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Sentinel lymph node biopsy for cutaneous melanoma in a real life setting: analysis of 47 cases treated at a private clinic in Brazil

Biópsia de linfonodo sentinela para melanoma cutâneo na vida real: análise de 47 casos tratados em clínica privada no Brasil

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ABSTRACT

Background: Sentinel Lymph Node (SLN) status has been shown to be the strongest independent prognostic factor of cutaneous melanoma (CM) stage I-II patients. Few papers on CM at private clinics (PC) are available.

Objective: To present clinical and histologic data, complications and frequency of SLN involvement in CM patients diagnosed and followed at a dermatology/cutaneous oncology PC in São Paulo/Brazil, who were submitted to SLNB.

Methods: Retrospective, single-center cohort of patients who attended PC from June 1998 to Jan 2020. Electronic files were selected and analyzed. Minimum period for considering the patient eligible was 1 year.

Results: 215 CM lesions were identified in 184 patients(1.2 melanoma/patient). Forty-seven patients (25.5%) were submitted to SLNB and 59 SLN for histologic examination (1.2 SLN/patient). 10,9% tested positive. SLN identification happened in 95.7%. In 38/47 (80,8%) patients single LBD was found, while multiple-LBD was found in 9/47(19.1%). Eighteen(72,0%) out of 25 trunk lesions drained to single basin, while in 7 patients multiple LBD was found. Complication rate was 6,0%.

Conclusion: Percentage of CM patients that undergo SLNB, node positivity for metastasis, draining basins and complications in this study were similar to studies in northern hemisphere patients. Clinical and epidemiologic characteristics of CM patients differ markedly between PC and PHS patients.

Keywords: Biopsy; Melanoma; Sentinel lymph node

RESUMO

Introdução: *O status do linfonodo sentinela (LNS) tem se mostrado o mais importante fator prognóstico independente no melanoma cutâneo (MC) em estágio I-II. Poucos artigos sobre MC em clínicas privadas (CP) estão disponíveis.*

Objetivo: *Apresentar dados clínicos e histológicos, complicações e frequência de envolvimento do LS em pacientes com MC acompanhados em CP de dermatologia/oncologia cutânea em São Paulo/Brasil, submetidos a biópsia de LS (BLNS).*

Métodos: *Coorte retrospectiva e unicêntrica de pacientes atendidos em CP de junho/1998 a janeiro/2020. Prontuários eletrônicos foram analisados. O período mínimo para considerar paciente elegível foi de um ano.*

Resultados: *Identificamos 215 MC em 184 pacientes (1,2 melanoma/paciente). No total, 47 pacientes (25,5%) foram submetidos à BLNS e 59 LN à exame histológico (1,2 LNS/paciente), sendo que 10,9% foram positivo. A identificação do LNS ocorreu em 95,7%. Dezoito (72,0%) das 25 lesões do tronco drenavam para cadeia única, enquanto em 7 pacientes drenavam para cadeias múltiplas. A taxa de complicação foi de 6,0%.*

Conclusão: *O percentual de pacientes com MC submetidos a BLNS, positividade de LS, cadeias de drenagem e complicações neste estudo foram semelhantes aos estudos em pacientes do hemisfério norte. As características clínicas e epidemiológicas dos pacientes com MC diferem acentuadamente entre os pacientes de CP e do serviço público de saúde.*

Palavras-chave: *Biópsia; Linfonodo sentinela; Melanoma.*

Original Article

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BACKGROUND

Sentinel Lymph Node (SLN) status is the most decisive independent prognostic factor of cutaneous melanoma (CM) stage I-II patients.[1] Accurate assessment of the regional LN status by SLN biopsy (SLNB) is becoming even more critical in the era of novel effective adjuvant therapies for the microscopic nodal disease.[2] Some points on SLNB's role and benefit in this setting are still controversial.[3]

Most published papers on SLNB for CM analyze patients from the northern hemisphere and Australia, large hospitals, or public health system (PHS). Very few articles on CM patients diagnosed and followed at private clinics (PC) are available in the literature.[4-8] We have not been able to find papers specifically addressing CM patients from PC who underwent SLNB, which leaves information gaps about what happens in this context.

OBJECTIVE

This study aims to present clinical and histologic data, describing complications and frequency of SLN involvement in CM patients diagnosed and followed at a dermatology/cutaneous oncology PC in São Paulo/Brazil. They were submitted to SLNB, and their data were compared with data from the literature.

