60 days after oral use of Lingonberry (Vaccinium vitis idaea L.) extract in association with sunscreen as the only topical treatment.

Methods: The study investigated the influence of the presence of melasma on the quality of life of volunteers before and after 60 days of oral use of lingonberry extract (Vaccinium vitis idaea L.) in combination with topical sunscreen and in patients who just wore sunscreen through the Melasma Quality of Life Scale Scale. Comparative and standardized dermatoscopic photographs of the lesions had the intensity of the pigmentation evaluated by an optical density analysis program.

Results: Evaluation of the Melasma Quality of Life Scale indicated a reduction of the discomfort caused by the pathology after the use of the phytotherapic drug in association with the sunscreen, which did not occur in the group that used the sunscreen alone. The analysis of the pigmentation density in the photographs showed a significant reduction in the degree of pigmentation after the use of phytotherapic drug, as well as no alterations in the control group.

Conclusion: The use of lingonberry may contribute to the treatment of facial melasma.

Keywords: melasma; phytotherapy; skin pigmentation

RESUMO

Introdução: *Melasma é hiperpigmentação crônica da pele, caracterizada por manchas acastanhadas irregulares distribuídas em áreas expostas ao sol, frequente nas mulheres brasileiras. Devido ao envolvimento facial, causa impacto na aparência, desconforto psicossocial e emocional, o que afeta a qualidade de vida das pacientes.*

Objetivo: *Mediante estudo clinico duplo-cego, longitudinal, comparativo e monocêntrico comparou-se a qualidade de vida e a intensidade de pigmentação do melasma, em mulheres, antes e 60 dias após o uso oral do extrato de Lingonberry (Vaccinium vitis idaea L.) em associação ao protetor solar, como único tratamento tópico.*

Métodos: *Por meio do questionário Melasma Quality of Life Scale investigou-se a influência da presença do melasma na qualidade de vida das voluntárias, antes e após 60 dias de uso oral do extrato de lingonberry (vaccinium vitis) em associação ao protetor solar tópico e em pacientes que apenas usaram o protetor solar. Fotografias dermatoscópicas comparativas e padronizadas das lesões tiveram a intensidade da pigmentação avaliada por um programa de análise de densidade óptica.*

Resultados: *A avaliação do questionário Melasma Quality of Life Scale indicou redução do desconforto causado pela patologia após o uso do fitoterápico em associação ao fotoprotetor, o que não aconteceu no grupo que usou apenas o fotoprotetor. A análise da densidade de pigmentação nas fotografias demonstrou redução significativa do grau de pigmentação após o uso do fitoterápico, bem como nenhuma alteração no grupo-controle.*

Conclusões: *O uso de lingonberry pode contribuir no tratamento do melasma facial.*

Palavras-chave: *melasma; fitoterapia; pigmentação da pele*

INTRODUCTION

The skin is the most visible phenotypic characteristic of the human being, and its color, one of its most variable factors. Knowledge about the genetic, evolutionary and cultural aspects related to the establishment of human skin color levels is restricted.[1] Human skin and hair pigmentation is related to melanogenic activity in melanin producing cells, as well as on the size, number, composition, and distribution of melanocyte cytoplasmic particles called melanosomes, as well as the chemical nature of the melanin they contain.[1]

Melasma is common melanoderma, characterized by macules on areas exposed to UV radiation, with brownish pigmentation of different intensities, mainly affecting adult women (aged 30 to 55 years) of childbearing age.[2]

The name melasma is derived from the Greek *melas*, which means black. Also known as chloasma, equally derived from the Greek *cloazein*: to be greenish. The name melasma is, therefore, more appropriate for the disease.[3]

The etiopathogenesis of melasma has not yet been fully elucidated; It is known, however, that several factors are involved in the expansion or in its emergence. Periods of partial reduction during the winter and periods of exacerbation during the summer are observed, and the lesions may appear abruptly due to intense sun exposure, or gradually, by constant exposure.

One of the most well-accepted theories for the appearance of this dyschromia is that ultraviolet radiation causes the peroxidation of the lipids of the cell membrane, with consequent formation of free radicals, which stimulate the melanocytes to produce melanin excessively, thus generating cutaneous hyperpigmentation.[4] The hormonal influence on the etiopathogenesis of melasma is structured by the high frequency of presence in pregnant women, users of oral contraceptives, and women in hormone replacement therapy.[4]

It is a dermatological disease diagnosed with a clinical examination, which presents characteristic chronicity, with frequent recurrences and great refractoriness to existing treatments.[5]

There is no consensus on the clinical classification of melasma. In the face, where it is more frequent, two main patterns are recognized: centrofacial, affecting the central regions of the forehead, supralabial and mental regions; And malar, which affects the zygomatic regions. Some authors also add a third, less frequent pattern called the mandibular.[5]

Melasma may be classified as transient or persistent. When the stimuli are interrupted for a year and the melasma disappears, it is classified as transient; if it does not disappear, is of the persistent type, having as a causal factor the solar radiation, among others.[5]

According to data from the Brazilian Society of Dermatology, in 2006 Brazil had 57,343 cases of face melasma diagnosed; melanodermas make up the third most common group of dermatological diseases in Brazil.[6]

Because it appears mainly on the face, melasma disturbs the patient, negatively affecting his or her psychological and emotional well-being, thus generating a negative impact on the quality of life, which often leads the person to seek the dermatologist.[7] Thus, the need arose for the development of a standardized and validated questionnaire in order to evaluate the quality of life of these patients. The MELASQoL (Melasma Quality of Life Scale) is an instrument that covers three situations affected by dermatosis: social life, recreation / leisure and emotional well-being.[8, 9] In Brazil, the questionnaire was translated into Portuguese in 2006 (MELASQoL- BP), following World Health Organization standards.[10] The response to MELASQoL of 300 patients of both genders from different demographic regions was investigated; Among the answers, 65% of the patients reported discomfort with facial melasma, 55% felt frustration, and 57% were ashamed of the discolored appearance of the skin.[11]

The treatment of melasma is often unsatisfactory, due to the great recurrence of the lesions and the absence of alternatives for definitive whitening. From the topical treatments available, hydroquinone is considered the most efficient drug, despite its adverse effects – irritant or allergic contact dermatitis, hypopigmentation, and postinflammatory hyperpigmentation.[12]

Controlled clinical studies indicate photoprotection and use of topical and / or oral whitening agents as the main treatment measures.[10, 13] Vegetable substances with antioxidant functions have been reported to be useful in the treatment of melasma. *Vacciniumvitis-idaea*, commonly called lingonberry or cowberry, is a small green shrub of the *Ericaceae* family that produces edible fruits as small as a pea. Its high antioxidant capacity is reflected by its high ORAC (Oxygen Radical Absorbance Capacity) of 16,000, thus indicating the great potential of the extract of this vegetable in acting against free radicals in the human organism.[14]

This study sought to investigate this substance in the control of melasma in Brazilian women.

METHODS

This is a double-blind, longitudinal, comparative, monocentric clinical study approved by the University Ethics Committee in Human Research at the University Hospital of the Fluminense Federal University (*Universidade Federal Fluminense*), in which 42 volunteers with facial melasma and aged between 30 and 55 years were investigated.

During the period of March and April of 2015, patients who had clinical complaints of melasma were selected and monitored at the Dermatology Outpatient Clinic at the University Hospital of the Fluminense Federal University, Niterói, Rio de Janeiro, Brazil.

All participants met the following inclusion criteria: presence of facial melasma in women aged between 30 and 55 years, who had not undergone topical or oral depigmentation treatment for at least six months, and agreed to have their photographs published for scientific purposes. Were excluded from the project, women who were pregnant or lactating, and women with active dermatoses in the area to be treated; who, in the 30 days prior to the study, used products based on hydroquinone, vitamin C, azelaic acid, kojic acid, phytic acid, glycolic acid, anti-inflammatories and retinoid derivatives.

After signing the Consent Form, the 42 volunteers were randomly divided into the control group (21), who used only the Photoprot® FPS 100 sunscreen (Biolab, São Paulo, Brazil) throughout the surface of the face, three times a day, according to the manufacturer's instructions; and the phytotherapic group (21), in which patients used sunscreen in combination with the lingonberry phytotherapic (*vaccinium vitis ideae*) for 60 days, the length of the study. At the initial visit, the volunteers were clinically evaluated and submitted to photographic recording of their macules by the non-polarized dermatoscope, Medicam 800 FotoFinder (FotoFinder Systems GmbH, Aichner, Birnbach, Germany). The dermoscopic images were captured with an increase in magnitude of 20x.

The impact of melasma on quality of life was assessed using the MELASQoL (Melasma Quality of Life scale), a Portuguese language version validated by Cestari et al.[15] at the beginning and at the end of the study.

Sixty days after the first photographic record of the macules, the volunteers returned to the dermatology outpatient clinic for the control registry. In this visit, in addition to responding to the MELASQoL questionnaire, the volunteers evaluated the effect of the proposed protocol on the macules using the following parameters: 0 - worsened; 1 - stable; 2 - improved; 3 - improved significantly. The images generated by FotoFinder were evaluated by two dermatology physicians with the same options of responses contained in the evaluations of the volunteers (0 - worsened; 1 - stable; 2 - improved; 3 - improved significantly).[16]

The photographs were analyzed by the Scion Image Software, Version 4.03, (Scion Corporation, MD, USA). The dark areas (melasma) of the photographed skin, as well as the non-pigmented area of the adjacent one, were quantified; followed by the subtraction of the measured values, aiming to eliminate the variation of the intensity in skin color when comparing the macules among the volunteers.[17]

In order to investigate the influence of the study on the quality of life of the volunteers, the responses to the MELASQoL questionnaire, before and after treatment, were analyzed by the paired t-test. For the analyses of the optical densities of the macules, before and after the treatment, in each group and between the groups, the Anova test with Tukey's Post Hoc Analysis was used. The level of statistical significance was set to $p < 0.05$. The program used for data analysis was Prism 6.

RESULTS

All volunteers in the study reported the presence of melasma macules for more than two years. Among the 42 volunteers, 38 (control group: 18, phytotherapic group: 20) completed the study; four left it for personal reasons.

Initial analysis of MELASQoL revealed that 65.79% of patients were uncomfortable with their skin appearance, 55.26% experienced frustration or embarrassment due to their skin condition, 42.11% felt depressed, and 23.68% do not feel attractive. For 34.21% of the volunteers, however, melasma does not impact the relationships they have with other people; for 39.47% it does not affect the desire to be with other people; 26.32% of patients have no difficulty in showing affection; 47.37% do not feel less productive; and for 44.74% of the volunteers, melasma does not affect their sense of freedom (Table 1). The evaluation of the total MELASQoL score indicated no significant change after treatment in the control group ($p = 0.058$); however, a significant reduction was observed in the total MELASQoL score in the phytotherapic group ($p = 0.002$). The average MELASQoL score was 39.5 before treatment and 38.4 after the study in the control group; its value decreased from 40.6 before medical intervention to 33.2 after the use of the phytotherapic in combination with the sunscreen (Table 2).

Table 1: Results of each MELASQoL question at baseline (n = 42)

	Not bothered at all	Not bothered most of the time	Not bothered sometimes	Neutral	Bothered sometimes	Bothered most of the time	Bothered all the time
The appearance of your skin	2.63	-	7.89	2.63	15.79	23.68	26.32
Frustration about your skin	5.26	-	7.89	10.53	23.68	23.68	7.89
Embarrassment about your skin condition	10.53	5.26	10.53	10.53	18.42	13.16	10.53
Feeling depressed due to your skin condition	26.32	2.63	7.89	15.79	7.89	13.16	2.63
The effects of your skin condition on your interaction with other people	23.68	10.53	-	13.16	13.16	10.53	7.89
The effects of your skin condition on your desire to be with people	21.05	15.79	2.63	7.89	13.16	10.53	7.89
Your skin condition makes it difficult to show affection	31.58	5.26	2.63	23.68	13.16	10.53	5.26
The discoloration in the skin makes you feel unattractive to others	15.79	7.89	2.63	23.68	13.16	10.53	5.26
The discoloration in the skin making you feel less vital or productive	28.95	10.53	7.89	10.53	5.26	7.89	5.26
The discoloration in the skin affect your sense of freedom	34.21	5.26	5.26	18.42	7.89	7.89	0

Regarding the evaluation of the efficacy of the treatment, in the opinion of the patients, improvement of melasma was achieved in 33.3% of the volunteers in the control group and in 66.6% of the volunteers in the phytotherapic group. In the evaluation of dermatologist physicians, the treatment showed improvement in 30% of the patients in the control group and in 80% of the patients in the phytotherapic group.

The quantitative analyses of optical density have indicated that the control group had no significant change in pigment density before and after the use of the topical photoprotection; the phytotherapic group, however, presented a significant reduction ($p = 0.01$) in the intensity of pigmentation during the study (Figure 1) (Graph 1).

DISCUSSION

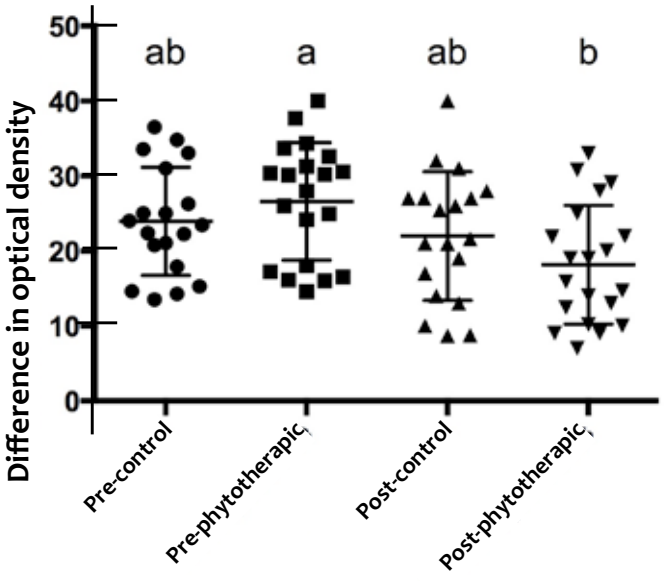
Melasma, due to being a very frequent dermatosis, is extensively investigated and has a large number of publications.[18,19]

The MELASQoL questionnaire, in the Brazilian version, was validated to evaluate the impact of this pathology, allowing for cultural identity to be preserved by using it in national clinical and research practices.[10, 20] In the present study, the average total MELASQoL score was 38.40 ± 10.50, close to the averages found in other Brazilian studies.[20, 21]

Tabela 2: Comparison of total MELASQoL scores before and after the treatment

	Control		Phytotherapic	
	MELASQoL Pre	MELASQoL Post	MELASQoL Pre	MELASQoL Post
N	18	18	19	19
Average	39.5	38.4	40.6	33.2
Median	37.5	36	39	35
Standard deviation	17	17.5	13.8	13.7
Minimum	11	10	18	13
Maximum	69	69	69	60
p-value*	0.058		0.002	

* Paired t-test



Graph 1: Optical density of the hyperpigmented macules photographed with the FotoFinder 800 device, on the face of the volunteers in the control and phytotherapic groups, before and after the study. Significant difference in the optical density marking was detected only in the phytotherapic group, before and after the Anova study $p = 0.001$

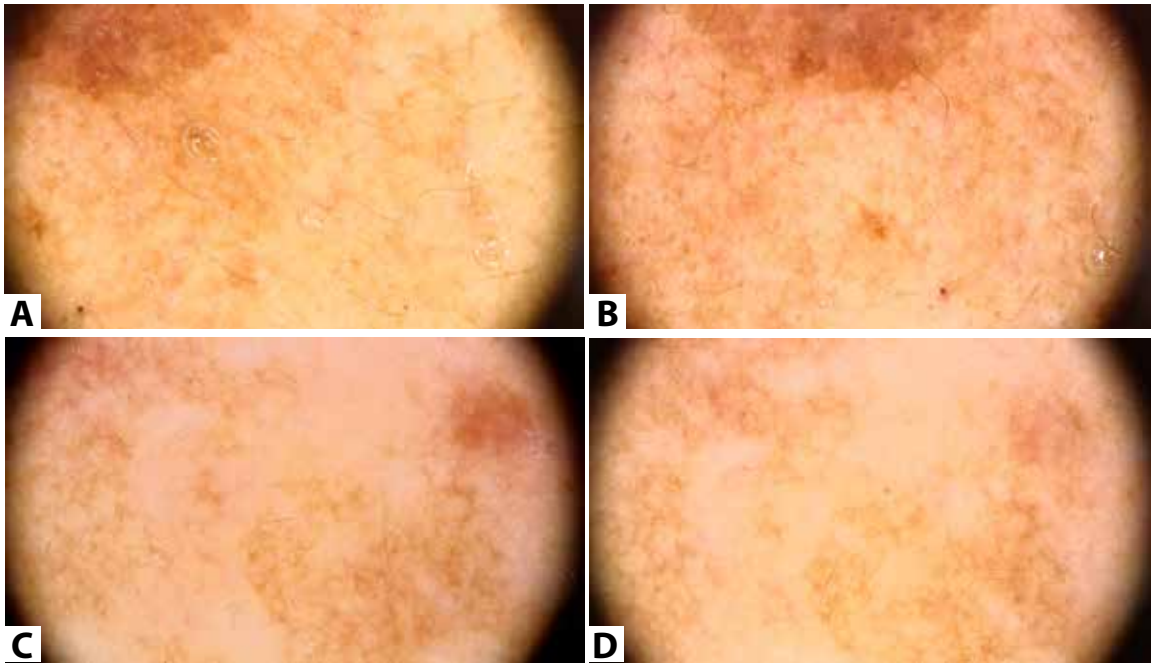


Figure 1: Photographs of melasma, captured with the FotoFinder device. **A)** Volunteer of the control-group before the study; **B)** Volunteer of the control-group after the study; **C)** Volunteer of the phytotherapic group before the study; B) Volunteer of the phytotherapic group after the study

Emotional well-being was the most affected are by melasma; just like in the study conducted by Balkrishnan et al.,[22] social relations were also affected by melasma in our study, being that 66% of the volunteers reported that the macules influenced their sense of freedom, and 70% noticed that their relationships with other people had been affected, which also indicates the high degree of embarrassment generated by the presence of these macules on the face.

The absence of efficient treatment for the control or cure of melasma, as well as its frequent recurrence, still creates numerous lines of research with constant discussions on therapeutic modalities, of great clinical and scientific interest.[23-25]

In the present study, the oral use of the LingonMAX® concentrated nutrition composed of procyanidins, resveratrol and anthocyanidins, with both anti-inflammatory and antioxidant properties, presented great whitening potential of facial melasma according to the quantitative evaluation of the optical density of pigmentation in the photographs. This result is supported by previous studies, which indicated beneficial effects of the active principle in this pathology, although isolatedly.[26,27]

In 2002, Ni et al[28] concluded that oral use of procyanidins (75 mg / day) for 30 days reduced the extent of the area affected by melasma ($P < 0.001$) and average intensity of pigmentation ($P < 0.001$) in Chinese women. The study did not show an adverse reaction to the treatment. In 2004, Shahrir et al[29] conducted a double-blind controlled study with 30 women, in which the consumption of procyanidins (80mg / day) during 30 days resulted in significant improvement of the macules, highlighting the whitening potential of this vegetable compound.

Resveratrol, a polyphenol that can be found mainly in grape seeds, has an important antioxidant activity[30,31] and numerous pharmacological functions – including tyrosinase inhibitory activity, which converts tyrosine into L-3,4-dihydroxyphenylalanine (L-DOPA), and L-DOPA in dopaquinone, through hydroxylation and oxidation reactions, has also been shown to have a positive effect on melasma treatments.[7, 32] Some studies, however, have demonstrated that resveratrol alone does not inhibit melanin synthesis effectively, which increases when it is used in combination with other depigmenting agents.[33]

Despite the lack of scientific publications, anthocyanidins, also called anthocyanins, are natural pigments responsible for a wide variety of colors in fruits, flowers and leaves, ranging from red-orange to purple and blue,[34] also have a depigmenting action. Its natural function is to protect plants and fruits against ultraviolet light (UV), and to avoid the production of free radicals.[35] Thus, because they have antioxidative functions, inhibitory action of the enzyme tyrosinase, anthocyanidins appear to be promising substances in the control of melasma. No adverse effects were observed during the present study, which suggests safety in the oral use of lingonberry extract (*vaccinium vitis*) (100mg / day) as an adjuvant in the control of facial melasma.

CONCLUSION

Controlling melasma often requires alternating depigmenting agents. The results obtained in the present study allow us to conclude that lingonberry extract may be an effective strategy in the control of melasma, also allowing future comparative clinical studies to ratify its efficiency and tolerability.