METHODS

A retrospective, single-center study selected and analyzed the electronic files of a cohort of patients diagnosed with CM attending a PC from June 1998 to January 2020. Data collected consisted of gender, primary tumor's anatomic location, melanoma clinical type, Breslow thickness, and history of SLNB. Among those submitted to SLNB, we also assessed SLN status, lymph node basins drainage, number of excised SLN, surgical complications associated with SLNB, and eventual local or distant relapses.

The same surgical team, consisting of dermatologic and oncologic surgeons, operated on all but seven patients at different hospitals in São Paulo. Pathologists from the different hospitals where surgeries were performed determined SLN histologic status. After removal, SLN were submitted to serial sectioning and permanent preparations for histological and immunohistochemical examination, according to current recommendations at the time. SLN was identified using Tc-labeled radiopharmaceutical preoperative lymphoscintigraphy and subsequent intraoperative detection with gamma probe associated or not with blue-dye.

Follow-up was also based on information contained in the electronic charts. The minimum period for considering the patient eligible was one year.

RESULTS

A total of 215 CM lesions were identified in 184 patients (1,2 melanoma/patient). Forty-seven patients (25,5%) were submitted to SLNB, which harvested 59 SLN for histologic examination (1,2 SLN/patient). In 2/47 (4,2%) patients no SLN was identified. Five/47 patients (10,6%) tested positive.

Primary lesions that led to the indication of SLNB were located on the trunk (26), lower limbs (14), upper limbs (6), and head & neck (2) (Table 1). Pre-operatory lymphoscintigraphy allowed identification of lymph node basins drainage (LBD) in all but one patient. In 38/47 (80,8%) patients single LBD was found while multiple-LBD was observed in 9/47 (19,1%).

Eighteen (72,0%) out of 25 lesions drained to single basins, while in 7 patients these lesions drained to multiple basins. Among them, there was a case where CM was located in the interscapular (midline) region and drained to 4 distinct basins (bilateral axilla and bilateral cervical) (Table 3).

Regarding surgical details, SLN identification happened in 95,7% (45/47) of cases. We observed complications four times (3 cases): one patient developed lower limb lymphorrhea and deep venous thrombosis, while two developed lymphorrhea. The complication rate was 6,0% (Table 2).

Thirty-nine patients were eligible for follow-up (at least 12 months). The follow-up period varied from 13 to 177 months. Total follow-up period for the 39 patients was 2410 months, with an average of 61,8 months. False-negatives were identified in 2 cases: 4,0% (per-protocol – PP: 2/47) or 5,1% (intention to treat – ITT: 2/39).

DISCUSSION

Eggermont[1] stated almost two decades ago that SLNB had utterly changed the management of primary CM. Accurate assessment of the regional LN status by SLNB has become even more critical in the present era of novel effective adjuvant

Table 1: Clinical and histologic data of 47 CM patients from PC submitted to SLNB

Gender (n=47)	Anatomical Site (n=47)	Clinical type (n=47)	Sentinel LN status (n=47)	Breslow (mm) (n=47)	
M: 24	Trunk - 25	SSM - 29		<= 0,8 -	12
			Positive – 5 (10,6%)		
	Low limbs - 14	Nodular - 6		>= 0,8/<= 1,0 -	10
F: 23	Up limbs - 6	Acral – 4		>1,0 / <= 4,0 -	18
	H&N - 2	LM / LMM - 0	Negative – 42 (89,4%)	> 4,0 -	6
		Other - 8		ND -	1

Subtitle: H&N – head and neck, SSM – Superficial Spreading Melanoma, LM – Lentigo Maligna LMM – Lentigo Maligna Melanoma, ND – not determined.

Table 2: Data from 47 CM patients from PC who underwent SLNB and world literature

Author - Year	Country	Patients studied (n)	SLN identification (%)	Positive SLN (%)	Complications (%)
Present study 2020	Brazil	47	95,7	10,6	6,4
Nelson *et al.* 2017[9]	Multicenter	2483	Nm	17,4	nm
Duprat *et al.* 2016[10]	Brazil	633	Nm	16,1	nm
Rovere *et al.* 2016[11]	Brazil	62	Nm	12,9	nm
Morton *et al.* 2014[12]	Multicenter	1165	Nm	18,9	nm
Bañuelos *et al.* 2015[13]	Spain	69	98,5	33,8	4,4
Beger *et al.* 2013[14]	Germany	201	94,4	16,4	5,5*
Kunte *et al.* 2010[15]	Germany	1049	97,2	24,9	nm
Debarbieux *et al.* 2009[16]	England	455	Nm	21,5	nm
Koskivuo *et al.* 2007[17]	Finland	305	Nm	16,4	nm
Cecchi *et al.* 2006[18]	Italy	111	100	15,3	nm
De Vries *et al.* 2005[19]	Netherlands	300	99	28,3	7,0
Arens *et al.* 2003[20]	Germany	381	95,8	25	nm