REFERENCES

1. Costin GE, Hearing VJ. Human skin pigmentation: melanocytes modulate skin color in response to stress. FASEB J. 2007;21(4):976-94.
2. Kasraee B, Safaee Ardekani GH, Parhizgar A, Handjani F, Omrani GR, et al. Safety of topical methimazole for the treatment of melasma. Transdermal absorption, the effect on thyroid function and cutaneous adverse effects. Skin Pharmacol Physiol. 2008;21(6):300-5.
3. Sanchez NP, Pathak MA, Sato S, Fitzpatrick TB, Sanchez JL, Mihm MC Jr. Melasma: a clinical, light microscopic, ultrastructural, and immunofluorescence study. J Am Acad Dermatol. 1981;4(6):698-710.
4. Katsambas AD, Lotti TM. European handbook of dermatological treatments: Springer; 2003.
5. Kang WH, Yoon KH, Lee ES, Kim J, Lee KB, Yim H, et al. Melasma: histopathological characteristics in 56 Korean patients. Br J Dermatol. 2002;146(2):228-37.
6. Handel AC, Miot LD, Miot HA. Melasma: a clinical and epidemiological review. An Bras Dermatol. 2014;89(5):771-82.
7. Miot LDB, Miot HA, Silva MG, Marques MEA. Fisiopatologia do melasma. Anais brasileiros de dermatologia. 2009;84(6):623-35.
8. Sharquie KE, Al-Tikreety MM, Al-Mashhadani SA. Lactic acid chemical peels as a new therapeutic modality in melasma in comparison to Jessner's solution chemical peels. Dermatologic surgery. 2006;32(12):1429-36.
9. Grimes P, Nordlund JJ, Pandya AG, Taylor S, Rendon M, Ortonne J-P. Increasing our understanding of pigmentary disorders. Journal of the American Academy of Dermatology. 2006;54(5):S255-S61.
10. Cestari TF, Balkrishann R, Weber MB, Prati C, Menegon DB, Mazzotti NG, et al. Translation and cultural adaptation to Portuguese of a quality of life questionnaire for patients with melasma. Med Cutan Iber Lat Am. 2006;34(6):270-4.
11. Cestari TF, Hexsel D, Viegas ML, Azulay L, Hassun K, Almeida AR, et al. Validation of a melasma quality of life questionnaire for Brazilian Portuguese language: the MelasQoL-BP study and improvement of QoL of melasma patients after triple combination therapy. Br J Dermatol. 2006;156 (Suppl 1):13-20.

12. Victor FC, Gelber J, Rao B. Melasma: a review. J Cutan Med Surg. 2004;8(2):97-102.
13. Pandya A, Berneburg M, Ortonne JÄ, Picardo M. Guidelines for clinical trials in melasma. British Journal of Dermatology. 2006;156(s1):21-8.
14. Li Y, Dou X, Cheng Q. Lingonberry extract, the preparing method and use thereof. Google Patents; 2009.
15. Cestari TF, Hexsel D, Viegas M, Azulay L, Hassun K, Almeida A, et al. Validation of a melasma quality of life questionnaire for Brazilian Portuguese language: the MelasQoL,ÄêBP study and improvement of QoL of melasma patients after triple combination therapy. British Journal of Dermatology. 2006;156(s1):13-20.
16. Costa A, Moisés TSA, Cordero T, Alves CRT, Marmirori J. Association of emblica, licorice and belides as an alternative to hydroquinone in the clinical treatment of melasma. An Bras Dermatol. 2010;85(5):613-20.
17. Wang HÄ, Chen CÄ, Wen ZÄ. Identifying melanogenesis inhibitors from Cinnamomum subavenium with in vitro and in vivo screening systems by targeting the human tyrosinase. Experimental dermatology. 2011;20(3):242-8.
18. Jadotte YT, Schwartz RA. Melasma: insights and perspectives. Acta Dermatovenerologica Croatica. 2010;18(2):124-9.
19. Chen Z, Chen Y, Zeng J, Wang Y, Ye T, Zhou Q, et al. Quality of randomized controlled trials reporting in the treatment of melasma conducted in China. Trials. 2015;16:156.
20. Freitag FM, Cestari TF, Leopoldo LR, Paludo P, Boza JC. Effect of melasma on quality of life in a sample of women living in southern Brazil. J Eur Acad Dermatol Venereol. 2008;22(6):655-62.
21. Purim KS, Avelar MF. Photoprotection, melasma and quality of life in pregnant women. Rev Bras Ginecol Obstet. 2012;34(5):228-34.
22. Balkrishnan R, McMichael AJ, Camacho FT, Saltzberg F, Housman TS, Grummer S, et al. Development and validation of a health-related quality of life instrument for women with melasma. Br J Dermatol. 2003;149(3):572-7.
23. Ibrahim ZA, Gheida SF, El Maghraby GM, Farag ZE. Evaluation of the efficacy and safety of combinations of hydroquinone, glycolic acid, and hyaluronic acid in the treatment of melasma. J Cosmet Dermatol. 2015;14(2):113-23.
24. Rodrigues M, Pandya AG. Melasma: clinical diagnosis and management options. Australas J Dermatol. 2015;56(3):151-63.
25. Zhong SM, Sun N, Liu HX, Niu YQ, Wu Y. Reduction of facial pigmentation of melasma by topical lignin peroxidase: A novel fast-acting skin-lightening agent. Exp Ther Med. 2015;9(2):341-4.
26. Puupponen-Pimia R, Nohynek L, Hartmann-Schmidlin S, Kahkonen M, Heinonen M, Maatta-Riihinen K, et al. Berry phenolics selectively inhibit the growth of intestinal pathogens. J Appl Microbiol. 2005;98(4):991-1000.
27. Rendon M, Berneburg M, Arellano I, Picardo M. Treatment of melasma. J Am Acad Dermatol. 2006;54(5):S272-S81.
28. Ni Z, Mu Y, Gulati O. Treatment of melasma with Pycnogenol. Phytother Res. 2002;16(6):567-71.
29. Shahrir M, Saadiah S, Sharifah I. The efficacy and safety of French Maritime pine bark extract in the form of MSS Complex Actinosome on melasma. Int Med J. 2004;3(2):130-2.
30. Holthoff JH, Woodling KA, Doerge DR, Burns ST, Hinson JA, Mayeux PR. Resveratrol, a dietary polyphenolic phytoalexin, is a functional scavenger of peroxynitrite. Biochem Pharmacol. 2010;80(8):1260-5.
31. Iuga C, Alvarez-Idaboy JR, Russo N. Antioxidant activity of trans-resveratrol toward hydroxyl and hydroperoxyl radicals: a quantum chemical and computational kinetics study. J Org Chem. 2012;77(8):3868-77.
32. Kim YM, Yun J, Lee CK, Lee H, Min KR, Kim Y. Oxyresveratrol and hydroxystilbene compounds. Inhibitory effect on tyrosinase and mechanism of action. J Biol Chem. 2002;277(18):16340-4.
33. Satooka H, Kubo I. Resveratrol as a k cat type inhibitor for tyrosinase: Potentiated melanogenesis inhibitor. Bioorg Med Chem. 2012;20(2):1090-9.
34. Tosun I, Ustun NS, Tekguler B. Physical and chemical changes during ripening of blackberry fruits. Scientia agricola. 2008;65(1):87-90.
35. Inhibition of lipid peroxidation and the active oxygen radical scavengingeffect of anthocyanin pigments isolated from Phaseolus vulgaris L. Biochem Pharmacol. 1996;52(7):1033-9.

Case Report

Daylight photodynamic therapy: clinical and aesthetic benefit with repeated sessions for facial actinic keratoses

Terapia fotodinâmica com luz do dia: benefício clínico e estético com sessões repetidas para ceratoses actínicas faciais

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ABSTRACT

Daylight photodynamic therapy (daylight-PDT) has been used in the treatment of facial and scalp actinic keratoses (AKs) as an alternative of similar efficacy but with greater tolerance than the conventional form of the procedure (c-PDT). Twelve patients performed 2 sessions of daylight-PDT with 30-day intervals without major adverse events. Improvement of AKs and photorejuvenation were observed. Repeated sessions of daylight-PDT are well tolerated and may increase clinical and aesthetic benefit in patients with face and scalp AKs.

Keywords: Keratosis, Actinic ; Photochemotherapy; Rejuvenation

RESUMO

A terapia fotodinâmica com luz do dia tem sido utilizada no tratamento das ceratoses actínicas de face e de couro cabeludo como alternativa de eficácia semelhante, mas com maior tolerância do que a forma convencional do procedimento. Doze pacientes realizaram duas sessões de terapia fotodinâmica com luz do dia com intervalos de 30 dias sem efeitos adversos importantes. Foi observada melhora das ceratoses actínicas e fotorrejuvenescimento. Sessões repetidas de terapia fotodinâmica com luz do dia são bem toleradas e podem aumentar o benefício clínico e estético em pacientes com ceratoses actínicas de face e de couro cabeludo.

Palavras-chave: *ceratose actínica; fotoquimioterapia; rejuvenescimento*

INTRODUCTION

Conventional Photodynamic Therapy (c-PDT) with methyl aminolevulinate cream and red light irradiation three hours after, has been successfully performed for face and scalp actinic keratoses (AKs), with complete response rates that may reach up to 90% within three months, after one or two sessions. A secondary aesthetic effect could also be observed, with the improvement of pigmentation, erythema, roughness, cutaneous paleness, telangiectasia and wrinkles. However, the painful sensibility and intense local cutaneous reactions following the procedure may limit the indication for new sessions.

Daylight Photodynamic Therapy (DLPDT) consist in a recent therapeutic alternative to the conventional method, with similar efficacy in the treatment of Grade I and II facial and scalp AKs. The absence of painful sensibility and intense local cutaneous reactions following the procedure favor the indication of

repeated sessions of DLPDT, which may be necessary in cases of recurring lesions or in patients who have AKs in greater number or extension. The authors have reported 12 cases of patients who were treated in a private practice and have undergone two DLPDT sessions, with a 30-day interval, and have observed that, in addition to the reduction in the number of AKs, there was an improvement in clinical parameters of photoaged skin.

METHODS

Twelve patients (eight men and four women) with ages ranging between 38 and 91 years, with at least three Grade I and II facial AKs each and signs of cutaneous aging, underwent two DLPDT sessions, 30 days apart from each other. Half of these patients had previously undergone c-PDT, however, they had not undergone any type of cosmetic or laser treatment in the six months preceding the aforementioned therapy.

The sessions took place in a private clinic in the city of Fortaleza, Ceará, Brazil, on days with bright sunlight or with few clouds in the sky, between 7am and 3pm. On the day of the DLPDT procedure, after the facial cleansing with saline solution with gauze, curettage of the facial AKs was performed, followed by the application of FPS50+ chemical sunscreen lotion (Actinica®, Galderma, France) on the face and other exposed regions. Next, approximately 1g of a thin layer of 16% methyl aminolevulinate cream (Metvix®, Galderma, France) was applied throughout the face, followed by exposure to the open air, under the shade for two hours. Following, the methyl aminolevulinate cream was removed and FPS50+ chemical sunscreen lotion was applied, the patient was released and instructed to maintain a rigorous regime of sunscreen application at home. The procedure was repeated after 30 days.

The number of AKs was evaluated clinically and through digital photographs taken before the DLFDT sessions, on the day of the follow-up visit, and 90 days after the first procedure. A AK lesion was defined as a small keratotic, isolated plaque, with adherent scales, well delineated, located in the area of chronic photo exposure. All patients were also similarly evaluated for overall facial photoaging, diffuse pigmentation, fine wrinkles, facial paleness, roughness, erythema and telangiectasias.

RESULTS

All 12 patients have followed through the end of the treatment. During exposure to open air, there was no report of pain nor were observed intense local cutaneous reactions. The most common side effects were mild pruritus and slight erythema on the areas corresponding to the AK lesions that were clinically visible (Figure 1). Regarding the results of the treatment, nine patients were satisfied even before the second session, and none were dissatisfied 90 days after the first session of DLPDT. Satisfaction regarding the clinical improvement of AK lesions and cutaneous rejuvenation were observed in all patients three months after undergoing two sessions of DLPDT, when the authors could observe an improvement in telangiectasias (Figure 2), pigmentation (Figure 3), roughness and erythema (Figure 4), and fine wrinkles (Figure 5).

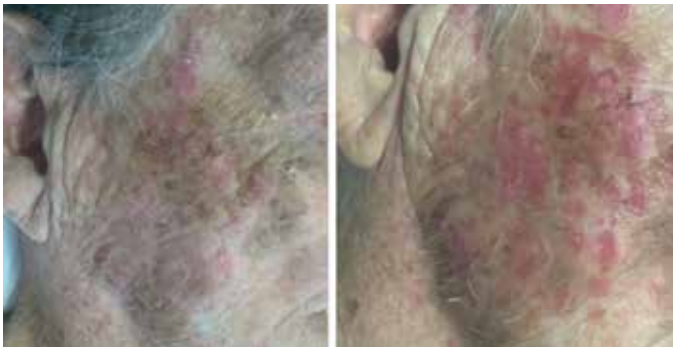

Figure 1: Erythema post-procedure corresponding to clinically visible AK lesions on the right malar region

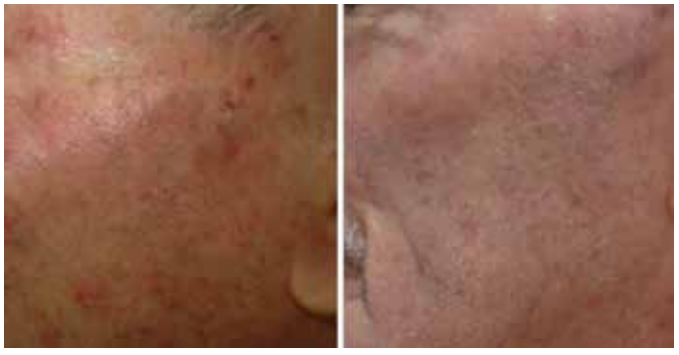

Figure 2: Improvement of telangiectasias

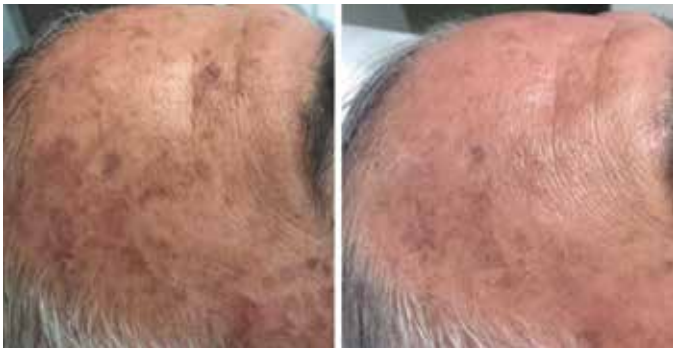

Figure 3: Improvement of AKs and pigmentation after two DLPDT sessions

DISCUSSION

The absence of painful sensitivity and intense local cutaneous reactions in the DLPDT sessions permits that, contrary the conventional form of PDT, the procedure be repeated with greater frequency. Taking into account the chronic and recurring characteristics of the AKs, the possibility of performing a procedure that allows a practically painless treatment of extensive areas of the face and the scalp and still produce secondary aesthetic gain, makes DLPDT a first choice in the treatment of AKs.

The effect regarding aesthetic improvement with c-PDT had already been demonstrated in previous studies. Regarding DLPDT, it was possible to observe that a second session performed after 30 days, aside from having an additional effect in

Figure 4: Improvement of telangiectasias, roughness and facial erythema

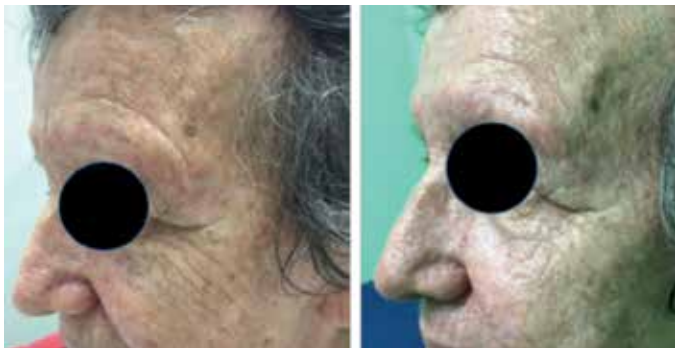

Figure 5: Improvement of fine wrinkles

the treatment of multiple AKs, yielded overall rejuvenation in all patients, thus contributing to the increase in satisfaction about the procedure.

New forms of photodynamic therapy have been performed with microneedling and ablative fractional laser aiming to increase the penetration of the methyl aminolevulinate cream and to improve the efficacy in treating AKs and in rejuvenation. The possibility of repeated sessions of DLPDT may yield a similar effect without the use of laser, LED or any other equipment.

In Brazil, this DLPDT procedure, which can be performed practically throughout the year, allows greater patient compliance by allowing repeated treatments of extensive areas of AKs with minimal discomfort, without disrupting the daily routine of the patient, and with high efficacy and secondary aesthetic gain.

CONCLUSION

Repeated sessions of DLPDT may be performed in such a manner that they are virtually painless and with the added gain of clinical efficacy in patients who have multiple AKs on their face and scalp. Secondary aesthetic gain may also be observed in a more evident manner with at least two sessions of DLPDT, which may be equivalent to the conventional form of PDT, or in combination with ablative methods, however offering the advantage of great tolerance to the procedure.

REFERENCES

1. Szeimies RM1, Karrer S, Radakovic-Fijan S, Tanew A, Calzavara-Pinton PG, Zane C, et al. Photodynamic therapy using topical methyl 5-aminolevulinate compared with cryo therapy for actinic keratosis: a prospective, randomized study. J Am Acad Dermatol. 2002;47(2):258–62.
2. Torezan LA. Estudo da pele do campo cancerizável antes e após a terapia fotodinâmica através dos métodos clínicos, histopatológicos e imunohistoquímicos. São Paulo (SP): Universidade de São Paulo; 2011. 152 p.
3. Braathen LR1, Morton CA, Basset-Seguin N, Bissonnette R, Gerritsen MJ, Gilaberte Y, et al. Photodynamic therapy for skin field cancerization: an international consensus. International Society for Photodynamic Therapy in Dermatology. J Eur Acad Dermatol Venereol. 2012;26(9):1063-6.
4. Rubel DM, Spelman L, Murrell DF, See JA, Hewitt D, Foley P, et al. Daylight photodynamic therapy with methyl aminolevulinate cream as a convenient, similarly effective, nearly painless alternative to conventional photodynamic therapy in actinic keratosis treatment: A randomized controlled trial. Br J Dermatol. 2014;171(5):1164-71.
5. Wiegell SR, Haederdsal M, Philipsen PA, Eriksen P, Enk CD, Wulf HC. Continuous activation of PpIX by daylight is as effective as and less painful than conventional photodynamic therapy for actinic keratoses; a ran- domized, controlled, single-blinded study. Br J Dermatol. 2008;158(4):740-6.
6. Duncan KO, Leffel DJ. Epithelial precancerous lesions. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz S, editors. Fitzpatrick's Dermatology in General Medicine. 6th ed. New York: Mc-Graw-Hill; 2003. p.719-36.
7. Morton CA, Wulf HC, Szeimies RM, Gilaberte Y, Basset-Seguin N, Sotiriou E, et al. Practical approach to the use of daylight photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: A European consensus. J Eur Acad Dermatol Venereol. 2015;29(9):1718-23.
8. ssa MCA, Pineiro-Maceira J, Vieira MTC, Olej B, Mandarim-Lacerda CA, Luiz RR, Azulay MM. Photorejuvenation with topical Methyl aminolevulinate and red light: a randomized, prospective, clinical, histopathologic and morphometric study. Dermatol Surg. 2010;36(1):39-48.
9. Clementoni MT, B-Roscher M, Munavalli GS. Photodynamic photorejuvenation of the face with a combination of microneedling, red light, and broadband pulsed light. Lasers Surg Med. 2010;42(2):150–9.
10. Haedersdal M, Katsnelson J, Sakamoto FH et al. Enhanced uptake and photoactivation of topical methyl aminolevulinate after fractional CO2 laser pretreatment. Lasers Surg Med. 2011; 43(8):804–13.

Case Report

Subungual squamous cell carcinoma: report of five cases and its importance in the differential diagnosis of nail lesions

Carcinoma espinocelular subungueal – relato de cinco casos e sua importância no diagnóstico diferencial das lesões do aparelho ungueal

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ABSTRACT

Subungual squamous cell carcinoma is a rare condition, and its diagnosis is often late. The clinical presentation is atypical and simulates other benign conditions, such as verruca vulgaris, onychomycosis and trauma-induced nail dystrophy. Although it is an unusual entity, we should be attentive to its early diagnosis, considering the biopsy in the chronic nail lesions refractory to treatments. We present five cases of subungual squamous cell carcinoma, in which pain was the most prevalent symptom, and their possible association with trauma and HPV infection should be considered.
Keywords: carcinoma, squamous cell; nails; nail diseases

RESUMO

O carcinoma espinocelular subungueal é condição rara, e seu diagnóstico é muitas vezes tardio. A apresentação clínica é atípica e simula outras condições benignas, como verruga vulgar, onicomicose e distrofia ungueal induzida por trauma. Embora seja entidade incomum, devemos estar atentos ao diagnóstico precoce, considerando a biópsia nas lesões ungueais crônicas refratárias aos tratamentos. Apresentamos cinco casos de carcinoma espinocelular subungueal, em que a dor foi o sintoma mais prevalente, e a possível associação com trauma e infecção por HPV deve ser considerada.
Palavras-chave: *carcinoma de células escamosas; unhas; doenças da unha*

INTRODUCTION

Even though Squamous Cell Carcinoma (SCC) of the nail bed is a rare disease, it is considered the most common subungual malignant tumor.[1] Its diagnosis can be difficult and late due to the fact that its clinical presentation is not specific and may mimic several benign inflammatory conditions.[2,3] Diagnosis can be achieved with proper biopsy, and treatment depends on the tumor's extent. The patients were treated at the Nail Clinic of the Instituto Lauro de Souza Lima (ILSL) in Bauru – SP, Brazil.

Conflict of interests: none

Financial support: none

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This study was performed at the Instituto Lauro de Souza Lima (ILSL), Bauru (SP), Brazil.

CASE REPORTS

Case 1: A 72-year-old male patient, mechanic by profession, complaining of pain in the nail of the fourth finger of the left hand that started three years before. At the examination, it was possible to observe a discreet nail dystrophy in the medial fold, which was associated with erythronychia of the same region (Figure 1A), exulceration and crusts better demonstrated through dermoscopy of the nail bed (Figure 1B), and presence of subungual friable granulation tissue (Figure 1C). In light of the hypothesis of a glomus tumor, longitudinal fusiform biopsy was performed in the nail bed, evidencing a clearly differentiated and invasive SCC (Figure 2). The radiography was normal. Excision of the whole nail apparatus and local grafting (the donor area of which was the skin of the internal region of the ipsilateral wrist) were performed (Figure 1D). The patient progressed with good healing.

Case 2: A 71-year-old male patient, farmer, diabetic, had been having severe pain for two years in the fifth finger of the right, and sporadic subungual purulent secretion. On examination, onycholysis in the medial fold involving 50% of the plate, and an exulcerated area with subungual crusts could be observed (Figure 3). A lateral longitudinal fusiform biopsy of the nail apparatus was performed evidencing moderately differentiated and ulcerated SCC invasion (Figure 4). The radiography detected a fracture of the distal phalanx of the affected finger. Surgical enlargement of the scar area was performed, which resulted only in local fibrosis. The patient was referred for follow-up with the oncologist.

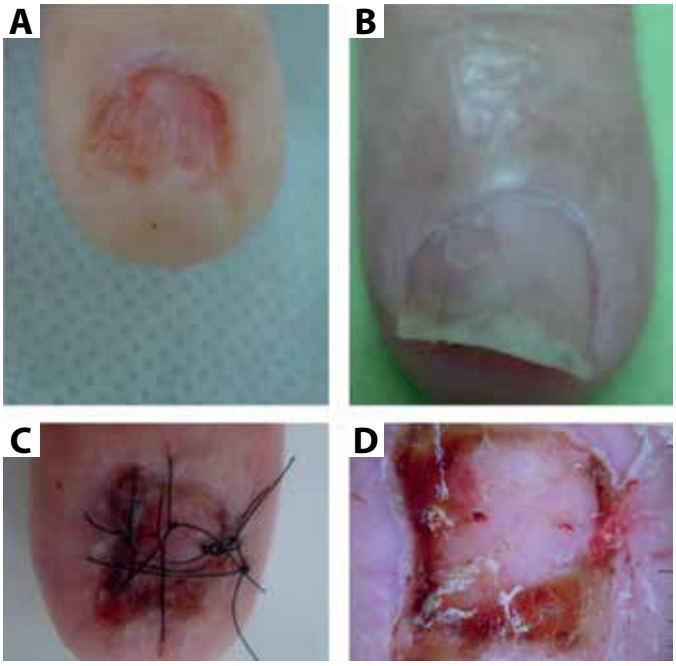


Figure 1: A - Nail dystrophy of the fourth finger in the left hand. **B -** Subungual area of friable ulceration in the medial fold after total excision of the nail plate. **C** – Better visualized by dermoscopy. **D** - After excision of the lesion and total skin graft

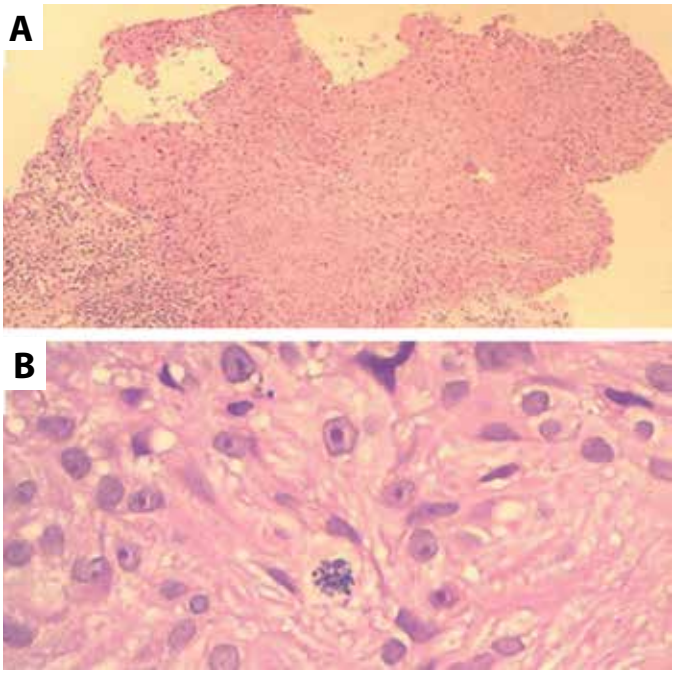
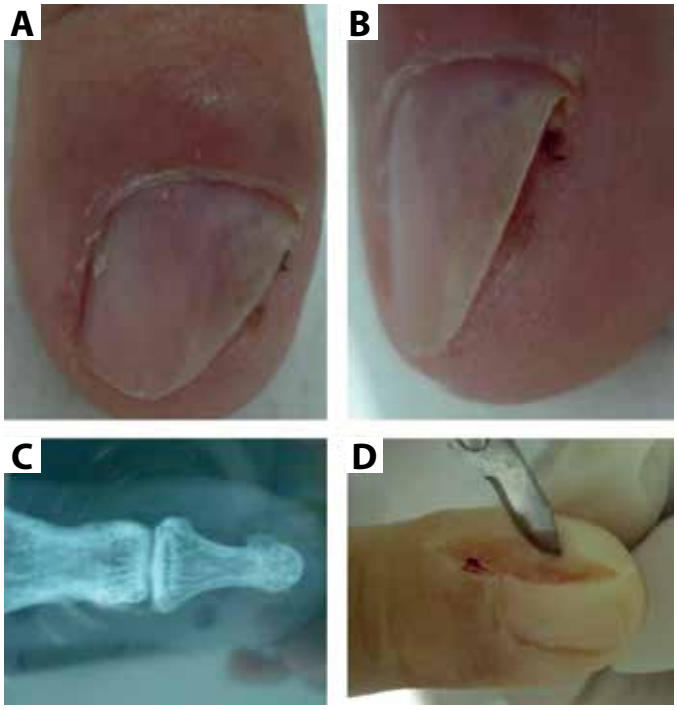


Figure 2 A: HE x2 - Area of ulceration with stratified squamous epithelium with atypia associated with stromal invasion. **B:** HE x40 - Atypical epithelial cells with mitotic figures. Well-differentiated and invasive SCC

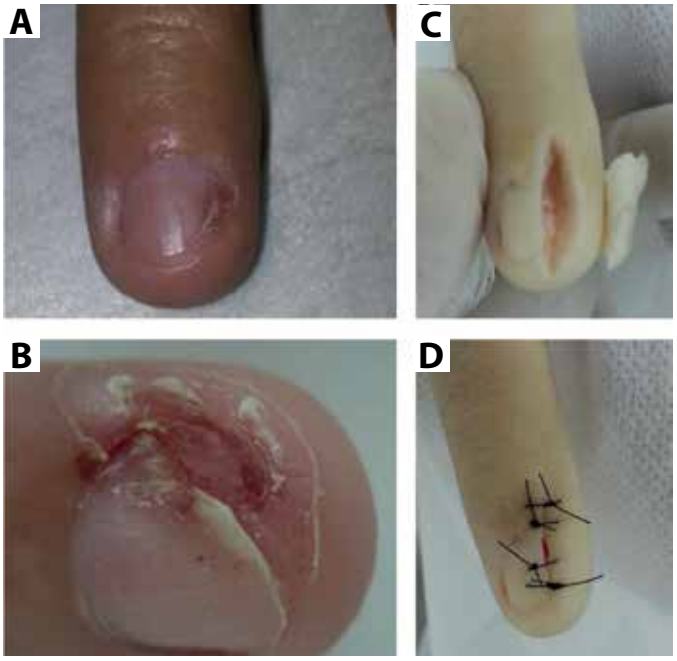
Case 3: A 47-year-old male patient, diagnosed with periungual viral wart in the fourth finger of the right hand, underwent several treatments, such as topical imiquimod therapy and cryotherapy, which yielded unsuccessful results. Upon examination, it was possible to observe onycholysis, exulceration of the medial fold and erythronychia (Figures 5A and B). A longitudinal fusiform biopsy was performed (Figures 5C and D) showing *in situ* SCC (Figure 6). Lesion exeresis was performed successfully, and the patient was followed up in an outpatient clinic.

Case 4: A 75-year-old male patient, retired, does gardening for a hobby, had pain when flexing and extending the distal phalanx of the second finger of the right hand. At the examination, it was possible to observe an ulcerated lesion with infiltrated base in hyponychium (Figures 7A and B). A transversal fusiform excisional biopsy was performed in the distal third of the nail apparatus (Figures 7C and D). The results suggested a moderately differentiated SCC, and free margins (Figures 7E and F).

Case 5: A 67-year-old female patient, retired, with history of nail "mycosis" on the left hallux for the previous 12 years; He reported that several antifungal treatments were unsuccessful. Upon examination, it was possible to observe onycholysis of the distal 2/3 of the nail plate, ulcerated lesion of the distal third of the nail bed, and presence of a fetid secretion (Figure 8A). The transversal fusiform biopsy of the ulcerated area of the nail bed showed *in situ* SCC. The hallux radiography was normal. The proposed treatment was excision of the nail apparatus with implementation of flap and local total skin grafting (Figure



Figures 3: A and **B** - Onycholysis of the medial fold of the fifth finger on the right hand and exulcerated area with subungual crusts. C - X-Ray shows a fracture to the distal phalanx. D - Longitudinal fusiform biopsy of the lesion



Figures 5: A and **B** -Onycholysis, ulceration and erythronychia of the medial fold of the fourth finger in the right hand. **C and D** - Excisional longitudinal fusiform biopsy

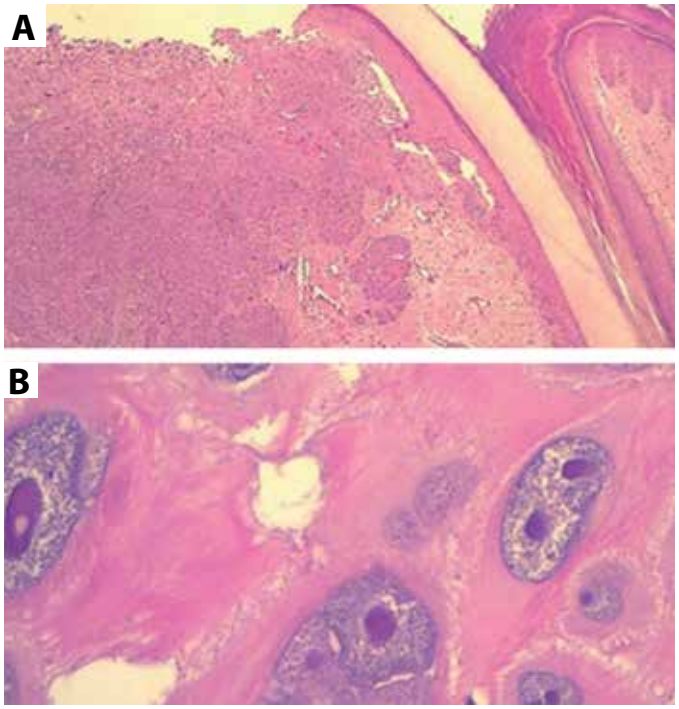


Figure 4: A – HE x2 - Blocks of atypical epithelial cells infiltrating the stroma. **B** - HE x40 – Greater detail of the cell atypia. Moderately differentiated and ulcerated invasive SCC

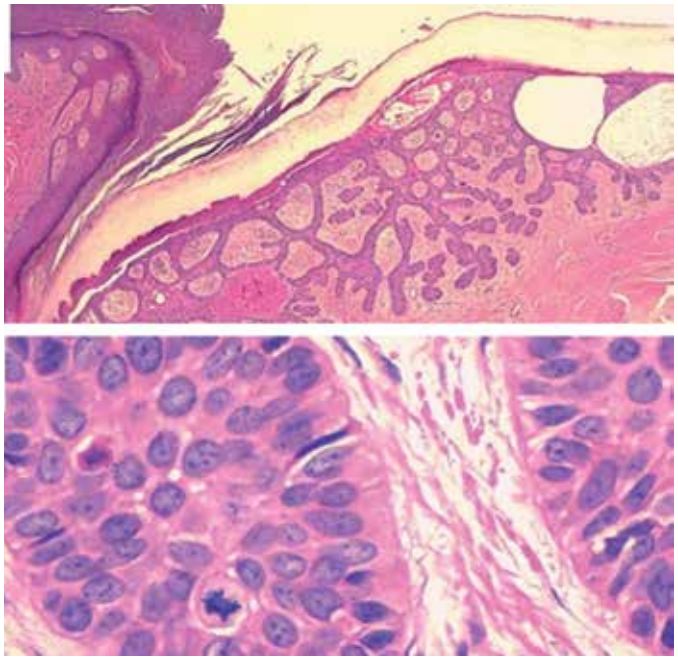
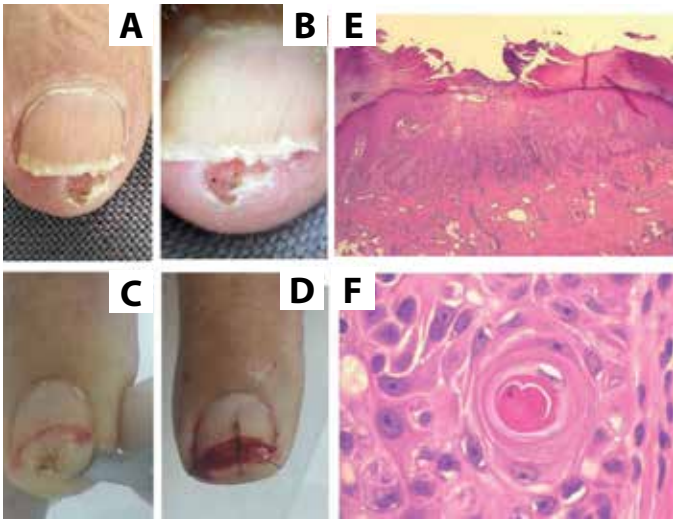


Figure 6: A - HE x2 - Nail bed with carcinomatous epithelial proliferation. B - HE x40 - Blocks of atypical epithelial cells infiltrating the stroma. Moderately differentiated SCC

8B). The histological examination of the excised lesion showed a little differentiated invasive SCC (Figures 8C, D and E). The patient progressed with amputation of the distal hallux phalanx and is being followed up.

DISCUSSION

Although the SCC of the nail bed is rare, it is the most common malignant neoplasm occurring in that body site.[1] The diagnosis is often late due to the rarity of the disease and the



Figures 7: A and **B:** Hyponychium ulceration of the second finger in the right hand and presence of longitudinal striae (senility) with evident filth in the nail plate, alterations related to the farming activity. **C and D** - Excisional transverse fusiform biopsy of the lesion in the distal third of the nail apparatus. **E** HE x2 - Moderately differentiated SCC. **F** - HE x40 – Keratin pearl in detail

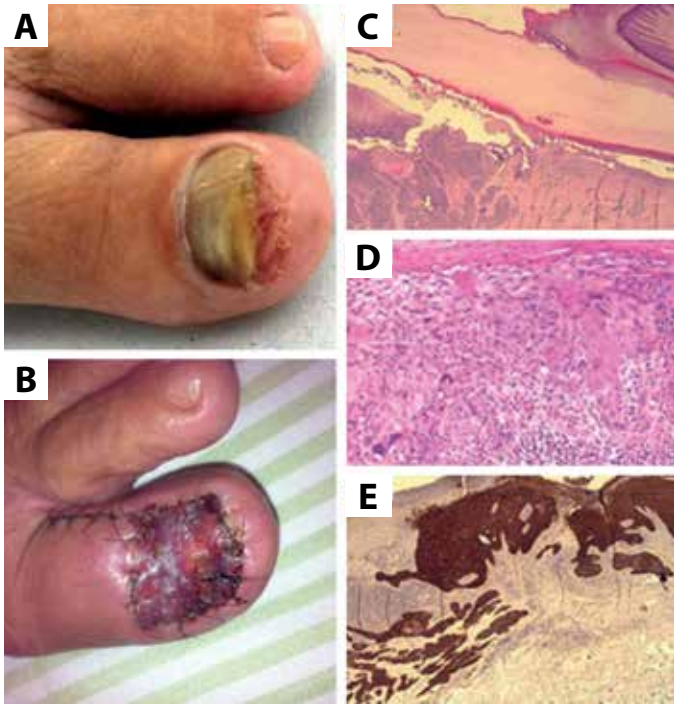


Figure 8: A - Onycholysis of the distal 2/3 of the nail plate, ulcerated lesion of the distal third of the nail bed and presence of fetid secretion. B - On the 12th postoperative day after the excision of the nail and preparation of advancement flap and total skin graft with good development. C and D - HE x2 – Invasive and little differentiated SCC. E - CK5 and 6 immunohistochemistry showing tumor positivity and invasion

lack of knowledge among the professionals.[2] Affected individuals usually are between 50 and 59 years old.[3] Most of the times, it arises as an erythematous, papular, scaly, ulcerated and even vegetative lesion, which can affect the nail bed, lateral folds and distal region of the nail.[4] The initial clinical appearance is mistakenly diagnosed with that of a subungual viral wart (as it was in Case 3), pyogenic granuloma, paronychia, keratoacanthoma, traumatic lesions or other benign conditions.[2, 3, 5] In general, it is possible to observe longitudinal erythronychia, leukonychia, melanonychia, onycholysis and, in rare cases, pain.[2, 3] The data found in the literature contrasts with the findings of the present study, since pain was a symptom present in all patients, with the hypothesis of glomus tumor having been suggested in one case for this reason. Dermoscopy has been an important diagnostic tool in elucidating the etiologies of nail diseases, differentiating lesions of non-melanocytic origin, such as subungual hematoma, bacterial or fungal infections, from melanocytic ones, originating from nevi, racial pigmentation and even melanoma.[6] Many patients have severe photodamaged skin on the back of their hands, nevertheless few develop subungual SCC, which strongly suggests that another factor is involved. Subungual SCC is most commonly observed in the fingernails,[3-5] and this can be explained by much greater exposure to sunlight and a possible role of the Human Papilloma Virus (HPV).[2-4] Human Papilloma Virus infections have been associated with Bowenoid SCC in the hands and subungual region as an important carcinogenic factor.[3, 5] The possibility of digital-genital transmission has been suggested.[3] In one study, HPV DNA was identified in 80% of patients with subungual SCC. Of these, 60% demonstrated a relationship with HPV Type 16.[7, 8] Two of our patients were farmers, meaning that the association with trauma and possible HPV infection could be reported. In the case of the patient who was a mechanic, in addition to the trauma, it is important to investigate the association with frequent exposure to chemical components (greases, oils) as a carcinogenic factor. Subungual SCC appears to have a less aggressive course than it would in other locations.[5] Bone invasion is found in approximately 20% of patients.[6] Metastases and lymph node involvement are atypical, although they have been reported in some cases.[3] Treatment depends on the extent of the tumor.[2-4] In the isolated involvement of the nail bed, a wide local excision is indicated, which usually involves a nail fold, matrix, nail bed and the removal of the periosteum[5] or, even in cases without bone involvement, Mohs Micrographic Surgery, which allows adequate excision with maximum preservation of normal tissue and function.[1, 4] Classical excisional surgery, a technique which was used in the in the studied cases, has led to excellent results in the treatment of lesions without bone involvement, with outcomes similar to

those obtained with Mohs surgery, however with a lower degree of complexity.[4] Reconstruction with local flap is also indicated for limited and superficial lesions, when necessary.[1, 5, 9] For tumors with bone involvement, amputation of the finger is the treatment of choice.[1, 3] Radiotherapy may be used in inoperable or extensive cases, and in those with bone involvement or when there is an indication of decrease in the size of the tumor, with a view to performing a surgery later on. Grootenboers et al. showed that with the use of radiotherapy there was local and permanent control of 92% of the patients, with only one case with severe adverse effect leading to digital amputation. Despite the low incidence of metastases, this neoplasm is still generally treated primarily by amputation.[10]

CONCLUSION

Subungual SCC may resemble other common clinical conditions affecting the nail apparatus, such as onychomycosis, verruca vulgaris and psoriasis. Lesions that are refractory to treatment or of unusual appearance should be offered consideration in the differential diagnosis with SCC. Therefore, if there is suspicion of this diagnosis, it is recommended that x-ray and biopsy of the nail apparatus, which are easy-to-perform, be carried out, allowing for early diagnosis and effective treatment. Long-term follow-up of patients is also important.