*Subtitle: nm – not mentioned, * head & neck and Breslow > 4,0 mm patients excluded.*

Table 3: Draining lymph node basins in 25 CM PC patients with truncal lesions

Single Basin (n=17)	Multiple basins (n=7)	Basin not identified (n=1)
Axilla - 16	Axilla + cervical - 2 Axilla bilateral - 2 Axilla + chest wall - 1	
Inguinal - 1	Inguinal bilateral - 1 Bilateral axilla and bilateral cervical -1	
Total: 17(68,0%)	**Total: 7 (28,0%)**	**Total: 1 (4,0%)**

immuno and targeted therapies for the microscopic nodal disease.[2]

The present study performed the histologic processing of the SLNs harvested at different hospitals, by different pathologists, for over 20 years. In each case, samples were processed according to current international recommendations at the time. Technical details varied over the period. This lack of standardization in the SLN assessment could be understood as a negative point - which might be so if the objective was to conduct a controlled study. This non-standardized methodology used in the study for 22 years by different pathologists in various hospitals reflects the "real-life" situation, which was the paper's objective.

The percentage of identified and excised SLN among the 47 patients reached 95,7% with an averaged of 1,2 SLN/patient, a number in concordance with international literature (Table 2).

The number of papers reporting on CM patients followed at PC is extremely small.[5-8,19] As early as 1997, Castro et al.[8] demonstrated that in Brazil, the proportion of Caucasians in dermatology PC and Public Health System (PHS) patients differs markedly. Other Brazilian authors corroborated this finding. It it is probably justified by historical aspects and the immense racial diversity in the country, where miscegenation makes its population unique, including Caucasians, Africans, Asians, and indigenous Brazilians. [21,22] Thin CM (Breslow ≤1,0 mm) is diagnosed in a much higher proportion among PC population.[8,19,21] CM patients studied in the present study tend to have characteristics that resemble northern hemisphere CM patients. In contrast, there is a higher proportion of non-Caucasian patients with acrally located, thick and ulcerated lesions among PHS population. Similar findings are also observed in Chile and Mexico. [5,23]

Murali et al.[24] found 6.7% positivity for metastatic melanoma cells in SLN when analyzing 432 patients with thin (≤1 mm) CM. Although there is a low but significant rate of SLN positivity in patients with primary CM of 0.51 to 1.0 mm in thickness, no SLN positivity was detected in the present study´s patients with primary tumor thickness of ≤0,48 mm.

The high number of Breslow <0,8 mm patients submitted to SLNB (12/47 – 25,5%) deserves comment: criteria indicative of SLNB varied during the study period. The presence of mitosis and regression would be decisive to indicate SLNB at some point in time and nowadays is no longer so.[25] In the present study, different reasons justified SLNB for Breslow <0,8mm patients: regression was identified in 5 cases, 1 acral lesion, 1 lesion with satelitosis, 2 of mitotic rate >1, one incomplete shave

biopsy, where Breslow thickness was determined as "at least", 2 cases where patients demanded to have the surgery for their own will.

Skip metastases

Skip metastases are one of the most significant drawbacks of the method and can be found at different rates. The present study identified two cases. The first was a truncal CM with Breslow thickness 4,5mm and Clark level IV draining to the left axilla. The SLN tested negative for metastases. Ten years later pulmonary and intestinal metastases were identified and quickly led the patient to death. The second was also a truncal CM with Breslow thickness 5,85 mm and vascular invasion draining to both inguinal basins. The three SLN tested negative for metastases. Two years later, cerebral metastases were identified.

Draining basins

Preoperative lymphoscintigraphy has proved to be a vital planning instrument to guide complete removal of all SLNs, mainly when the primary lesion is located on the trunk, as found in the present paper, where 7 out of 25 (28,0%) patients had more than one drainage basin identified (Table 3). Truncal CM presents multiple-LBD from 17% to 34,6% of cases, especially when the lesion is mid-line. The present study associated double axillary/cervical and bilateral axillary drainage with upper back lesions.