REFERENCES

1. Wong TC, Ip FK, Wu WC. Squamous cell carcinoma of the nail bed: Three case reports. J Orthopaedic Surg 2004:12(2):248-52.
2. Baran, R. Bowen's disease and squamous cell carcinoma of the nail unit. J Egypt wom Dermatol Soc. 2005; 2(1):1-8.
3. Dalle S, Depape L, Phan A, Balme B, Ronger-Savle S, Thomas, L. Squamous cell carcinoma of the nail apparatus: clinicopathological study of 35 cases. Br J Dermatol. 2007 156(5):871-4.
4. Pegas, JR, Fernandes, KKML, Prado, IDF, Bazzo, ILMS, Tebcherani, AJ, Cade, KV. Carcinoma espinocelular subungueal: relato de caso e revisão da literatura. Surg Cosmet. Dermatol. 2010; 2 (4) 316-8.
5. Patel PP, Hoppe IC, Bell WR, Lambert WC, Fleegler EJ. Perils of Diagnosis and Detection of Subungual Squamous Cell Carcinoma. Ann Dermatol. 2011; 23(Suppl. 3): s285-7.
6. Yip KM, Lam SL, Shee BW, Shun CT, Yang RS. Subungual squamous cell carcinoma: report of 2 cases. J Formos Med Assoc 2000; 99(8):646-9.
7. Guitart J, Bergfeld WF, Tuthill RJ, Tubbs RR, Zienowicz R, Fleegler EJ. Squamous cell carcinoma of the nail bed: a clinicopathological study of 12 cases. Br J Dermatol. 1990; 123(2):215-22.
8. Zabawski, EJ, Washak RV, Cohen JB, Cockerell CJ, Brown, SM. Squamous Cell Carcinoma of the Nail Bed: Is Finger Predominance Another Clue to Etiology? A Report of 5 Cases. Cutis. 2001;67(1): 59-64.
9. Jules B. Lipoff, AS, Klaus JB, Kishwer SN. Melanonychia Following Mohs Surgery for Recurrent Squamous Cell Carcinoma In Situ of the Nail Bed. J Cutan Med Surg. 2008;12(4): 194-7.
10. Choonhakarn C, Ackerman AB. Keratoacanthomas:a new classification based on morphologic findings and on anatomic site. Dermatopathology: Practical and Conceptual. 2001; 7(1):7-16

Case Report

Periungual pigmented Bowen's disease treated by micrographic surgery

Doença de Bowen pigmentada periungueal tratada por cirurgia micrográfica

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ABSTRACT

We report a case of pigmented Bowen's disease in the periungual region treated with Mohs micrographic surgery. Bowen's disease is a squamous cell carcinoma in situ. Although it is a common condition, the pigmented form is rarer, with periungual localization being even more uncommon. Pigmented Bowen's disease presents clinically as a non-uniform, desquamous or verrucous brownish lesion, and it is often confused with other diseases (pigmented actinic keratosis, seborrheic keratosis, melanoma, basal cell carcinoma, nevus). Dermoscopy is of great diagnostic and therapeutic value and is important in the evaluation of recurrence.

Keywords: Bowen's disease; carcinoma, squamous cell; dermoscopy

RESUMO

Apresenta-se um caso de doença de Bowen pigmentada na região periungueal, tratado com cirurgia micrográfica de Mohs. A doença de Bowen é um de carcinoma espinocelular in situ. Embora seja condição comum, a forma pigmentada é mais rara, sendo a localização periungueal ainda mais incomum. A doença de Bowen pigmentada se apresenta clinicamente como lesão acastanhada não uniforme, de superfície descamativa ou verrucosa, e é frequentemente confundida com outras doenças (queratose actínica pigmentada, queratose seborreica, melanoma, carcinoma basocelular, nevo). A dermatoscopia é de grande utilidade diagnóstica, terapêutica e na avaliação de recorrência.

Palavras-chave: *doença de Bowen; carcinoma de células escamosas; dermoscopia*

INTRODUCTION

Bowen's disease (BD) is a form of Squamous Cell Carcinoma (SCC) *in situ* originally described by John Bowen in 1912. Bowen's disease is currently considered synonymous with SCC *in situ* for lesions located in non-anogenital areas.[1]

The peak incidence of the disease occurs in the seventh decade of life, and most studies show a slight increase of incidence in women.[1]

The most frequent locations of SCC *in situ* are the head and neck (photo exposed areas), followed by the lower limbs, in women. The risk of progression of BD into an invasive form of SCC varies between 3% and 5%.[1]

CASE REPORT

A 67-year-old male patient, Fitzpatrick's phototype III, reported the appearance of a pigmented and asymptomatic lesion, the size of which was increasing at the base of the nail of the third finger of his right hand.

The patient was found to be immunocompetent, having denied the ingestion of arsenic, trauma, burns or exposure to ionizing radiation at the site of the lesion.

He reported a history of nodular basal cell carcinoma in the supralabial region, SCC in the frontal region and lesion with atypical melanocytic proliferation on the abdominal region.

Clinical examination revealed a lesion with brownish pigmentation, with slight desquamation, irregular borders and imprecise limits, located in the distal region of the third finger of the right hand, close to the base of the nail (Figure 1).

The dermoscopy showed the presence of brownish globules, a pigmented network with formation of stretch marks and some punctiform vessels (Figure 2).

The main diagnostic hypothesis raised by the authors was melanoma.

A punch biopsy performed, and the material was sent away for histopathological analysis, which came back with a Pigmented BD diagnosis (Figures 3 and 4).

After confirming the diagnosis, Mohs micrographic surgery was chosen as the course of treatment (Figure 5). Surgery was performed with local anesthetic nerve block. The area of the tumor was removed with minimal margins, positioning the blade at a 45-degree angle. The material was divided into the appropriate number of sections to allow for proper processing, and staining was used to allow for orientation of the material. Tumor free margins were obtained in three steps: in the Step 1, one section was performed; in Step 2, two sections were performed; in Step 3, two sections were performed. The initial lesion size was 7x7mm and the final defect, including the free margins, was 15x9mm. The surgical wound was closed with a graft removed from the right forearm. The nail matrix was fully preserved.

Figure 1: Lesion in the periungual region of the third right finger, with brownish pigmentation, slight scaling, irregular borders and imprecise limits

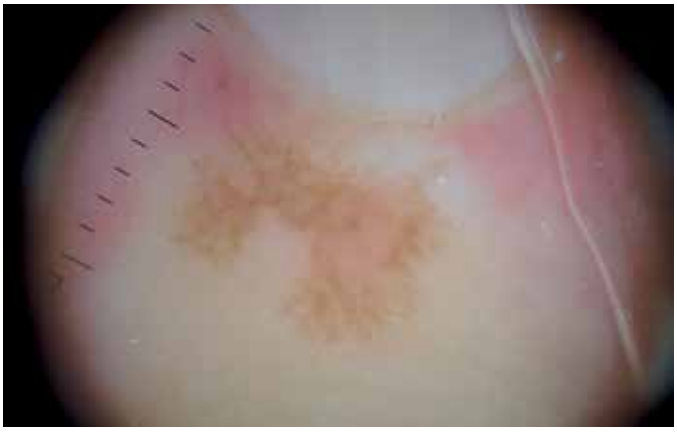

Figure 2: Dermoscopy - a pigmented network was observed, with formation of stretch marks in the periphery and globules

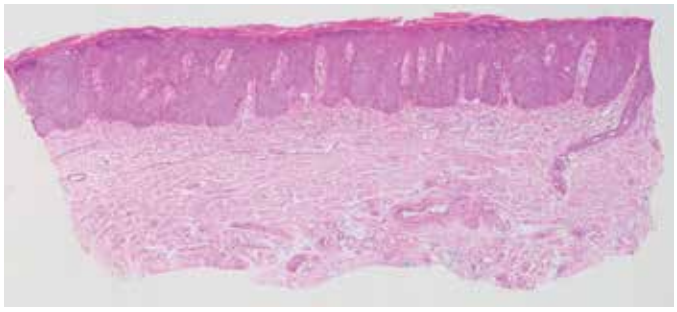

Figure 3: Periungual Bowen's Disease. Hyperkeratosis and acanthosis with elongated and widened epidermal cones. In this panoramic magnification, it is already possible to perceive nuclear stacking and the loss of epithelial polarity. HE, 20x

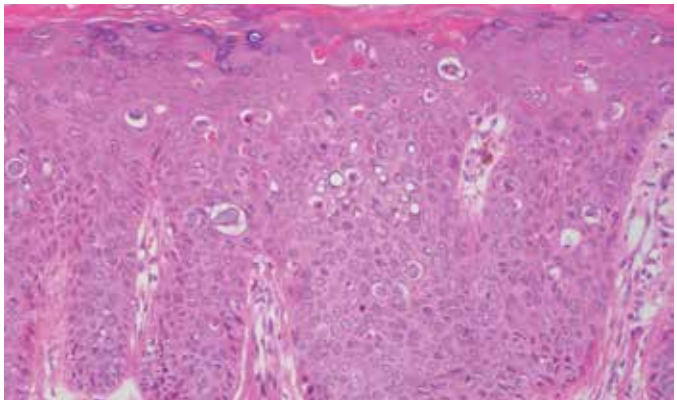

Figure 4: Periungual Bowen's Disease. Proliferation of squamous keratinocytes with pleomorphic nuclei, occupying the entire thickness of the epidermis. Dyskeratotic cells are easily identified. There is discreet melanin pigmentation in the cytoplasm of the basal keratinocytes, which, in association with the elongation of the epidermal cones, results in a reticular dermoscopic pattern. HE, 400x

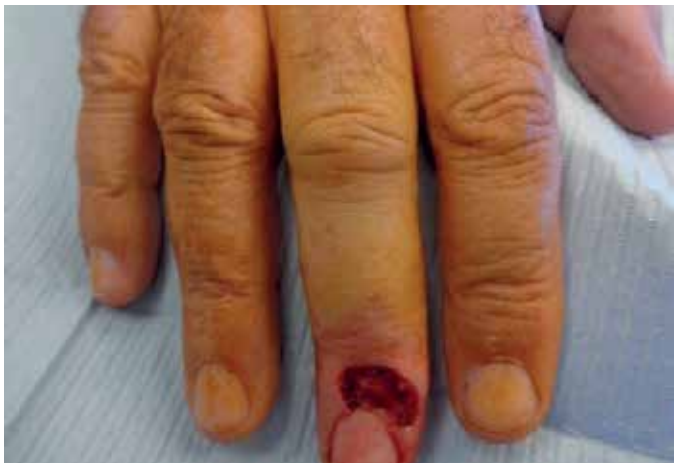

FIGURE 5: Mohs Micrographic Surgery surgical defect

After 18 months of follow-up, the patient did not present a recurrence (Figure 6).

DISCUSSION

Bowen's disease in the periungual region is uncommon and may assume different aspects, simulating melanoma lesions and affecting the nail plate[2] or even resembling chronic paronychia.[3,4]

Dermoscopy may aid in the diagnosis of BD, since the findings of glomerular vessels and desquamative surface are present in most cases.[2,5] However, in the pigmented form, findings of globules, pigmented network and striae are also frequent and cause the diagnosis to be confused with that of melanocytic lesions, leaving the final diagnosis for the histological examination. In the histology, the brown globules may correspond to the presence of melanophages and/or to a small increase in the number of pigmented keratinocytes.[5]

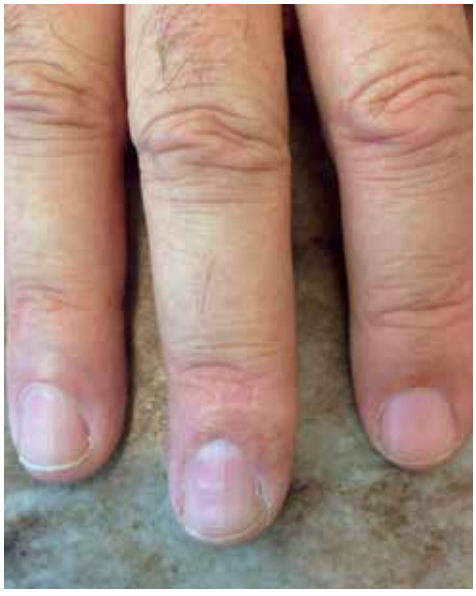

Figure 6: Eighteen months after the surgery, with no evidence of recurrence

The use of dermoscopy in BD is also recommended for evaluation of recurrence after treatment with photodynamic therapy or imiquimod.[6]

Regarding Curettage or Shave Biopsy, Punch Biopsy is the most widely recommended, for it will include the entire thickness of the epidermis and dermis in evaluating if the tumor is invasive or not.[1]

By definition, BD presents in histology the involvement of the entire epidermal layer, characterized by atypical keratinocytes at all levels of the thickened epidermis and also by mitotic figures in the upper layers of the epidermis.[5]

Regarding therapeutics, there are several options described[1] for SCC *in situ* such as the use of 5-Fluorouracil or Imiquimod, Photodynamic Therapy,[7] Radiotherapy, CO_2 Laser, Cryotherapy, conventional Surgical Excision and Mohs Surgery.

The best method for the treatment of SCC *in situ* should be chosen according to the size and location of the lesion, and the clinical condition of the patient.

The periungual region is quite rarely affected, and there are few cases reported in the literature.[9] BD at this location represents a therapeutic challenge due to the risk of causing severe functional disability.

In this case, due to the fact that the lesion was a SCC *in situ* and in the periungual region, the best course of action should take into account the preservation of the motor and sensory function of the finger, yielding the highest probability of cure.

The available treatments were discussed with the patient, thus explaining the risks and benefits of each one of them.

Finally, the authors decided to use Mohs Micrographic Surgery, since this technique, when performed by an experienced surgeon, is capable of yielding high cure rates,[9] and gives the patient the chance to have a lower surgical wound if the tumor does not present extensive impairment. On the other hand, if a common surgical excision was performed, a protocol margin of 5mm would be required, which, in the area of the lesion (distal phalanx of the third finger), would present a higher risk of functional and aesthetic alterations of the finger.

In addition to this, the use of a topical treatment, such as Imiquimod or Photodynamic Therapy, was discussed with the patient and discarded in view of the possibility of recurrence and eventual bone involvement in the future, which could lead to amputation of the distal phalanx.[10]

CONCLUSION

The periungual location of the Pigmented BD represents a diagnostic and therapeutic challenge, even though it is a SCC *in situ*.

In the dermoscopy of the Pigmented BD some findings may lead to the suspicion of melanoma, and only histopathological examination can clarify the diagnosis.

There are several therapeutic possibilities, and the choice of the best treatment depends on the evaluation of the risk of recurrence, the possibility of functional and aesthetic sequelae.

REFERENCES

1. Morton CA, Birnie AJ, Eedy DJ. British Association of Dermatologist´s guidelines for the management of squamous cell carcinoma *in situ* (Bowen´s disease) 2014. Br J Dermatol. 2014;170(2):245-60.
2. Haenssle HA, Blum A, Hofmann-Wellenhof R, Kreusch J, Stolz W, Argenziano G, et al. When all you have is a dermoscope - start looking at the nails. Dermatol Pract Concept. 2014;4(4):2
3. Giacomel J, Lallas A, Zalaudek I, Argenziano G. Periungual Bowen Disease mimicking chronic paronychia and diagnosed by dermoscopy. J Am Acad Dermatol. 2014;71(3):e65-7.
4. Fung V, Sainsbury DC, Seukeran DC, Allison KP. Squamous cell carcinoma of the finger masquerading as paronychia. J Plast Reconstr Aesthet Surg. 2010;63(2):e191-2.
5. Zalaudek I, Argenziano G, Leinweber B, Citarella L, Hofmann-Welenhoff, Malvehy J, R et al. Dermoscopy of Bowen´s disease. Br J Dermatol. 2004;150(6):1112-6.
6. Mun JH, Park JM, Song M, Jwa SW, Kim HS, Ko HC, et al. The use of dermatoscopy to monitor therapeutic response of Bowen disease: a dermatoscopic pathological study. Br J Dermatol. 2012;167(6):1382-5.
7. Zink BS, Valente L, Ortiz B, Caldas A, Jeunon T, Marques-da-Costa J. Periungual Bowen's disease successfully treated with photodynamic therapy. Photodiagnosis Photodyn Ther. 2013;10(4):535-7.
8. Pugliano-Mauro M, Goldman G. Mohs surgery is effective for high-risk cutaneous squamous cell carcinoma. Dermatol Surg. 2010;36(10):1544-53.
9. Singh S, Khaitan BK, Sharma MC, Seenu V, Kumawat M, Chatterjee P. Bowen's disease on finger: A diagnostic and therapeutic challenge. Indian J Dermatol Venereol Leprol 2013;79(2):227-230.
10. Gong HS, Cho JH, Roh YH, Chung MS, Baek GH. Bone invasion by squamous cell carcinoma in situ (Bowen's disease) of the finger during treatment with imiquimod 5% cream: case report. J Hand Surg Am. 2010;35(6):999-1002.

Case Report

Topical immunotherapy in the treatment of alopecia areata: the importance of the maintenance phase - report of two cases

Imunoterapia tópica no tratamento da alopecia areata: a importância da fase de manutenção - relato de dois casos

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Conflict of interests: none

ABSTRACT

Alopecia areata is a relatively common autoimmune condition. It has an unpredictable course and its etiology has not yet been fully elucidated. Its treatment must be individualized, and aims at suppressing the phase of activity of the disease. Thus, many alternatives are available; however, none of them have been curative or preventive so far. We report the cases of two patients, aged 18 and 43 years, diagnosed with alopecia areata, who underwent topical immunotherapy with diphencyprone, and obtained different results. The application procedures, the results obtained and the clinical follow-up are described.

Keywords: therapeutics; immunotherapy; alopecia areata; autoimmune diseases

RESUMO

A alopecia areata é afecção autoimune relativamente comum. Tem curso imprevisível e etiologia ainda não elucidada por completo. Seu tratamento deve ser individualizado, e visa suprimir a fase de atividade da doença. Para tal, estão disponíveis numerosas alternativas, porém, até então, nenhuma delas se mostrou curativa ou preventiva. Relatam-se aqui os casos de duas pacientes, com 18 e 43 anos, com diagnóstico de alopecia areata, submetidas à imunoterapia tópica com difenciprone, tendo obtido resultados díspares. São descritos os procedimentos de aplicação, os resultados obtidos e o seguimento clínico.

Palavras-chave: *terapêutica; imunoterapia; alopecia em áreas; doenças autoimune*

INTRODUCTION

Alopecia Areata (AA) is a systemic, autoimmune condition characterized by loss of hair, without any association with scarring or inflammatory processes.[1] Its course is unpredictable, and the response to treatments is extremely variable.

The worldwide prevalence of AA ranges from 0.1% to 0.2%; 85.5% of cases occur in patients aged up to 40 years. The incidence is equal in both genders; extensive cases, however, are predominant in men.[1, 2] Its etiology remains uncertain; it is known that it is influenced by genetics, autoimmune and environmental factors.

The influence of genetic factors is evident when the incidence in first-degree relatives, the concordance between monozygotic twins, and the genetic linkage analysis are observed. Madani et al. have demonstrated that AA is a polygenic disease of incomplete penetrance.[3] The association of human leukocyte antigens (HLA) with susceptibility to AA (HLA-DRB1 *0401 and DQB1 *0301) has also been noted.[4]

The autoimmune character of the condition is strengthened by the concomitance of AA with other autoimmune disorders and by the therapeutic response to immunosuppressants. Studies have shown that environmental factors can trigger autoimmune aggression; Among them, emotional or physical stress, infections and hormone activity.[4] The corticotrophin releasing hormone and the α-Melanocyte-stimulating hormone stand out; both have increased expression in individuals with AA.[1]

In summary, genetically predisposed individuals, when exposed to environmental factors, develop autoimmune disorders with T-lymphocyte-mediated inflammation against the capillary bulb, generating dysregulation in the follicular cycle.

The diagnosis of this entity is clinical; trichoscopy and anatomopathological examination may help. During the trichoscopy it is possible to find black dots, yellow dots and exclamation mark hairs. In the anatomopathological examination, in the acute phase, there is lymphocytic infiltrate ($CD4^+$ T and $CD8^+$ T) peribulbar in anagen hairs, with a "swarm of bees" aspect. During activity, the CD4 / CD8 ratio is increased and is responsible for maintaining the follicles in the dystrophic state in the anagen phase, leading them into early telogen phase.[1] In the subacute phase, a large number of hairs in the catagen and telogen phases are found, and in the chronic phase the miniaturization of the follicles can be observed. The treatment for AA is aimed at suppressing the activity phase. The options are numerous, although no therapy has proven to be curative or preventative.[3]

CASE REPORTS

Two AA patients with more than 50% of the scalp area compromised, were treated at the Trichology Outpatient Clinic of the Dermatology Service at Celso Piero Hospital, Pontifícia Universidade Católica de Campinas (PUC-Campinas), between December 2012 and June 2015.

Patient 1: 43-year-old female, Caucasian, previously diagnosed with anxiety disorder. She reported progressive hair loss over the previous two years, and denied having undergone any previous treatment.

Patient 2: 18-year-old female, brown-skinned, student; during the first visit, reported progressive capillary loss for one year, and previous use of topical minoxidil, without clear signs of improvement.

After clinical diagnosis, photographic documentation of the lesions and advice regarding the character of the condition and its possible treatment paths, both of them underwent topical diphencyprone (DPCP) immunotherapy.

The authors used DPCP in acetone vehicle, stored in an amber bottle. Available concentrations are: 0.001%, 0.025%, 0.05%, 0.1%, and 2%; the drug was obtained in a compounding pharmacy in the aforementioned dilutions (Figure 1).

The applications were performed on the scalp, with swab soaked in the solution (Figure 2). In all sessions, the patients were instructed to avoid exposure to the sun and keep the substance in place, without contact with water for 48 hours. After this period, it was recommended they removed it under running water.

Figure 1: Presentation of DPCP in acetone vehicle, stored in an amber bottle. Available concentrations are: 0.001%, 0.025%, 0.05%, 0.1% and 2%

Figure 2: Applications performed on the scalp, with swab soaked in the solution

The first application (sensitization) was performed with 2% DPCP, in a 2cm diameter area.[5] After two weeks, adequate response was observed (mild erythema and mild pruritus in the treated area, 36 hours after the application), and weekly applications ipsilateral to the sensitized side begun with 0.001% DPCP. The concentration of the substance was gradually increased during each application (0.001%, 0.025%, 0.05%, 0.1%) up until the patient had a more intense response than the one defined as adequate; at this point, the concentration was established for each of the patients, and the treatment continued with weekly applications.

After the appearance of re-epilation on the side initially treated, bilateral treatment was started.

RESULTS

Patients presented onset of re-epilation after two months of treatment, with an cosmetically acceptable appearance after nine months. Both patients tolerated a maximum concentration of 0.05% and had no side effects.

An excellent response was reached in both cases, however Patient 1, after 11 months of treatment, with almost complete re-epilation, abandoned the follow-up for two months. During that period, she abruptly stopped DPCP applications.

Upon her return, she presented again diffuse capillary loss, and DPCP applications were restarted. However, given the inefficacy of the treatment, other drugs were combined: intralesional 5mg/ml methylprednisolone acetate, 1mg/kg/day prednisone for 60 days and 15mg/week methotrexate for 120 days. Despite these measures, the patient still coursed with progressive capillary loss (Figure 3).

Patient 2 attended regular follow-up sessions without complications. She presented complete re-epilation, and is in a slow and gradual process of drug withdrawal (Figure 4).

DISCUSSION

Alopecia areata is a relatively common condition. It does not pose a threat to life, but it causes psychological stress and impacts on the quality of life.[1]

Its treatment is determined by the patient's age and the condition's degree of involvement.[6] For those over ten years of age, with an area greater than or equal to 50% of the scalp compromised, the first option is topical immunotherapy,[7] whose mechanism of action is not elucidated. It is known that the application of a primary sensitizer causes dermatitis, with consequent deviation of the perifollicular lymphocytes involved in the pathogenesis of AA to the epidermis. This results in the alteration of the perifollicular relationship between $CD4^+$ / $CD8^+$ lymphocytes, causing apoptosis of autoreactive T-lymphocytes, and the modulation of proinflammatory cytokines.[8] There are three primary sensitizers described: dinitrochlorobenzene (DNCB), squaric acid dibutyl ester (SADBE) and diphencyprone (DPCP), the current choice. DNCB is proscribed due to its mutagenic potential, and SADBE, being unstable in acetone, is reserved for patients not responsive to DPCP sensitization.[3]

The use of DPCP in the treatment of AA was described in 1983 by Happle et al.[9] and several studies have proven its efficacy. The most commonly reported side effects are pruritus, moderate local eczema, regional lymphadenopathy, and contact urticaria. Rarely observed are, erythema multiforme, dyschromia and vitiligo.[5, 8, 10]

Response to therapy may occur up to two years after starting the treatment; 59% of patients respond within the first six months, 26% between six months and one year, 10% between one and two years, and 5% after two years.[10] It is, therefore, recommended that treatment not be discontinued before two years.

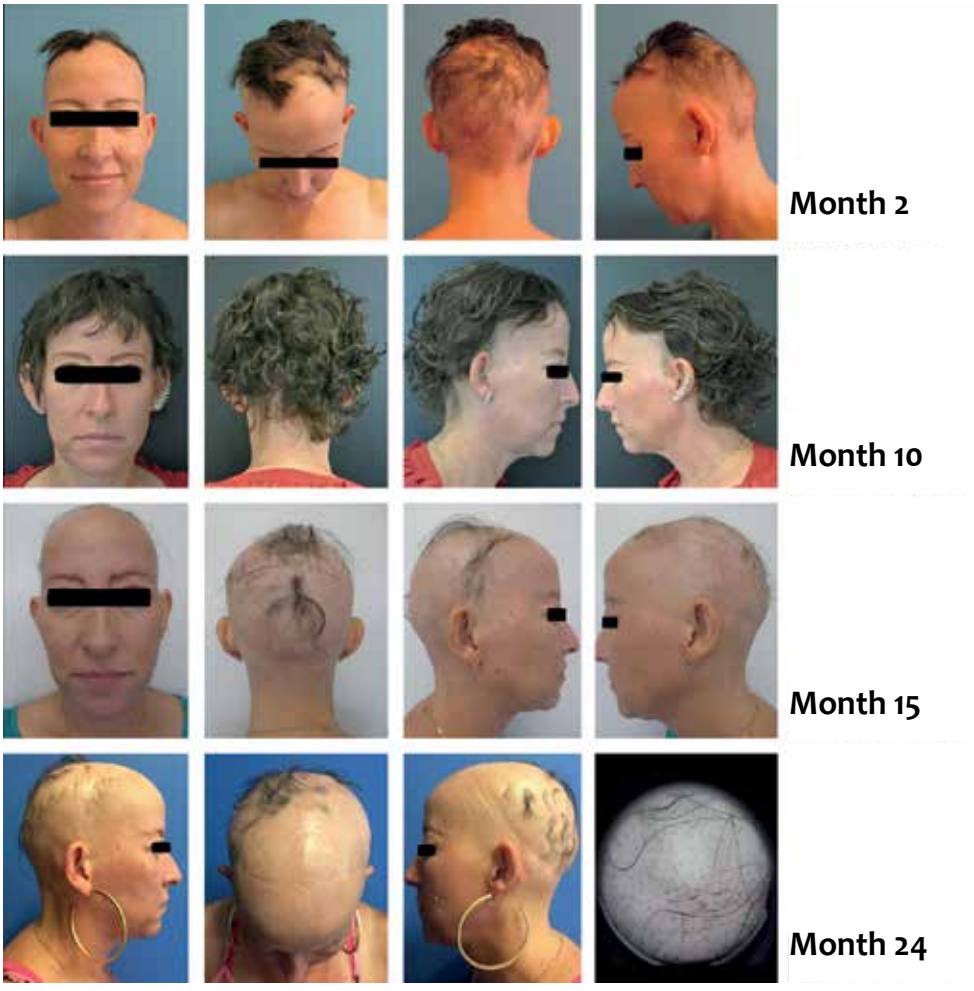

Figure 3: Patient 1's development

Figure 4: Patient 2's development

Data regarding the efficacy of DPCP immunotherapy is variable. The largest clinical trial ever performed showed a total success rate of 60%; however, among those with *Alopecia Totalis* (AT) / *Alopecia Universalis* (AU), this rate was 17.4%. Still in this trial, it was found that 38% of patients with a good response maintained it after 31 months of follow-up, with this being attributed to a slow reduction in concentration, followed by drug discontinuation.[7]

Factors associated with worse response to topical immunotherapy were, early age at disease onset, prolonged time of hair loss, length of illness, personal history of atopy and AA, nail involvement, and other associated autoimmune disorders. The main factor associated with recurrence was abrupt withdrawal from therapy.

REFERENCES

1. Islam N, Leung PSC, Huntley AC, Gershwin ME. The autoimmune basis of alopecia areata: a comprehensive review. Autoimmun Rev. 2015; 14(2):81-9.
2. Lundin M, Chawa S, Sachdev A, Bhanusali D, Seiffert-Sinha K, Sinha A. Gender Differences in Alopecia Areata. J Drugs Dermatol. 2014;13(4):409-13.
3. Madani S, Shapiro J, et al. Alopecia areata update. J Am Acad Dermatol 2000;42(4):549-66.
4. Alzolibani AA. Epidemiologic and genetic characteristics of alopecia areata (part 1). Acta Dermatoven APA 2011; 20(4): 191-8.
5. Donovan J, Salsberg JM. The safety and efficacy of diphencyprone for the treatment of alopecia areata in children. Arch Dermatol. 2012;148(9):1084-5.
6. Messenger AG, McKillop J, Farrant P, McDonagh AJ, Sladden M. British association of dermatologists' guidelines for the management of alopecia areata. Br J Dermatol. 2012; 166 (5):916-26.
7. El-Zawahry BM, Azzam OA, Zaki NS, Abdel-Raheem HM, Bassiouny DA, Khorshied MM. PTPN22 gene polymorphism in Egyptian alopecia areata patients and its impact on response to diphencyprone immunotherapy. Gene. 2013; 523(2):147-51.
8. Durdu M, Özcan D, Baba M, Seçkin D. Efficacy and safety of diphenylcyclopropenone alone or in combination with anthralin in the treatment of chronic extensive alopecia areata: A retrospective case series. J Am Acad Dermatol 2015; 72(4): 640-50.
9. Happle R, Hausen BM, Wiesner-Menzel L. Diphencyprone in the treatment of alopecia areata. Acta Derm Venereol 1983;63(1):49-52.
10. Chiang KS, Mesinkovska NA, Piliang MP, Bergfeld WF. Clinical Efficacy of Diphenylcyclopropenone in Alopecia Areata: Retrospective Data Analysis of 50 Patients. J Investig Dermatol Symp Proc. 2015;17(2):50-5.

Case Report

Use of platelet-rich plasma in the treatment of difficult-to-control alopecia areata

A utilização de plasma rico em plaquetas no tratamento da alopecia areata de difícil controle

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ABSTRACT

Alopecia areata can cause significant psychological problems due to the unpredictable nature of the disease, which results in hair loss. We report the case of a patient presenting alopecia areata of difficult treatment, with satisfactory response after intralesional applications of corticosteroid, but that showed recurrence and atrophy; it was then decided to perform intralesional applications of platelet-rich plasma, with improvement of the condition. The technique showed good results in this isolated case, proving to be a potentially useful therapy in the treatment of alopecia areata.

Keywords: alopecia areata; adrenal cortex hormones; platelet-rich plasma

RESUMO

A alopecia areata pode causar problemas psicológicos significativos devido à natureza imprevisível da doença, que resulta na perda de cabelos e/ou pelos. Relata-se o caso de paciente apresentando alopecia areata de difícil tratamento, com resposta satisfatória após aplicações intralesionais de corticosteroide, mas que apresentou recidiva e atrofia; optou-se então por realizar aplicações intralesionais de plasma rico em plaquetas, com melhora do quadro. A técnica mostrou bom resultado nesse caso isolado, revelando-se terapêutica potencialmente útil no tratamento da alopecia areata.

Palavras-chave: *alopecia em áreas; corticosteroides; plasma rico em plaquetas*

INTRODUCTION

Alopecia Areata (AA) is a chronic inflammatory condition that results in loss of scalp's and/or body hair, affecting up to 2% of the population.[1] Several factors have been implicated in its etiopathogenesis.[2] The clinical picture is characterized by a single or multiple alopecia plaques, and can involve up to 100% of the scalp's and body hair.[2] Diagnosis is clinical, nevertheless dermoscopy and biopsy may be useful as complementary tests. The factors that indicate a worse prognosis are the extension or the ophiasis pattern of the hair loss.

The course of AA is variable. There are many therapeutic options that vary according to the extent of the clinical picture. There are currently two main evidence-based options, which are the glucocorticoids (topical and/or intralesional) and contact immunotherapy.[1]

The purpose of the use of platelet rich plasma (PRP) is to accelerate tissue regeneration, based on the principle of plate-

let influence in the processes of hemostasis, inflammation, regeneration and healing, where the production of platelet-derived growth factors (PDGF) takes place, stimulating cell proliferation and differentiation until the repair and total regeneration of the damaged tissue have ended.[3]

CASE REPORT

A 43-year-old female patient with a history of hair loss with onset one year before presented diffuse plaques of alopecia on the scalp, clinically characteristic of AA (Figure 1). A number of black spots were observed on the dermoscopy under polarized light, evidencing activity of the disease, as well as vellus hair, monilethrix hair, and broken hair (Figure 2).

Also, the patient had a history of gastric bypass surgery (three years before), and two previous episodes of Alopecia Areata, both treated with intralesional corticosteroids.

The laboratorial tests results showed TSH levels to be at 12.3 and Ferritin at 4. After treatment and normalization of the aforementioned parameters, the use of 5% Minoxidil Topical Solution and 10 mg/ml Intralesional Triamcinolone was started. There was an initial positive response, however recurrence and atrophy were observed after three months. Systemic corticosteroid was then introduced, with absence of response. The condition then coursed with progression of the picture in the scalp and involvement of the eyebrow, when a decision was made for introducing intralesional PRP applications, after the patient signed the a Term of Consent. Three applications were performed with three-week intervals. At each session the patient underwent blood tests performed by a responsible biologist; the PRP was then processed at average concentration of 6.5x as compared to the patient's baseline volume, following the procedures described in the Cantadori Protocol (Reg. 508.102 – Rio de Janeiro National Library), in compliance with all the biosafety and asepsis norms.

Injections were performed by a physician with sterile material and 26 G½ needles. A volume of 0.2ml of PRP was applied in the intradermal plane, at each point of the affected region, observing a 2cm spacing.

After the first session, important re-epilation could already be observed, with improvement of atrophy (Figure 3). At the end of the three sessions, it was possible to observe re-epilation of the area in the clinical and dermoscopic exams (Figures 4 and 5).

DISCUSSION

In AA cases, an apparent improvement followed by recurrence can be distressing. One of the most important aspects of the treatment is to advise the patient about the nature of the disease and the limitations of the existing treatments.

Platelet rich plasma is a product derived from laboratory processing of autologous blood, described in the early 1970s by Matras and his team. Currently some areas such as plastic surgery, orthopedics, dentistry, and cardiovascular surgery already use it. In dermatology, PRP has been used with the purpose of promoting the acceleration of wound healing, as an adjuvant in rejuvenation and alopecia treatments, and even after laser sessions.[4]

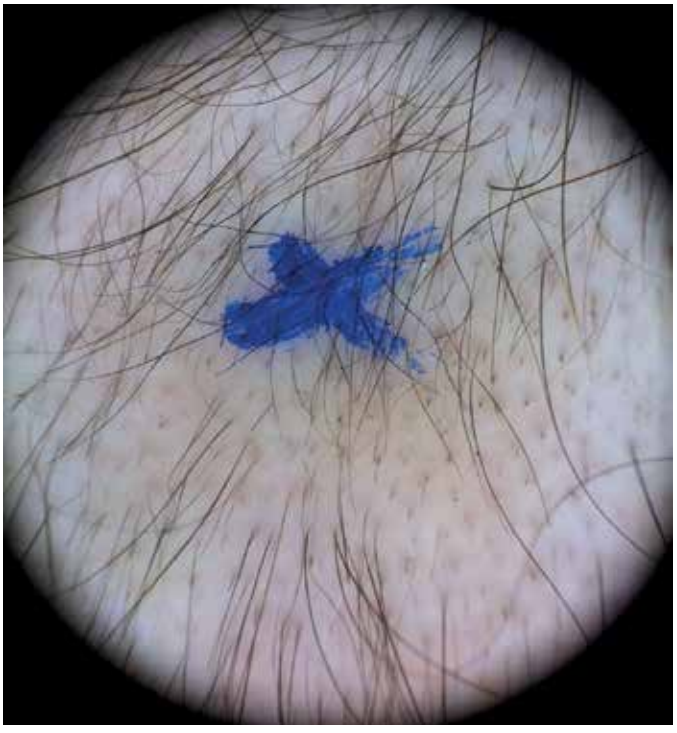

FIGURE 1: Dermoscopy performed under polarized light before the treatment, where it is possible to visualize: several black spots, which demonstrate disease activity, in addition to vellus, monilethrix and broken hairs

FIGURE 2: Dermoscopy performed under polarized light after the treatment, where it is possible to visualize: several vellus and intense re-epilation in the site. Existence of only one tonsured hair in the same area analyzed prior to treatment

FIGURE 3: Diffuse alopecia plaques on the scalp before treatment

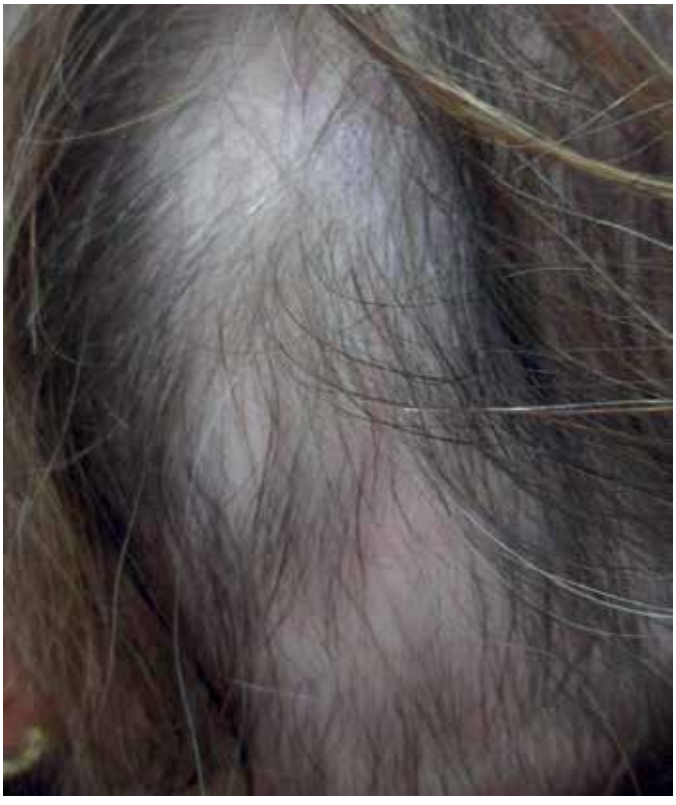

FIGURE 4: After the first session. it was already possible to observe important re-epilation of the areas, as well as improvement of atrophy in the region

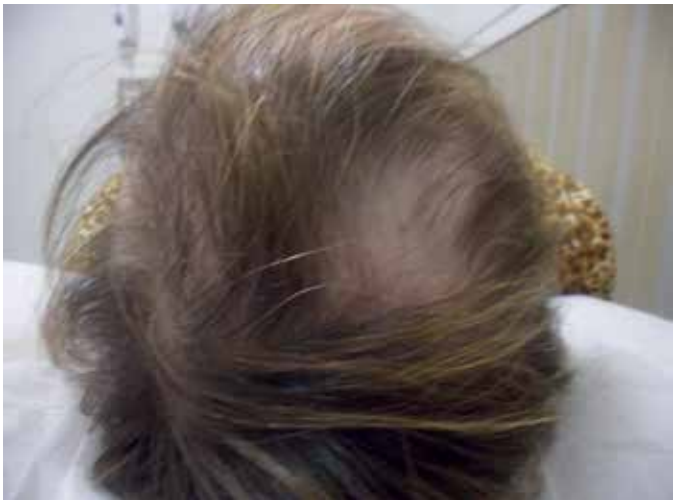

FIGURE 5: Thirty days after the third session

In PRP there is an accumulation of growth factors (GF) due to the concentration of platelets (approximately one million per cubic millimeters of blood). These growth factors are known in the literature as PDGF, transforming growth factor-α (TGF-α), transforming growth factor-α(TGF-α), endothelial cell growth factor (ECGF), in addition to adhesive glycoproteins such as fibronectin and thrombospondin, which are important constituents of the provisional extracellular matrix.[5] Other GFs are also cited by different authors, such as epidermal growth factor (EGF) and insulin-like growth factor (IGF). Monocytes are activated and transformed into macrophages, whose function is to remove damaged components, performing the biological cleansing in the tissue; in addition to phagocytosis, they also secrete chemotactic factors, which attract other inflammatory cells, produce prostaglandins that function as important biological modulators in the maintenance mechanisms of homeostasis, and potent vasodilators that increase the permeability of microvessels.[3] Macrophages still produce many GFs, such as PDGF, TGF-α FGF and VEGF, which stand out as the major cytokines necessary in the formation of granulation.