The significance of multiple-LBD in truncal melanoma patients undergoing SLNB has long been debated. Currently, it it is widely accepted that multiple-LBD is not an independent risk factor for SLN metastasis and has no independent prognostic significance. Among matched pairs, multiple-LBD did not affect rates of LN metastasis overall survival, overall recurrence, locoregional recurrence, or distant recurrence.[26-28]

Complications

SLNB is an invasive procedure and is not free of risks. Complications and sequelae are far less common when compared to complete LN dissection. Wrightson et al. reported on a total of 2120 patients submitted to SLNB. Overall, 96 (4.6%) of them developed major or minor complications. In contrast, 103 (23.2%) of 444 patients experienced complications when SLNB was followed by complete LN dissection, a number five times higher. [29]

CM complication rates reported after SLNB are highly variable in the literature, ranging between 1.8% and 29.9%.[30-32] In a systematic literature review, Moody et al.[25] found an overall complication rate of 11.3% among SLNB patients, most temporary. Incidence of infection was 2.9%; seroma, 5.1%; hematoma, 0.5%; lymphedema, 1.3%; and nerve injury, 0.3%.

The frequency of complications observed in the present study (6,0%) fits the interval described in Moody et al. review paper.[25] One patient developed lower limb lymphorrhea and deep venous thrombosis, while two developed lymphorrhea.

CONCLUSION

Despite the relatively small number of patients studied, we could observe that data obtained from CM patients at PC submitted to SLNB closely resembled those described in northern hemisphere patients regarding the percentage of individuals that undergo SLNB, node positivity for metastasis, age, draining basins, and complications.

Clinical and epidemiologic characteristics of CM patients in Brazil differ markedly between PC and PHS population. The present study's findings are restricted to CM Brazilian patients from PC and should not be extrapolated to Brazilian patients from the PHS. ●

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Development and validation of an artificial neural network to support the diagnosis of melanoma from dermoscopic images

Desenvolvimento e validação de rede neural artificial para suporte ao diagnóstico de melanoma em imagens dermatoscópicas

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ABSTRACT

Introduction: With the advancement of digital image analysis, predictive analysis, and machine learning methods, studies have emerged regarding the use of artificial intelligence in imaging tests such as dermoscopy.

Objective: Construction, testing, and implementation of an artificial neural network based on characteristics of dermoscopic images.

Methods: 1949 images of melanocytic nevi and melanomas were included, both from the authors' files and from dermoscopic image banks available on the internet, and routines and plugins were developed to extract 58 features applied to a multilayered neural network construction algorithm. Also, 52 dermatologists assessed 40 random images and compared the results compared.

Results: The training and testing of the neural network obtained a correct percentage of classification of 78.5% and 79.1%, respectively, with a ROC curve covering 86.5% of the area. The sensitivity and specificity of dermatologists were 71.8% and 52%. For the same images and a cutoff point of 0.4 (40%) of the output value, the application obtained 62% and 56% values, respectively.

Conclusions: Multilayer neural network models can assist in the dermoscopic evaluation of melanocytic nevi and melanomas regarding the differential diagnosis between them.

Keywords: Artificial intelligence; Diagnosis; Melanoma; Nevus

RESUMO

Introdução: *Com o avanço da análise digital de imagens, análises preditivas e métodos de aprendizagem de máquina, surgiram estudos referentes ao uso da inteligência artificial nos exames de imagem como a dermatoscopia.*

Objetivo: *Construção, teste e implementação de uma rede neural artificial baseada em características de imagens dermatoscópicas. Métodos: Foram incluídas 1949 imagens de nevos melanocíticos e melanomas, tanto de arquivos dos autores, quanto de bancos de imagens dermatoscópicas disponíveis na internet, e desenvolvidas rotinas e plugins para a extração de 58 características aplicadas a um algoritmo de construção de rede neural multicamadas. Quarenta imagens aleatórias foram também avaliadas por 52 dermatologistas e os acertos comparados.*

Resultados: *O treinamento e o teste da rede neural obtiveram uma porcentagem correta de classificação de 78,5 e 79,1%, respectivamente, com uma curva ROC abrangendo 86,5% da área. A sensibilidade e especificidade dos dermatologistas foi de 71,8 e 52%. Para as mesmas imagens e um ponto de corte de 0,4 (40%) do valor de saída, o aplicativo obteve valores de 62 e 56%, respectivamente. Conclusões: Modelos de rede neural multicamada podem auxiliar na avaliação dermatoscópica de nevos melanocíticos e melanomas, quanto ao diagnóstico diferencial entre eles.*

Palavras-chave: *Diagnóstico clínico; Inteligência artificial; Melanoma; Nevos e melanomas*

Original article

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INTRODUCTION

Melanoma, like most cancers, has a better prognosis and availability of less morbid treatments if diagnosed early. There are several tools for the early diagnosis of melanoma. Dermoscopy is the most prominent one given the accessibility of the skin to visual assessment and the practicality of the exam. Also, it can be performed on an outpatient basis at the time of dermatological consultation.[1]