Many authors cite GFs as modulators of the inflammatory response, as well as their ability to induce the remodeling and healing process in several types of lesions, presenting no harm to the patient.[7]

In his thesis on the application of PRP in hair micrograft surgeries, Mates verified the action of GF in hair growth and density, showing abrupt reduction of apoptosis, stimulation of angiogenesis and new and efficient mitoses for the resumption of the new anagen phase.[8] Another study also cites a cellular marker for proliferation (Ki-67), which is present in greater amounts in PRP-treated patients. In the studied patient, the authors observed improvement of her condition shortly after the first application. The following could be involved in its mechanism of action: the effect of stimulation on the hair follicle, angiogenesis and the modulatory action of the local inflammatory response.

It is also not possible to completely exclude the possibility of spontaneous re-epilation.

In the medical literature, a study of 45 patients with AA demonstrated a significant increase in hair growth in patients treated with PRP, with complete remission in more than half of the cases, and a low rate of recurrence.[9] In another study, 20 patients who had been diagnosed with AA were treated with PRP for one year, with only one recurrence and total absence of side effects.[10]

CONCLUSION

Despite many studies, the treatment of AA in some cases still poses a great challenge. Alopecia areata can cause significant psychological problems due to its unpredictable nature. In this manner, studies that propose new therapeutic options become relevant.

The PRP infiltration technique was proven a promising method for difficult-to-control cases or for those that appear in important areas of atrophy. In the isolated case studied in the present paper, an apparently effective response was observed, nonetheless further studies are necessary to better evaluate the results and elucidate the mechanisms of action.

REFERENCES

1. Garg S, Messenger AG. Alopecia areata: evidence-based treatments. Semin Cutan Med Surg. 2009;28(1):15-8.
2. Alkhalifah A. Alopecia areata update. Dermatol clinics 2013; 31(1): 93-108.
3. Pontual MAB; Magini R. S. Plasma Rico em Plaquetas PRP e fatores de crescimento das pesquisas científicas à Clínica Odontológica. Ed. Santos, SP, 2004
4. Monteiro MR .Plasma rico em plaquetas em dermatologia. Surg Cosmet Dermatol 2013;5(2):155-9.
5. Mendonça RJ, Coutinho-Netto J. Aspectos Celulares da Cicatrização. An Bras Dermatol. 2009; 84 (3): 257-62.
6. Rocha JCT. Terapia Laser, Cicatrização Tecidual e Angiogênese. RBPS 2004;17(1):44-48.
7. Herculano J, Gonçalves JC, Cury VF. Moduladores Biológicos e Fatores de Crescimento na Regeneração Periodontal. PerioNews. 2011; 5(2):151-6.
8. Vasconcelos RCF, Azuaga K, Arenas GCF, Vasconcelos JGF, Borelli NS. A aplicação do plasma rico em plaquetas no tratamento da alopecia androgenética. Surg Cosmet Dermatol 2018;8(2):130-7.
9. Trink A, Sorbellini E, Bezzola P, Rodella L, Rezzani R, Ramot Y, Rinaldi F. A randomized, double-blind, placebo- and active controlled, half head study to evaluate the effects of platelet-rich plasma on alopecia areata. Br J Dermatol. 2013; 169(3): 690-4.
10. 10) Singh S. Role of platelet-rich plasma in chronic alopecia areata: Our centre experience. Indian J Plast Surg. 2015; 48(1): 57- 9.

Case Report

Subungual exostosis: satisfactory aesthetic and functional outcome five years after exeresis

Exostose subungueal: resultado estético e funcional satisfatório cinco anos após a exerese

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ABSTRACT

Case report of a 16-year-old female patient with diagnosis of subungual exostosis in the right hallux with clinical and histopathological diagnosis, submitted to total excision of the lesion and follow-up for five years with excellent aesthetic result.

Keywords: exostoses; bone neoplasms; dermatologic surgical procedures

RESUMO

Relato de caso de paciente do sexo feminino de 16 anos de idade com diagnóstico de exostose subungueal no hálux direito com diagnóstico clínico e histopatológico, submetida a exérese total da lesão e acompanhamento durante cinco anos com excelente resultado estético.

Palavras-chave: *exostose; neoplasias ósseas, procedimentos cirúrgicos dermatológicos*

INTRODUCTION

Subungual exostosis is a benign bone tumor, encapsulated by fibrocartilage, which mainly affects the distal hallux phalange, with a higher occurrence in adolescents and young female adults.[1] Its etiology remains unknown, with a probable association with previous traumas, which would explain its greater occurrence in the first toe. Clinically, it presents as a painful nodule or painful hardened tumor at the distal end that produces lifting and deformity of the nail. Among the differential diagnoses, malignant tumors, viral wart, fibroma, pyogenic granuloma or subungual osteochondroma can be cited. Performing an imaging examination, such as an ultrasound or radiography allows for the visualization of abnormal bone growth with opacity and soft tissue involvement. Histologically, the tumor consists of a trabecular bone nucleus surrounded by a fibrocartilage capsule.[2-4] Treatment is based on surgical removal and follow-up to avoid local recurrences.[5-6]

CASE REPORT

A 16-year-old patient, female, phototype II, presented a painful bone excrescence in the right hallux (Figure 1) during a dermatologic examination. An ultrasound of the preoperative lesion was performed, which elucidated the irregularity of the bone contour of the distal phalanx of the first toe. A complete marginal excision of the lesion was performed with the material that had been submitted for histopathological analysis, which confirmed the diagnosis of bone exostosis (Figures 2 and 3). Five months after surgery (Figure 4) both the radiography and ultrasound were unaltered, showing normal nail plates. During the postoperative period the patient was already saying how satisfied she was by the absence of pain and by the good appearance of the region. After five years, it was possible to observe an excellent aesthetic result, without nail dystrophy and absence of functional impairment of the affected hallux (Figure 5).

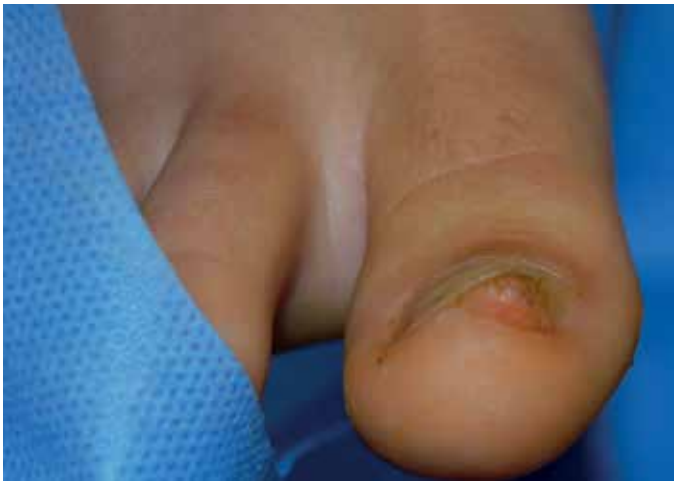

Figure 1: Painful bony protrusion in the right

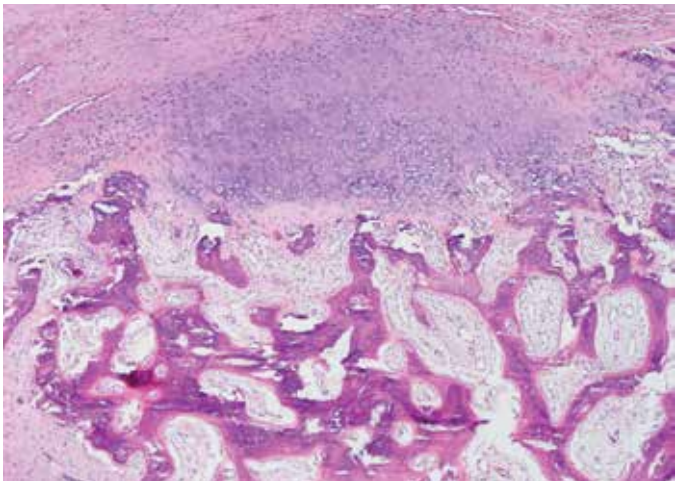

Figure 3: Nail bed presenting a nodular hyperplastic lesion in the reticular chorion, the central area of which consists of osteoid tissue surrounded by hyaline cartilaginous tissue

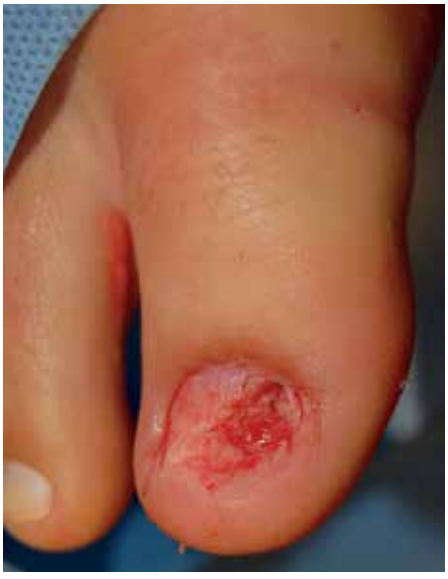

Figure 2: Complete surgical exeresis of subungual exostosis

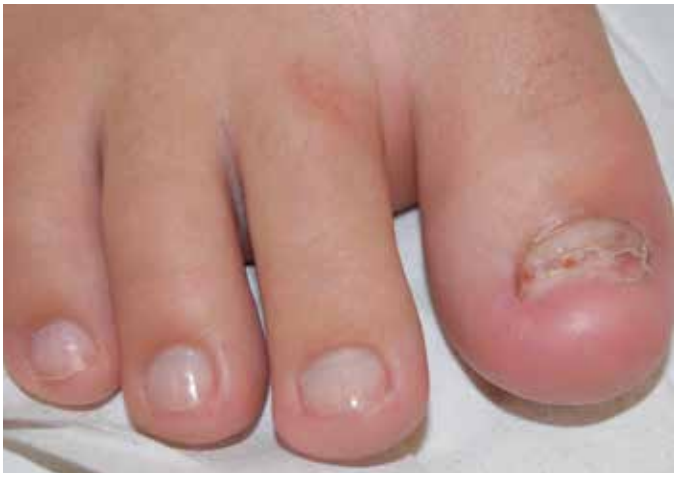

Figure 4: Five months after surgery

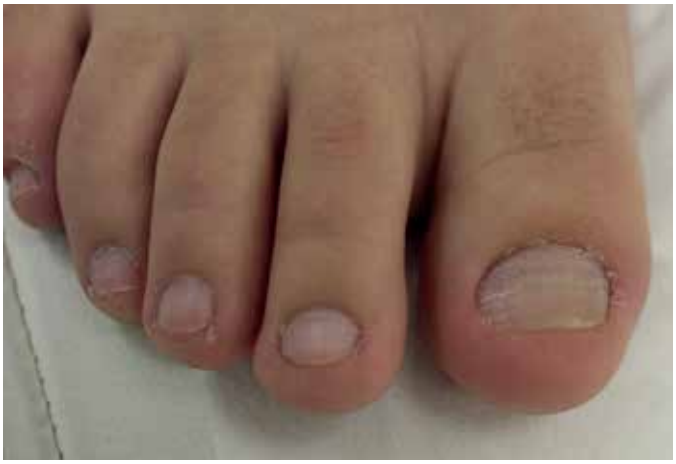

Figure 5: After five years, excellent aesthetic results without nail dystrophy

DISCUSSION

Subungual exostosis is a rare benign tumor, however it represents the bone condition most frequently associated with lesions in the nail, with probable traumatic etiology. The diagnosis is clinical and may be paired with radiography. In the case reported, the patient presented alteration on the distal phalanx with irregularity of the bone contour, characteristic of the disease. Pain is a very common symptom because it is a bone alteration. The presence of this symptom becomes important when considering differential diagnoses, such as malignant tumors, viral wart, fibroma, pyogenic granuloma or subungual osteochondroma.[7] Surgical treatment with the resection of the whole tumor area is the recommended therapy, aiming to minimize damage to the nail bed and ungual matrix, and to avoid onychodystrophy, a common complication of the treatment. The patient in this case, after five years of the exeresis, presented excellent aesthetic result, without nail dystrophy, absence of functional impairment of the affected hallux, and, most importantly, no local recurrence.

REFERENCES

1. Larralde, M; Boggio, P; Abad, ME; Pagotto, B; Castillo, A. Exostosis subungueal en un adolescente de 14 años.Arch Argent Pediatr. 2009;107(4): 349-52.
2. DaCambra MP; Gupta SK; Ferri-de-Barros F. Subungual exostosis of the toes: a systematic review. Clin orthop Relat Res.2014;472(4): 1251-9.
3. Small, O. Exostosis subungueal: a propósito del manejo quirúrgico / Subungueal exostosis: surgical management. Dermatol peru. 2009;19(2): 144-9.
4. Sampaio SAP, Rivitti EA. Onicoses."In": Sampaio SAP, Rivitti EA. Dermatologia. 3ªed. São Paulo: Artes Médicas; 2007. p.441-53.
5. Simon MJ; Pogoda P; Hövelborn F; Krause M; Zustin J; Amling M; Barvencik F. Incidence, histopathologic analysis and distribution of tumours of the hand. BMC Musculoskelet Disord. 2014; 15: 182.
6. Damron TA. Subungual exostosis of the toes: a systematic review. Clin Orthop Relat Res.2014; 472(4):1260-1
7. Valero J; Gallart J; Gonzalez D; Deus J; Lahoz M. Subungual squamous cell carcinoma and exostosis in third toe--case report and literature review. J Eur AcadDermatol Venereol. 2014; 28(10): 1292-7

Case Report

Microneedling in the treatment of atrophic acne scars: case series

Microagulhamento no tratamento de cicatrizes atróficas de acne: série de casos

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ABSTRACT

Acne scars present at the end of the inflammatory phase of acne vulgaris have been treated with procedures that stimulate the production of collagen, such as microneedling. Six patients with acne scars were selected. Microneedling was performed with 2.5 mm needles. Subjective improvement was observed in all patients. In the technique of percutaneous collagen induction there is release of cytokines, growth factors and angiogenesis, with final production of type I collagen, making microneedling an excellent option for the treatment of acne scars, both for its cost/ benefit and for not drawing patients away from their daily activities.

Keywords: acne vulgaris; cicatrix; treatment outcome

RESUMO

Cicatrizes de acne presentes ao fim da fase inflamatória da acne vulgar vêm sendo tratadas com procedimentos que estimulam a produção de colágeno, como o microagulhamento. Foram selecionados seis pacientes que apresentavam cicatrizes de acne. O microagulhamento foi realizado com agulhas de 2,5mm. Observou-se melhora subjetiva em todos os pacientes. Na técnica de indução percutânea de colágeno há liberação de citocinas, fatores de crescimento e angiogênese, com produção final de colágeno tipo I, tornando o microagulhamento excelente opção para o tratamento das cicatrizes de acne, tanto por seu custo/benefício quanto por não afastar o paciente de suas atividades diárias.

Palavras-chave: *acne vulgar; cicatriz; resultado de tratamento*

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INTRODUCTION

Acne vulgaris is one of the most common skin diseases. After the end of the active inflammatory phase, most patients have atrophic scars.[1] Studies have confirmed its psychosocial impact demonstrating a higher incidence of disorders such as introverted personality and depression in patients with severe acne scars,[2] and thus an aesthetic and psychological problem. Ablative procedures aimed at stimulating and remodeling collagen have long been advocated in Dermatology. Currently, there is a trend towards less invasive procedures, aiming at reducing complications and promoting the patient's rapid return to daily activities. Microneedling has been described as a practically painless, simple and minimally invasive technology.[3] It is a good option in this context and it is based on the stimulation of collagen production, without causing total de-epithelialization, which is observed in some ablative techniques.

CASE SERIES

The procedure was performed in six patients (five females and one males). Their ages ranged from 21 to 33 years old, with an average of 26.6 years old. The phototype (Fitzpatrick's classification) in four patients was IV, and in two was III (Table 1). Four of the six patients took isotretinoin orally before the procedure, with a target dose between 120 and 150mg/kg. They underwent microneedling at least six months after the end of the medication. None of the patients presented comorbidities or used any systemic medication. At the physical examination, they presented distensible and non-distensible acne scars distributed mainly in the malar and temporal regions, including some ice-pick scars. There were no inflammatory lesions at the time of the procedure.

Initially, the areas with the highest concentration of scars were demarcated for the procedure. The patients were then submitted to tumescent anesthesia (2% lidocaine 20mL, 20mL distilled water, 0.4mL 1mg/mL adrenaline, 4mL 8.4% sodium bicarbonate). A device with 2.5mm needles was used in multidirectional movements until Auspitz signs were observed. The occlusive dressing was carried out with a combination of clobetasol and neomycin, with an initial change after 24 hours (Figure 1). Reassessments were performed after seven, 30 and 60 days.

All patients reported subjective improvement of the lesions, which was also observed by the medical team. On a visual scale of 1 to 10 (1 being completely dissatisfied and 10 being completely satisfied), all patients were graded above 5. The best outcome was observed for distensible scars, with little difference in the aspect of the ice-pick scars (Figure 2). None of the patients developed infectious intercurrences. The only complication was post-inflammatory hyperchromia, which affected two patients (Table 1). Whitening creams in combination with hydroquinone, corticoid and retinoic acid were used, yielding progressive improvement.

DISCUSSION

Acne scars can result from increased tissue proliferation or tissue loss. Atrophic scars are usually caused by loss of collagen after acne inflammatory process. They can be classified as ice-pick, rolling and boxcar acne scars. There is no standard therapy.[4] There are a range of options, such as peelings, punch techniques, subcision, dermabrasion, cutaneous fillers,[4] that have a low rate of success; and ablative lasers, with a high success rate, however at a high cost and demanding a longer recovery time.

In this context, microneedling emerges as a cost effective technique, with a good response while not demanding patients to keep away from their daily activities. It is a safe procedure that can be performed at the practice without complications.[5]

The Dermaroller device is a cylinder with 192 microneedles (ranging from 0.25 to 3mm in length and with diameters of 0.1mm) that is used only once. It must be firmly pressed and rolled against the skin.[2,6] The needles penetrate the stratum corneum and create microducts that reach the dermis, causing minimal damage to the epidermis, which recovers rapidly.[5,6]

The procedure can be performed with topical anesthesia applied about 45 minutes before, and the Dermaroller should be rolled 15 to 20 times horizontally, vertically and obliquely, under an average vertical pressure estimated around 6N.[7] By applying the device 15 times in the area, approximately 250 holes/cm^2 will be inflicted. The bleeding that occurs is easily controlled. Three or four sessions are required, with intervals ranging from two to six weeks.[6] Erythema may occur for up to two days.[2] The most evident results begin to be observed at between four and

Table 1: Profile of patients who underwent to microneedling

Patient	Gender*	Age (years old)	Phototype	Isotretinoin before the procedure	Complications
C.R.S.	M	21	III	Yes	Absent
A.C.A.	F	24	IV	Yes	Absent
R.P.	F	26	III	Yes	Post-inflammatory hyperchromia
L.C.B.A.	F	26	III	No	Post-inflammatory hyperchromia
M.S.A.	F	30	IV	No	Absent
D.J.S.	F	33	IV	Yes	Absent

*** M** = Male; **F** = Female

Figure 1: Sequence with pre and post-operative photographs of a patient with scars

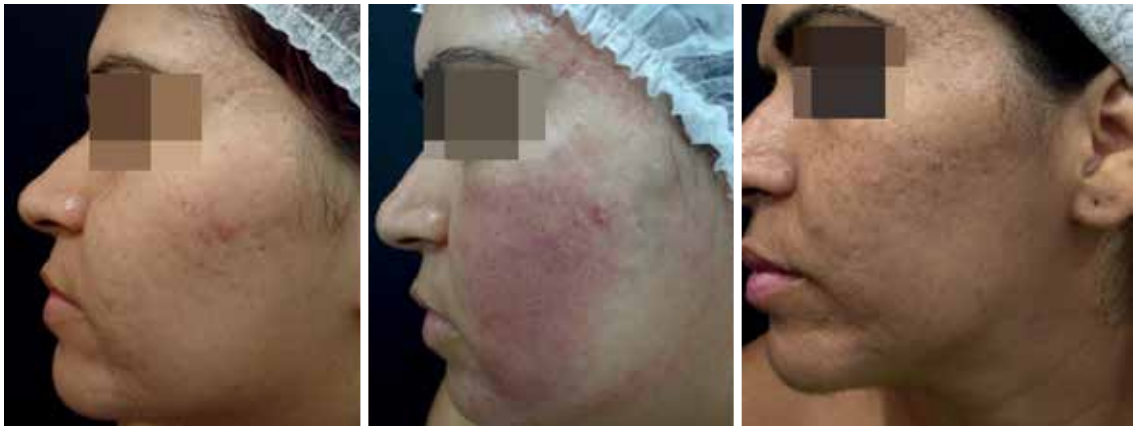

Figure 2: Sequence with pre and post-operative photographs of a patient with scars

six weeks, nevertheless the deposition new collagen is slow and the skin's texture may keep on improving over the 12 following months.[8]

This technique works by trying to create multiple small lesions in the papillary dermis, triggering a cascade of growth factors and cytokine release – mainly Interleukin 1α, 8 and 6, tumor necrosis factor α and granulocytes and macrophages colony stimulation factor – resulting in dermal vasodilation, migration of keratinocytes, neocollagenesis, and neoangiogenesis.[9]

Three phases of the healing process, following the trauma with the needles, can be delineated. During the first one (injury phase), there is the release of platelets and neutrophils responsible for the release of growth factors acting on keratinocytes and fibroblasts, such as the growth and transformation factors α and α (TGF-α and TGF-α), the platelet derived growth factor, connective tissue-activating protein III (CTAP-III), and connective tissue growth factor.[7] In the second phase (healing phase), neutrophils are replaced by monocytes, and angiogenesis, epithelization and fibroblast proliferation occur, followed by the production of type III collagen, elastin, glycosaminoglycans and proteoglycans. At the same time, the fibroblast growth factor, TGF-α and TGF-α are secreted by monocytes. Approximately five days after the injury has been inflicted, the fibronectin matrix is formed, thus allowing the deposition of collagen just below the basal layer of the epidermis. In the third phase (maturation phase), type III collagen, which is predominant in the early stage of the healing process, is slowly replaced by type I collagen – which is more durable, lasting for a period ranging from five to seven years.[7] Microneedling also has the advantage of combining the transdermal delivery of selected drugs, thus optimizing the desired results.[3,5] Chawla et al. carried out a microneedling study with platelet-rich plasma (PRP) and vitamin C, with superiority of

PRP. Fabbrocini et al. also combined PRP with microneedling with a good response.[8]

Garg and Baveja carried out a study that combined the use of subcision, Dermaroller and 15% TCA peel, with the use of topical tretinoin, which led to good results even in acne scars Grades 3 and 4.[4] It is also possible to perform the delivery of energy into the dermis with the association of radiofrequency, which leads to good results when treating scars, hyperhidrosis and rhytides.[10]

CONCLUSION

Microneedling is becoming an excellent option for the treatment of acne scars, with overall improvement of the skin's texture and attenuation of the atrophic scars, presenting good clinical outcomes, without any serious complication after the procedure, in addition to the patient's personal satisfaction.

REFERENCES

1. Liebl H, Kloth LC. Skin cell proliferation stimulated by microneedles. J Am Coll Wound Spec. 2012;4(1):2-6.
2. Majid I. Microneeddling therapy in atrophic facial scars: an objective assessment. J Cutan Aesthet Surg. 2009;21(1):26-30.
3. Kalil CLPV, Frainer RH, Dexheimer LS, Tonoli RE, Boff AL. Estudo comparativo, randomizado e duplo-cego do microagulhamento associado ao drug delivery para rejuvenescimento da pele da região anterior do tórax. Surg Cosmet Dermatol. 2015;7(3):211-6.
4. Garg S, Baveja S. Combination Therapy in the Management of Atrophic Acne Scars. Journal of Cutaneous and Aesthetic Surgery. 2014; 7(1):18-23.
5. Chawla S. Split face comparative study of microneedling with PRP versus microneedling with vitamin C in treating atrophic post acne scars. J Cutan Aesthet Surg. 2014;7:209-12.
6. El-Domyati M, Barakat M, Awad S, Medhat W, El-Fakahan H, Farag H. Microneedling Therapy for Atrophic Acne Scars - An Objective Evaluation. J Clin Aesthet Dermatol. 2015;8(7):36-42.
7. Lima, EVA, Lima, MA, Takano, D. Microagulhamento: estudo experimental e classificação da injúria provocada. Surg Cosmet Dermatol. 2013;5(2):110-4.
8. Fabbrocini G, Annunziata MC, D´Arco V, De Vita V, et al. Acne Scars: pathogenesis, classification and treatment. Dermatol Res Pract. 2010; 2010:893080.
9. Bal SM, Caussian J, Pavel S, Bouwstra J A. In vivo assessment of safety of microneedle arrays in human skin. Eur J Pharm Sci. 2008;35(3):193-202.
10. Kim ST, Lee KH, Sim HJ, Suh KS, Jang MS. Treatment of acne vulgaris with fractional radiofrequency microneedling. J Dermatol. 2014;41(7): 586-91.

Case Report

Reconstruction of two defects on the face close to each other: reports of two cases

Reconstrução de dois defeitos na face próximos entre si: relatos de dois casos

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ABSTRACT

Basal cell carcinoma corresponds to the majority of malignant cutaneous malignancies in Brazil, predominating in middle-aged white individuals, mainly affecting the upper two-thirds of the face and occurring due to several etiological factors. The ideal treatment consists of complete removal with free lesion margins. For better functional and aesthetic results, reconstruction of the surgical wound with flaps or grafts may be necessary. Two types of reconstruction are described in patients with double surgical defects on the face, close to each other: one with a single rotation flap and another with a double rotation flap, also called Yin-Yang.

Keywords: skin neoplasms; carcinoma, basal cell; surgical flaps

RESUMO

O carcinoma basocelular corresponde à maioria das neoplasias cutâneas malignas no Brasil, predominando nos indivíduos brancos de meia-idade, atingindo principalmente os dois terços superiores da face e ocorrendo devido a vários fatores etiológicos. O tratamento ideal consiste na remoção completa com margens livres de lesão. Para melhor resultado funcional e estético, pode ser necessária a reconstrução da ferida operatória com retalhos ou enxertos. Descrevem-se dois tipos de reconstrução em pacientes portadores de duplos defeitos cirúrgicos na face, próximos entre si: um com retalho de rotação simples e outro com retalho de dupla rotação, também chamado Yin-Yang.

Palavras-chave: *neoplasias cutâneas; carcinoma basocelular; retalhos cirúrgicos*

INTRODUCTION

Basal Cell Carcinoma (BCC) accounts for 70% of [all] malignant skin neoplasms in Brazil, mainly affecting middle-aged white individuals.[1] BCC preferably affects the upper two thirds of the face (60 [to] 80%), and its main etiology is attributed to exposure to ultraviolet radiation. Other risk factors were taken into account, to be inclusive of personal and family history of skin cancer, immunosuppression, exposure to fluorescent radiation, smoking, radiotherapy, PUVA Therapy and exposure to arsenic, coal tar and organophosphorus compounds.[1] Despite its low mortality rate (0.05% to 0.08%), once the diagnosis of the lesion has been defined by anatomopathological examination, appropriate treatment must be established, because recurrent BCC or late treatment thereof presents high rates of therapeutic failure. The ideal treatment consists in a complete removal of the lesion with free margins. For a better functional and aesthetic result, the reconstruction of the surgical wound or grafts may be needed. There are two types of

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reconstruction, which are recommended for patients with surgical defects that are bilateral or close to each other. resulting from the removal of BCCs. A simple rotation flap was used on the first patient and a dual rotation flap, also known as "yin-yang rotation flap" was used on the second patient.

CASE REPORT 1

A 53-year-old female patient, Phototype III, originally from *Impirá, Bahia* (NE of Brazil), with positive personal history of skin cancer. The dermatological examination indicated the presence of two asymptomatic lesions for two years, one measuring 3cm on the right supraorbital region, and another measuring 1cm on the right temporal region. During the dermoscopy, it was possible to observe absence of pigmentary network, ulcerations, maple leaf-like lesions and arboriform telangiectasias. Incisional biopsy was performed in the lesions, confirming BCCs via the anatomopathological study. The exeresis was designed to have 4mm margins, marked by dermoscopy (Figure 1A). For the closure, a simple rotation flap was performed, with the secondary defect being approximated by primary suture (Figure 1B). The patient showed good progression during the immediate (Figure 1C) and late post-operative (Figure 1D). The anatomopathological exam for both lesions confirmed the free margins.

CASE REPORT #2

An 85-year-old male patient, Phototype II, originally from *Campinas, São Paulo* (SE of Brazil), with a current personal history of skin cancer. During the dermatological examination, two asymptomatic lesions (with onset three years before) were observed, one measuring 1cm on the right malar region, and another measuring 0.8cm on the right zygomatic region. During the dermoscopy of both lesions, arboriform telangiectasias, ovoid nests and white amorphous areas were evidenced. Incisional biopsy was performed in the lesions, confirming BCCs via the anatomopathological study. Both lesions were removed during the same surgery, with 4mm margins, after pre-operative marking by dermoscopy (Figure 2A). During the procedure, the defects were closed using the healthy skin in between them, with two rotation flaps, thus constituting a double rotation flap, whose is similar in shape to the Chinese "yin-yang" symbol (Figure 2B). The patient showed good progression during the immediate (Figure 1C) and late post-operative (Figure 1D). Following the exeresis, the anatomopathological exam for both lesions confirmed free margins.

DISCUSSION

The proximity of both surgical defects offers a reconstructive challenge, mainly due to the primary closure.[2,3] Therefore, in cases like these, a decision is made to use skin flaps or grafts is many times made aiming at achieving better aesthetic and functional outcomes.[4] Grafts are skin fragments removed from donor areas and transferred to the surgical wound, from whence new blood supply is obtained. They may be classified according to 1) their composition, as: full-thickness, split-thickness or composite skin graft; 2) the genetic origin of the graft's tissue: as autologous, allogeneic, isogeneic, and xenogeneic; 3) its shape, as: stamp skin graft, mesh skin graft or chip skin graft. The most common complications in the use of grafts are the hematomas. Flaps are skin and subcutaneous segments with their own vascular bed, adjacent to the surgical wound, and used to fill it when primary closure of the edges is not possible. The donor region should contain excess skin with enough mobility to reach the receiver area without excessive traction or vascular distress to the pedicle. They are classified under several criteria: advance-

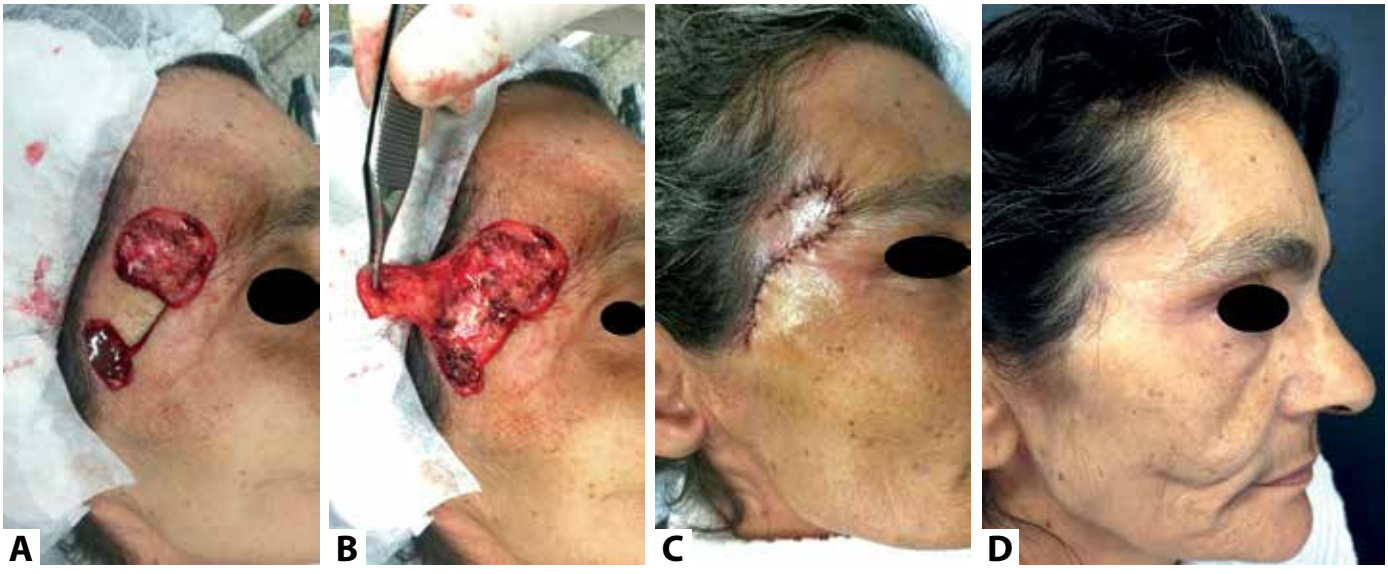

Figure 1: A) Exeresis of BCCs located close to each other, in the right supraorbital region and in the right temporal region; **B)** Simple rotation flap covering two facial defects; **C)** Immediate post-operative of simple rotation flap covering two facial defects; **D)** Late post-operative of simple rotation flap covering two facial defects

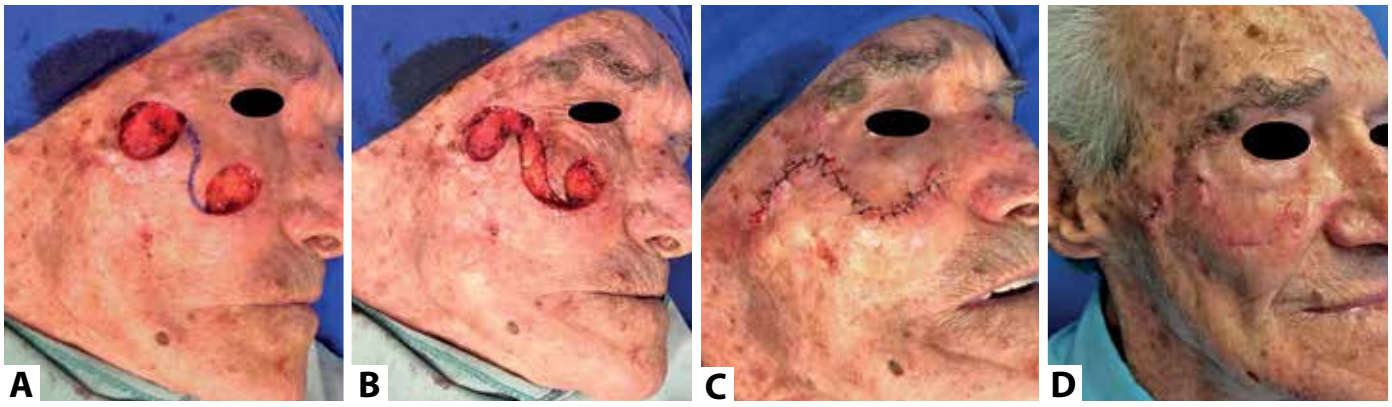

Figure 2: A) Exeresis of BCCs located close each other, in the right malar region and in the right zygomatic region; **B)** Double rotation flap, also known as "yin-yang"; **C)** Immediate post-operative of "yin-yang" rotation flap covering two facial defects; **D)** Late post-operative of "yin-yang" rotation flap covering two facial defects

ment, rotation or transposition (regarding the main movement); arterial or random (depending on blood supply to the flap); and rhomboid (Limberg), bilobed and others (regarding the shape). The most common complications are necrosis and infection.[5, 6] Reconstruction of nearby surgical defects on the face varies significantly depending on the location and distensibility of adjacent tissue.[3, 7] The defects of the aforementioned surgical cases were reconstructed by simple and dual rotation flaps, used to repair large tissue losses or entire aesthetic units. The movement of the flap for the surgical defect was basically that of rotation, creating, thus, a secondary defect adjacent to the first, as demonstrated in Case 1, which was approximated by a primary suture. As for the double skin flap (Case 2), also known as "yin-yang", a curved line is drawn by joining the lower portion of the first defect to the upper portion of the second, creating a figure similar to that of the Chinese "yin-yang" symbol, followed by a double rotation.[8] It was necessary to remove two small compensation triangles, superior to the medial defect and inferior to the lateral defect.[9]

The dual "yin-yang" rotation flap has already been used for the closure of major face defects, in combination with the Mustardé flap, leading to excellent results in a series of nine cases.[10] It has also been applied for surgical closure in the sacral region, by using two trapeze-shaped flaps with a subcutaneous pedicle.

In both surgical cases aforementioned, the execution of skin flaps progressed without any complications, both with favorable aesthetic and functional outcomes.

CONCLUSION

Flaps are preferably used due to preservation of skin color, texture and thickness, in addition to the facts that they avoid the formation of a secondary surgical wound, which emerges when a graft is harvested. Several techniques are described for the closures of facial defects nevertheless, there are few that focus on the simultaneous closure of wounds located close to each other. The proximity of two defects means a surgical challenge in the management of the lesion's closure, bearing in mind that the aesthetic and functional outcomes are of paramount importance.

REFERENCES

1. Chinem VP, Miot HA. Epidemiology of basal cell carcinoma. An Bras Dermatol. 2011;86(2):292-305.
2. Mureau MAM, Hofer SOP. Maximizing results in reconstruction of cheek defects. Clin Plastic Surg. 2009;36(3):461-76.
3. Comparin C, Filho GH, Freitas CAF. Reconstrução complexa de hemiface direita: o desafio de dois carcinomas basocelulares. XXVI Cong Brasileiro de Cirurgia Dermatológica - Porto Alegre, 2014.
4. Bernstein G, Senkarik M. Surgical Anatomy of the skin. Connecticut: Appleton & Lange; 1988. p.217-22.
5. Baker SR. Retalhos locais em reconstrução facial. Rio de Janeiro: Di Livros; 2009. p.585-603.
6. Kopke LFF. Retalhos. In: Kadunc B, Palermo E, Addor F, Metsavaht L, Rabello L, Mattos R, et al. Tratado de Cirurgia Dermatológica, Cosmiatria e Laser da Sociedade Brasileira de Dermatologia. Rio de Janeiro: Elsevier; 2012. 56:724-9.
7. Dobratz EJ, Hilger PA. Cheek defects. Facial Plast Surg Clin North Am. 2009;17(3):455-67.
8. Behan FC, Rozen WM, Tan S. Yin-Yang flaps: the mathematics of two Keys toneis land flaps for reconstructing increasingly large defects. ANZ J Surg. 2011;81(7-8):574-5.
9. Boggio P, Gattoni M, Zanetta R, Leigheb G. Burow's triangle advancement flaps for excision of two closely approximated skin lesions. Dermatol Surg. 1999;25(8):622-5.
10. Belmahi A, Oufkir A, Bron T, Ouezzani S. Reconstruction of cheek skin defects by the 'Yin-Yang' rotation of the Mustarde´ flap and the temporo parietal scalp. J Plast Reconstr Aesthet Surg. 2009;62(4):506-9.

Case Report

Cutaneous metastasis as the first manifestation of squamous cell carcinoma of the esophagus: case report and literature review

Metástase cutânea como primeira manifestação de carcinoma espinocelular de esôfago – relato de caso e revisão de literatura

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ABSTRACT

Cutaneous metastases of internal malignancy are rare, and their incidence ranges from 0.7 to 9% among all cancers. They account for 2% of all skin tumors. They occur due to the growth of cancer cells in the dermis or subcutaneous cellular tissue, originating from internal neoplasia. Cutaneous metastasis arising from squamous cell carcinoma of the esophagus is rare, accounting for less than 1% of cases. We report a case of squamous cell carcinoma of the esophagus diagnosed after metastatic cutaneous manifestation in the abdomen that evolved to death due to disseminated metastatic tumor invasion.

Keywords: carcinoma, squamous cell; skin seoplasms; neoplasm metastasis

RESUMO

As metástases cutâneas de malignidade interna são raras, e sua incidência varia de 0,7 a 9% entre todos os casos de câncer. Representam 2% de todos os tumores da pele. Ocorrem devido ao crescimento de células cancerígenas na derme ou tecido celular subcutâneo, originadas de neoplasia interna. A metástase cutânea originada de carcinoma espinocelular esofágico é rara, e representa menos de 1% dos casos. Relata-se um caso de carcinoma espinocelular de esôfago diagnosticado após manifestação cutânea metastática em abdômen que evoluiu para êxito letal devido à invasão tumoral metastática disseminada.