Despite being widely used, its increased diagnostic accuracy for melanoma compared to examination with the naked eye has been more effectively evidenced in the last two decades. A meta-analysis published in 2008 showed a significant increase in sensitivity, from 71% to 90%, but no significant difference in specificity. Likewise, Hoorens et al. identified a 3.5% reduction in specificity despite a substantial increase in the sensitivity for diagnosing malignant skin neoplasms.[2-4]

With the advancement of digital image analysis, predictive analysis, and machine learning methods, studies regarding the use of artificial intelligence in imaging exams such as dermoscopy have emerged. Thus, the results obtained by convolutional neural networks with thousands of neurons stand out, and recent studies indicate diagnostic accuracy for melanoma superior to the examination by specialists. On the other hand, such mathematical models and algorithms usually require high computational power to obtain the results.[5,6]

Less complex models of predictive analysis or artificial intelligence through machine learning have a lower computational cost. They can be applied as collaborative tools in dermatological assessment, although they may present less accurate results.[7,8]

In the present study, we constructed, tested, and implemented an artificial neural network based on global dermoscopic imaging of melanocytic nevi and melanomas to predict the type of image analyzed.

METHODS

Images of melanocytic nevi and melanomas were included, both from the authors' files and from dermoscopic image banks available on the internet (The International Skin Imaging Collaboration - ISIC - https://www.isic-archive.com/). We included only images of lesions with a histopathologically confirmed diagnosis, and non-pigmented lesions. We excluded non-pigmented lesions, with coarse hair, of the mucosa, in the nail or palmoplantar region, or those that extrapolated the image field of the dermoscopic photo for better performance of the model. Images that showed peripheral objects, such as dermatoscope edges, were cut in a rectangular shape to exclude them (Figure 2-A, D).9

The study was conducted between April and July 2018. The images were pre-processed using the imageJ 1.48 software, and routines and plugins were developed to extract 58 image characteristics. After segmentation between lesion and background, image features included the distribution, variability and color entropy (25 items), histogram (16 items), shape (five items), borders (four items) and size (two items), and the distribution of shape filters applied to the image (six items). Each image was assessed in two different dimensions to reduce the effects of cropping objects. However, overall, the lesions covered more than one-fifth of the pixels in the images submitted to feature extraction.

The 58 characteristics obtained from each of the 1,949 images (50.3% melanoma) were tabulated and analyzed using the IBM SPSS 20v software (Multilayer Perceptron Network) with the standardization of input data. The sample was divided into 80% training and 20% testing, with hyperbolic tangent activation function, softmax function output, and optimization conjugate gradient method, obtaining a network with a hidden layer of seven perceptrons.

A percentage value (pseudoprobability) resulting from the softmax function in the output layer, ranging from 0-100%, characterizes the result of the neural network. So values higher than 50 were predicted as melanoma and values lower than 50, as nevus (Figure 1).

With an average of 9.3 years of dermatological practice and 7.6 years of dermoscopy use, 52 dermatologists randomly selected 40 images from the image bank excluded from the neural network training. The evaluators were informed that these were melanocytic lesions and answered whether each lesion was benign or malignant (including in situ).

RESULTS

The training and testing obtained a correct rating percentage of 78.5% and 79.1%, respectively, with a ROC curve covering 86.5% of the area (Figure 1). The weights and parameters obtained from the neural network were used to develop an application (Figure 2) hosted on a public web server, allowing the experimental online evaluation of dermoscopic images (http://200.145.131.197/mmview/index.php/).

Difficulty or uncertainty in analyzing lesions by dermatologists had a mean value of 3.3 on a scale of 0 to 5. The overall sensitivity and specificity of the 2,080 assessments by dermatologists were 71.8% and 52%, respectively. For the same images and a cutoff point of 0.4 (40%) of the output value, the application obtained 62% and 56% values, respectively.

DISCUSSION

The study results demonstrate that less complex predictive methods such as artificial neural networks can bring significant results despite their limitations. The online and open availability of the studied algorithm can add information in decision-making about melanocytic lesions, mainly when more extreme values are obtained. Nevertheless, it should be recognized that the tool has performance limitations. It was trained only with selected images of nevi and melanoma, not with coarse hair or pigmented lesions.