Palavras-chave: *carcinoma de células escamosas; neoplasias cutâneas; metástase neoplásica*

INTRODUCTION

Esophagus cancer is an extremely lethal neoplasm, with most patients diagnosed with local tumor invasion or distant metastasis. Cutaneous metastases of internal malignancy are rare, and their incidence has varied between 0.7% in a series of 865 autopsies reported by McWhorter and Cloud, to 9% in another study with 7,518 cases reported by Spencer and Helm; in a previous evaluation of five comprehensive studies, Rosen demonstrated a global incidence of approximately 2%.[1] In a 2003 meta-analysis, 1,080 cases were found to have cutaneous metastasis out of 20,380 cases of cancer patients, implying an incidence of 5.3%. Melanoma, leukemia and lymphoma cases were excluded.[1] In the same study it was observed that the tumor with greatest incidence of cutaneous metastasis was the breast adeno-

carcinoma, which was found in 24% of the cases.[1] Cutaneous metastasis occur due the growth of cancer cells on the dermis or subcutaneous cell tissue, originating from internal neoplasms, and may happen due to hematogenous, lymphatic, or contiguous dissemination, and, in rare cases, iatrogenic implantation.[2,3] Neoplasms with lymphatic dissemination, such as that of the breast, commonly lead to regional cutaneous metastases, and cancers of the lung and colon lead to distant hematogenous cutaneous metastasis.[2] According to a meta-analysis, the most common location are the thorax (28.4% of cases), followed by the abdomen (20.2% of cases).[1] Cutaneous metastases are classified as synchronous and metachronous, depending on the time elapsed between diagnosis of the primary site and its emergece.[2] Synchronous metastases occur when the they are diagnosed simultaneously with the primary tumor; and metachronous ones, when they develop months or years after the appearance of the primary cancer. Most cases of cutaneous metastases are metachronous, and in 0.5% of the cases they are the first sign of the primary neoplasm.[2] They may arise in various appearances: sclerodermiform, alopecia, zosteriform, inflammatory, telangiectasia, cicatricial, pseudomyxomatous, among others.[3,4] The most common form is the nodular one, which appears as painless, round or oval, and firm nodules.[3] These nodules may arise singly or in sets and, in this last case, they occur in different anatomical sites. The histological examination of the lesions allows that the diagnosis be directed to the origin of the primary site.[2,3] Epidermoid carcinoma is associated with tumors of the lung, the esophagus and the oral cavity.[3] When cutaneous metastasis has an unknown origin, immunohistochemical markers can be requested.[3] Some studies have shown that half of the patients with cutaneous metastases die within the first six months of diagnosis.[3] Cutaneous metastases in esophageal squamous cell carcinoma are rare and represent less than 1% of all cases.[4] The authors of the present study report a rare case of synchronous cutaneous metastasis in the abdomen originating from esophageal squamous cell carcinoma, which aided to direct the diagnosis of the primary site.

CASE REPORT

A 59-year-old male patient, smoker (50 packs/year) and former alcoholic, sought help at the Dermatology Service of the Instituto Lauro de Souza Lima, in Bauru (São Paulo, Brazil), reporting the appearance of nodules on his abdomen two months before. He also reported a gradual loss of weight of 5kg, dysphagia and anorexia during this period. During the physical examination, it was observed that the abdomen was depressed with a 6cm tumor, pedunculated, friable and oval on the surface of the right flank, and another 1cm erythematous and oval nodule on the left flank (Figure 1); Bilateral inguinal lymph node enlargement was also observed, ranging from 1cm to 3cm, with hardened lymph nodes adhered to deep planes. A biopsy was performed, and an abdomen ultrasound, chest x-ray, tumor markers and general tests were requested. The examinations showed: squamous cell carcinoma (SCC) in both lesions, evidenced in the anatomopathological examination (Figure 2), GGT = 383, ALP = 494, AST = 60, ALT = 21, total bilirubin of 5.17 (direct 2.32, and indirect 2.85), CA 15-3 = 101U/ml, Ferritin = 798, Serum Iron = 18, ESR = 109, HGB = 10.5 and chest x-ray with diffuse and small circular opacities in both hemithoraxes (Figure 3). The patient progressed with significant dysphagia, and a nasoenteral tube was implemented, which did not progress. Endoscopy was then performed, which revealed an exophytic mass that needed to be investigated. It was then hypothesized the presence of an esophageal SCC with cutaneous, pulmonary and hepatic metastases, with the patient passing away in a short period of time.

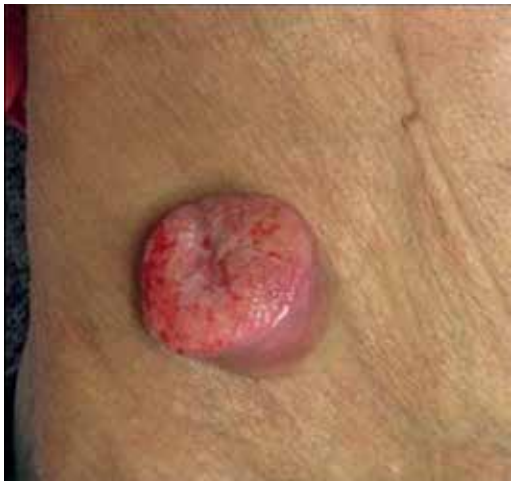

Figure 1: Round, 6cm, pedunculated, friable tumor on the surface of the right flank

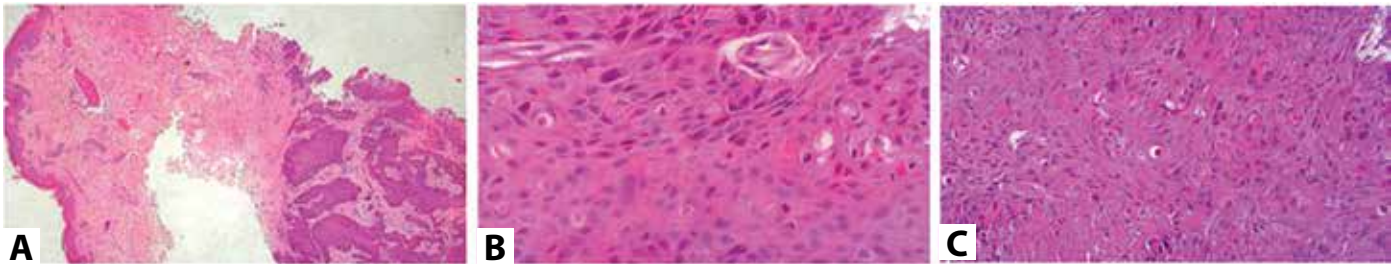

Figure 2: **A.** 30x magnification, HE. Tumor is deeply embedded, mass of spinous cells occupying the entire subcutaneous tissue; **B.** 400x magnification, HE. Presence of atypical cells, dyskeratoses and mitotic figures; **C.** 100x magnification, HE. Atypical cells, necrosis and dyskeratosis

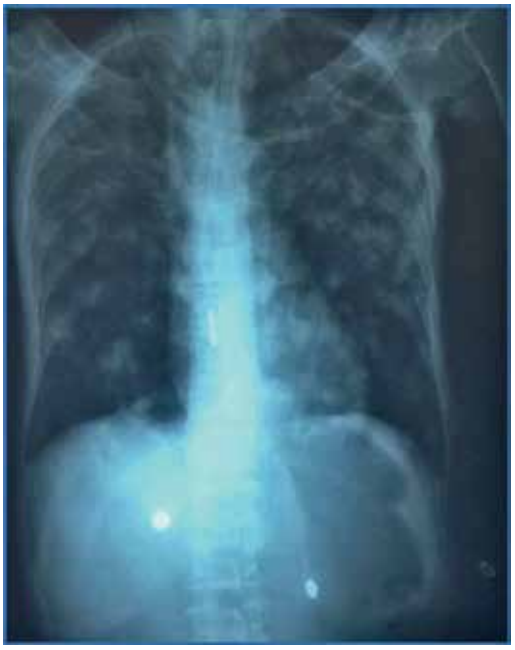

Figure 3: Thorax x-ray showing small, diffuse, oval-shaped images on both hemithoraxes. Nasoenteral probe impacted in the distal third due to the presence of an exophytic mass

DISCUSSION

Esophageal cancer is an extremely lethal neoplasm with an insidious onset, leading to progressive and late obstruction. Most patients are diagnosed based on a local or metastatic tumor invasion, being no longer able to undergo curative treatment. The cutaneous metastases originating from the esophageal tumor represent less than 1% in their totality, and appear only in 1% of all patients with metastatic esophageal carcinoma. In the case reported, the authors observed a rare type of cutaneous metastasis, which preceded the diagnosis of the primary tumor, thus highlighting the importance of the knowledge that the dermatologist must have in all different forms of this entity.

REFERENCES

1. Krathen RA, Orengo IF, Rosen T. Cutaneous metastasis: a meta-analysis of data. South Med J. 2003;96(2):164-7.
2. Azcune R, Spelta MG, Moya J, Lado Jurjo ML, Fontana,MI, Barbarulo AM, et al. Metástasis cutáneas de carcinomas internos, nuestra experiencia a propósito de 94 casos. Dermatol Argent 2009; 15:117-24.
3. Casimiro LM, Corell JJV. Metástasis cutáneas de neoplasias internas. Med Cutan Iber Lat Am. 2009;37(3):117-129.
4. Baijal, Rajiv, et al. "Cutaneous metastasis in esophageal squamous cell carcinoma." Indian J Med Paediatr Oncol. 2013; 34(1): 42–3.

Case Report

Clear cell hidradenoma: atypical presentation on the scalp

Hidradenoma de células claras: apresentação atípica no couro cabeludo

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ABSTRACT

Nodular hidradenoma is a benign adnexal neoplasia. Recently a subdivision in two groups has been suggested: tumors with eccrine differentiation or poroid hidradenoma and tumors with apocrine differentiation or clear cell hidradenoma. They present as well delimited dermal nodule, with a variable dimension between 0.5 and 3 cm, asymptomatic, slow growing and endophytic. Histopathology shows typical biphasic cell pattern, with polyhedral cells with eosinophilic cytoplasm and large cells with abundant clear cytoplasm and small nucleus. Malignant transformation is rare. We report a case of clear cell hidradenoma with unusual clinical characteristics and a review of the literature.

Keywords: Neoplasms, adnexal and skin appendage; skin neoplasms; acrospiroma; surgical flaps

RESUMO

Hidradenoma nodular é neoplasia anexial benigna. Recentemente foi sugerida subdivisão em dois grupos: tumores com diferenciação écrina ou hidradenoma poroide e tumores com diferenciação apócrina ou hidradenoma de células claras. Se apresentam como nódulo dérmico bem delimitado, com dimensão variável entre 0,5 e 3cm, assintomático, de crescimento lento e endofítico. A histopatologia evidencia padrão celular bifásico típico, com células poliédricas com citoplasma eosinofílico e células grandes com abundante citoplasma claro e núcleo pequeno. Transformação maligna é rara. Relata-se um caso de hidradenoma de células claras com características clínicas incomuns e realiza-se revisão da literatura.

Palavras-chave: *neoplasias de anexos e de apêndices cutâneos; neoplasias cutâneas; acrospiroma; retalhos cirúrgicos*

INTRODUCTION

Initially described by Mayer[1] in 1941, nodular hidradenoma is a benign adnexal neoplasm, of eccrine or apocrine differentiation. Due to different interpretations of its histological characteristics, several denominations and classifications have been suggested throughout the years, thus causing controversies. More recently a sub-division into two subgroups has been suggested: tumors with eccrine or poroid hidradenoma differentiation and tumors with apocrine or hidradenoma differentiation of clear cells.[2] It is found in middle-aged adults, being more prevalent in women. Clinically, it manifests as a solid or cystic, well-delineated nodule, with a variable diameter of 0.5 to 3cm, asymptomatic, of slow growth and endophytic. The most commonly affected places are the scalp, the face, the chest and the proximal extremities.[3] Cases of clear cell hidradenoma in the scalp with uncommon clinical characteristics have been reported.

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CASE REPORT

A 32-year-old male, first reported the development of an ulcero-vegetant nodular lesion on the surface of the scalp a year and a half ago, with progressive growth, reaching 4cm in diameter (Figure 1). Drainage of serous discharge was also reported. He denies comorbidities, uses medication, presents allergies, and has family or personal history with skin diseases. Skull CT scan has shown an expansive formation with soft tissues density, heterogeneous contrast enhancement, in topography adjacent to the occipital bone, thus causing the skin surface to bulge, with bone cortical intact. It has been theorized that epidermoid carcinoma, basal cell carcinoma, cutaneous metastasis, cutaneous lymphoma and amelanotic melanoma. Lesion excision was performed with a 5mm margin and closed with an O-to-Z double rotation flap (Figures 2 and 3). Histological examination has shown multilobulated, well circumscribed tumor, constituted by a biphasic cell pattern, with polyhedral cells of eosinophilic cytoplasm and cells with clear cytoplasm in abundance, as well as cystic spaces (Figures 4 and 5). The final diagnosis was clear cell hidradenoma.

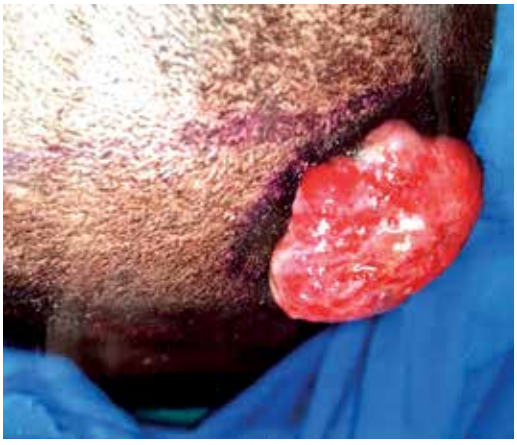

Figure 1: Nodular lesion of an ulcero-vegetant surface, measuring 4cm in diameter, on the scalp

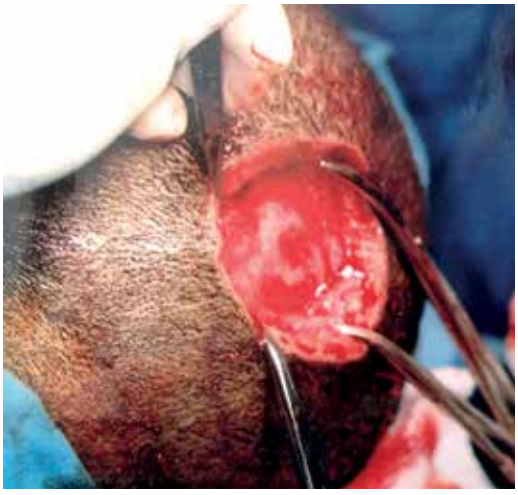

Figure 2: Lesion Exeresis

Figure 3: Closure with O-to-Z Double Rotation Flap

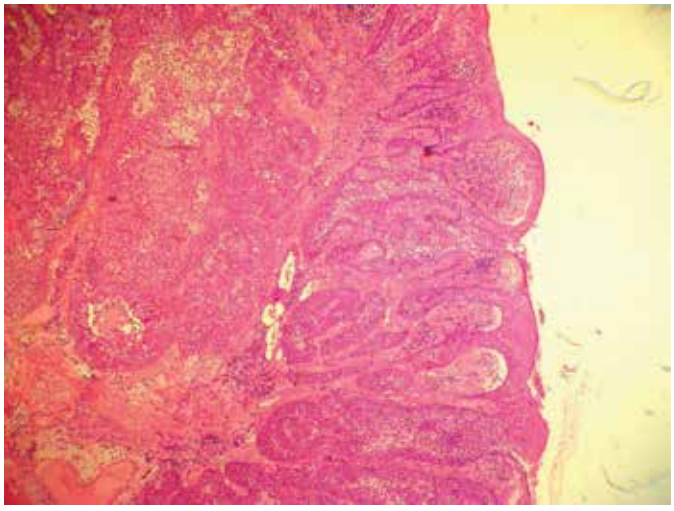

Figure 4: Formed multilobulated tumor made up of a biphasic cell pattern HE, x40

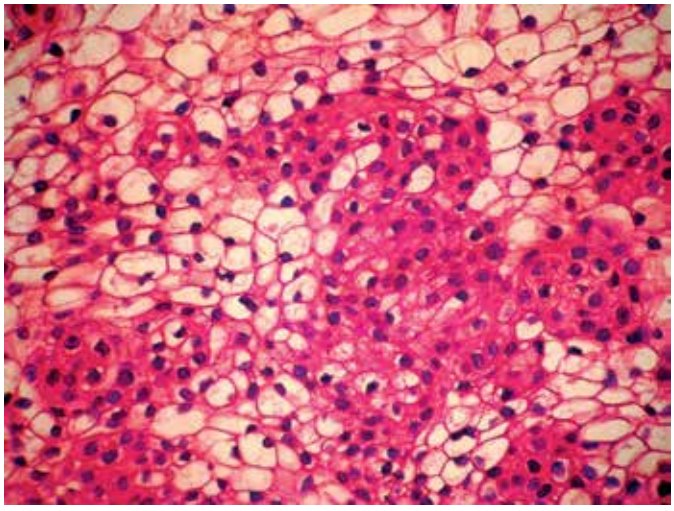

Figure 5: Neoplasia composed of large cells with clear cytoplasm in abundance with a small nucleus, and polyhedral cells with eosinophilic cytoplasm and bigger nucleus HE, x400

DISCUSSION

The nodular hidradenoma, described in 1941 by Mayer,[1] is a benign adnexal neoplasm, which is not clearly identified in the medical literature. Some authors consider it is a rare entity,[2] others mention it as being relatively common.[4, 5] There is considerable confusion in the literature regarding the appropriate designation, and it has already been called *nodular hidradenoma*, *clear cell hidradenoma*, *cystic nodule hidradenoma*, *clear cell myoepithelioma*, and *eccrine acrospiroma*. This reflects different approaches among authors regarding its histological characteristics and histogenesis.[4] Even though it is traditionally classified as an eccrine differentiation, the idea that these tumors may show eccrine or apocrine differentiation is now accepted.[6] More recently, a subclassification into two different groups has been suggested: tumors with eccrine differentiation or poroid hidradenoma, and tumors with apocrine differentiation or clear cell hidradenoma.[2] Some authors, however, classify the poroid hidradenoma separately from the nodular hidradenoma.[4]

Present mainly in middle-aged adults, it is more commonly found in women. It is arises as a well-delineated, solid or cystic skin nodule, with a dimension varying between 0.5 and 3cm, on the scalp, face, chest and proximal extremities. In general, it is asymptomatic, rarely includes pain and drainage of serous discharge. The growth is slow and endophytic, but there are rare cases in which the growth is exophytic.[3] Traditionally, the differential diagnosis includes other adnexal tumors, being clinically indistinguishable. Uncommon appearances include tumors with more than 3cm in diameter,[7] tumors with eroded surface, tumors with predominant cystic component and in uncommon places, such as the plantar region.[8]

The histopathology of the clear cell hidradenoma is characterized by the presence of a well circumscribed, but not encapsulated, tumor. Two cell types are predominant: polyhedral cells with eosinophilic cytoplasm, and large cells with clear cytoplasm in abundance with a small nucleus. Cystic spaces are common, as a result of tumor cell degeneration. Apocrine secretion due to decapitation can be observed. Some tumors may present squamous, sebaceous or mucinous epithelial differentiation.[2] There is a variable proportion among cell types, but the clear cells predominate in one-third of the cases.[3]

The case that was reported presents the typical histopathology of the clear cell hidradenoma, thus showing an uncommon clinical presentation, given the dimensions of the tumor and its exophytic growth with eroded surface. The surgery is curative, but reoccurrence may happen even in the case of incomplete excision.[9] A malignant transformation is very rare, being that most hidradenocarcinoma recurr.[10]

REFERENCES

1. Mayer I. Zur histologie der hidroadenome. Frankfurter Zeit f Pathol. 1941;55:548-80.
2. Nandeesh BN, Rajalakshmi T. A study of histopathologic spectrum of nodular hidradenoma. Am J Dermatopathol. 2012;34(5):461-70.
3. Winkelmann R, Wolff K. Solid - cystic hidradenoma of the skin. Arch Dermatol. 1968;97(6):651-61.
4. Kazakov DV, McKee PH, Michal M, Kacerovska D. Lesions with Predominant Apocrine and Eccrine Differentiation. In: Dmitry V. Kazakov MD PhD, Cutaneous adnexal tumors. Wolters Kluwer Health: 2012. p1-171.
5. Hernandez-Perez E, Cestoni-Parducci R. Nodular hidradenoma and hidradenocarcinoma. A 10-year review. J Am Acad Dermatol. 1985;12(1 pt 1):15-20.
6. Gianotti F, Alessi E. Clear cell hidradenoma associated with the follicu-losebaceous apocrine unit. Histologic study of five cases. Am J Dermatopathol 1997;19(4):351-7.
7. Demirci GT, Atis G, Altunay IK, Sakiz D. A giant benign clear cell hidradenoma on the anterior trunk. Dermatol Reports. 2011;3(3):e45.
8. Shin HT, Clear cell hidradenoma on the palm. Ann Dermatol. 2014;26(3):403-4.
9. Will R, Coldiron B. Recurrent clear cell hidradenoma of the foot. Dermatol Surg. 2000;2697):685-6.
10. Yildrim S, Akoz T, Apaydin I, Ege G, Gideroglu K. Malignant clear cell hidradenoma with giant metastasis to the axilla. Ann Plast Surg. 2000;45(1):102.

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