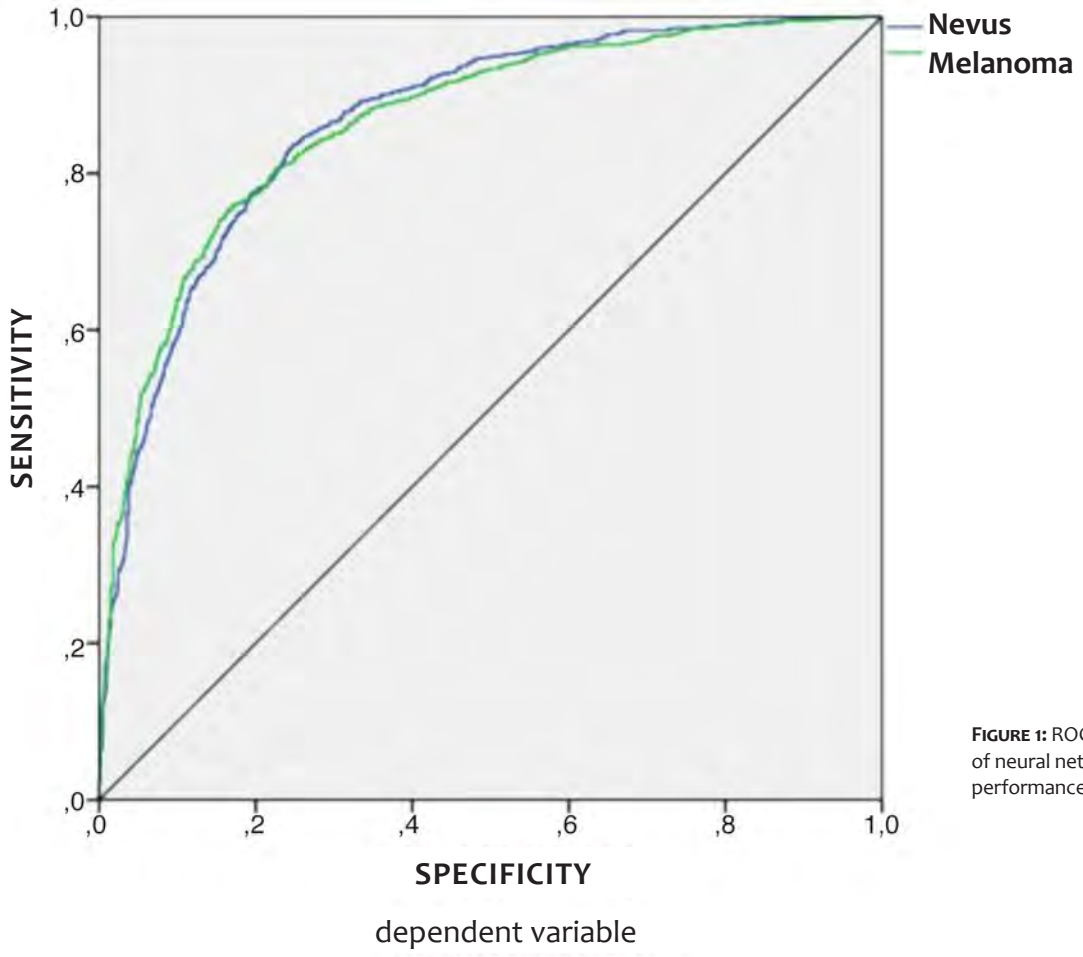

Figure 1: ROC curve of neural network performance (n=1.949)

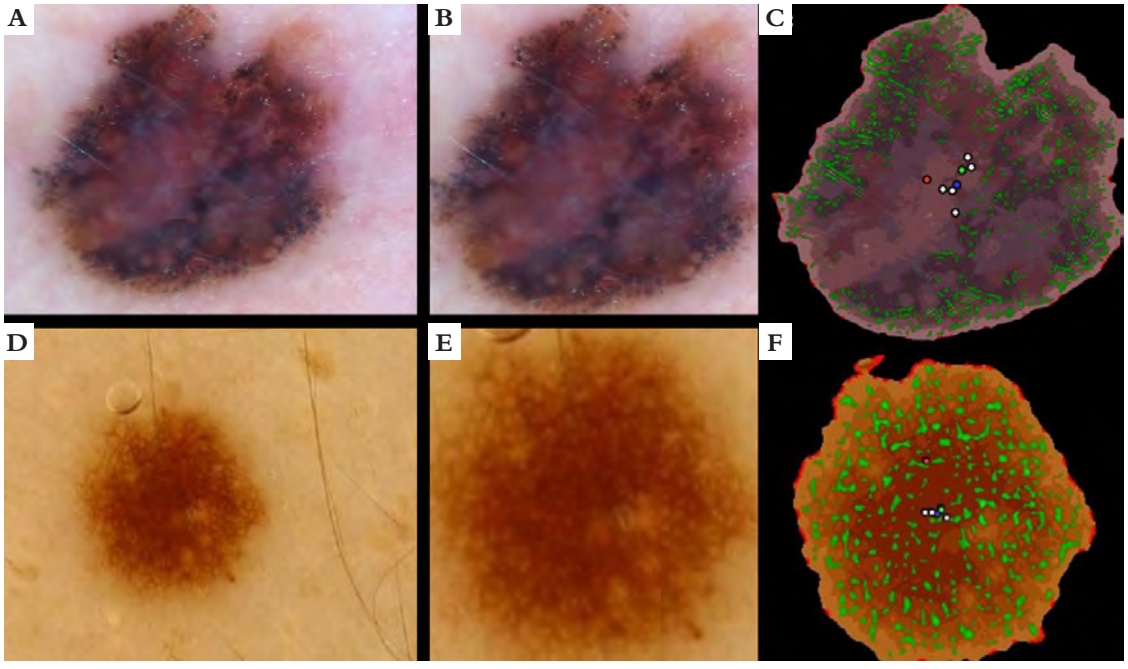

Figure 2: Examples of analyzed melanoma and nevus images

A - Melanoma image submitted;
B - Selected area cropped;
C - Illustration of characteristics found, including distribution of color clusters, sharp edges, and shape filters (final score = 98,4%);
D - Nevus image submitted;
E - Selected area cropped;
F - Illustration of characteristics found (final score = 7%)

Other classification algorithms such as k-nearest neighbors algorithm (k-NN) and Support Vector Machine (SVM) may have different performances than the artificial neural network, and the group will explore them later. Also, extracting new variables from image analysis can lead to system performance gain.[10]

Computer vision methods have evolved significantly with cloud computing-based systems, spreading the use of convolutional neural networks with up to billions of neurons. Still, they depend on a high number of images for learning and significant maintenance costs. Nevertheless, machine learning will probably become more frequent in medical activities, especially in image analysis, as it is in other human activities.

CONCLUSIONS

We developed and implemented a neural network based on dermoscopic images, which can collaboratively assist in the differential diagnosis between melanocytic nevus and melanoma. ●

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Perioral reconstruction after Mohs micrographic surgery: analysis of 108 cases

Reconstrução perioral após cirurgia micrográfica de Mohs: análise de 108 casos

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ABSTRACT

Introduction: The perioral region is commonly affected by non-melanoma skin cancer. Mohs micrographic surgery is the treatment of choice in this area because it has the highest cure rate and preserves healthy tissue. Several methods are available for restoring the perioral region, and their selection is influenced by the surgical wound characteristics and the surgeon's preference.
Objective: Describe the authors' experience in perioral reconstruction after Mohs micrographic surgery and analyze the repair methods most frequently performed.
Methods: Retrospective study of consecutive cases submitted to Mohs surgery and perioral reconstruction.
Results: The study included 108 cases from 103 patients. The mean number of Mohs surgery stages was 1.4, and the mean defect size was 16 mm. Primary closure was the most used technique for reconstruction, followed by flaps (mainly V-Y, single advancement, and rotation). The association of repair methods was used in 28.7% of cases, mostly combined with flaps. Four patients had complications (necrosis and graft infection, trapdoor effect, and partial wound dehiscence).
Conclusion: Primary closure was the most frequent repair method, followed by flaps. Knowing reconstruction strategies and possibilities of associations is essential for proper restoration of the perioral region, maintaining its function, sensation and aesthetics.
Keywords: Lip; Lip neoplasms; Mohs surgery; Skin neoplasms

RESUMO

Introdução: *a região perioral é comumente acometida por câncer de pele não melanoma. A cirurgia micrográfica de Mohs é o tratamento de escolha nessa área, com as maiores taxas de cura e preservação de tecido sadio. Há inúmeros métodos de reconstrução da região perioral, sendo sua escolha influenciada por características da ferida operatória e preferência do cirurgião.*
Objetivos: *descrever a experiência dos autores na reconstrução perioral após cirurgia micrográfica de Mohs e analisar os métodos de reconstrução mais utilizados.*
Métodos: *estudo retrospectivo de casos de reconstrução perioral submetidos à cirurgia de Mohs.*
Resultados: *foram incluídos 103 pacientes, totalizando 108 casos. O número médio de estágios da cirurgia micrográfica de Mohs foi de 1,4, e o tamanho médio dos defeitos, de 16mm. O fechamento primário foi a técnica mais empregada para reconstrução, seguido por retalhos, principalmente VY, avanço simples e rotação. A associação entre métodos de reparo foi utilizada em 28,7%. Quatro pacientes tiveram complicações (necrose e infecção do enxerto, trapdoor e deiscência parcial de sutura).*
Conclusões: *fechamento primário foi o método mais frequente de reparo, seguido pelos retalhos. Conhecer as estratégias de reconstrução e possibilidades de associações é fundamental para a adequada restauração da região perioral, mantendo-se funcionalidade, sensibilidade e estética do local.*
Palavras-chave: *Cirurgia de Mohs; Lábio; Neoplasias cutâneas; Neoplasias labiais*

Original Article

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INTRODUCTION

The perioral region is commonly affected by non-melanoma skin cancer. While basal cell carcinoma (BCC) often affects the cutaneous portion, squamous cell carcinoma (SCC) is more prevalent in the vermilion (mucosa).[1] Surgical removal, either by wide local excision or micrographic surgery is the treatment of choice for malignant skin tumors in the perioral region.[2]

Mohs micrographic surgery (MMS) is preferable in the perioral region, as it has the advantages of a higher cure rate and preservation of healthy tissue.[3] The highest cure rate comes from the complete examination of the surgical margins during the procedure.[4] Wide local excision on the other hand assesses approximately 1% of the margins.[5] The preservation of healthy tissue in the MMS can save the patient from more complex reconstructions. However, challenging reconstructions may be necessary even with MMS, and a thorough margins examination is essential to perform them safely.[2]

When choosing the repair method for this area the size of the surgical wound, its location (subunit affected), and its depth should be considered, among other factors. A satisfactory surgical outcome is achieved when the site's functionality, mobility, sensitivity, and esthetics are maintained.[2]

This study aims to describe the authors' experience in perioral reconstruction after MMS and to analyze the most used reconstruction methods.

METHODS

This is a retrospective study of consecutive cases submitted to MMS and perioral reconstruction performed by the authors between January 2017 and August 2020. The cases are from the authors' private clinics and from a university hospital where one of the authors works. The ethics committee approved the study, protocol 30743520.2.0000.0103.

Except for one surgery performed under local anesthesia and sedation, all procedures were performed under local anesthesia. Postoperatively, antibiotics (cephalexin 500 mg 6/6 hours for seven days, cefadroxil 500 mg 12/12 hours for four days, or amoxicillin 500 mg 8/8 hours for seven days) were used in more complex, long duration surgeries or when a significant portion of mucosa was removed.

For data analysis, we reviewed photographic documentation and data such as age, gender, Fitzpatrick skin phototype, tumor characteristics, size of the wound and anatomical subunits involved, number of MMS stages, reconstruction performed, antiplatelet or anticoagulants use, and postoperative complications.

The perioral subunits were divided into upper cutaneous lip (UCL), lower cutaneous lip (LCL), philtrum, apical triangle, superior vermilion, and inferior vermilion (Figure 1).[6] The reconstruction methods were divided into secondary intention healing, primary closure, flaps, or graft. When more than one method was used, it was called combined reconstruction. For analysis of repair methods, only those that repaired perioral subunits were considered.

Complications were divided into two groups, short or long-term. Bleeding that required re-intervention, hematoma, infection, dehiscence, and necrosis of the flap/graft (partial or total) were considered short-term. Considerable anatomical distortion and functional impairment (difficulty speaking and impaired mobility) were defined as long-term.

RESULTS

The study included 108 cases from 103 patients. Table 1 describes the demographic and surgical data. BCC was the most prevalent tumor in all perioral subunits, except in the lower vermilion, where only SCCs were found (ten invasive and one in situ).

Figure 1 shows the perioral subunits. The upper cutaneous lip (n=83) was the subunit mostly affected, followed by the lower vermilion (12), apical triangle (5), philtrum (4), lower cutaneous lip (3), and upper vermilion (1). In 35 cases, the tumor extended over more than one perioral subunit, and in 12, the extension reached another facial unit (mainly malar, in eight cases). Only three cases had full-thickness lip defects.

Seventy-seven cases underwent reconstruction with a single method, and 31 cases underwent combined methods. The most used procedure was flaps combined with other methods. Flaps were used in 50 cases, half as a single technique and half associated with other methods. The following flaps were used: V-Y (n=15), single advancement (n=14), rotation (n=11), transposition (n=4), double advancement (n=3), hinge (n=2), and tunneled island flap (n=1).

For tumors primarily involving the UCL, 47 cases were restored primarily (Figure 2). In nine cases, primary closure was combined with a full-thickness skin graft (Figure 3), and one with graft and advancement flap. Flaps were the second most common technique in this cosmetic subunit (Figure 4), 33 cases, and rotation was the most used type (n=10) (Figure 5). Two patients were referred by plastic surgery to perform MMS and, after its completion, returned for reconstruction with the plastic surgeon. Both were restored with primary closure.

In the lower vermilion, ten cases were repaired with primary closure. Among them three were combined with an advancement flap and two with secondary intention healing. An extensive but superficial case was left to heal by secondary intention. The most used method was also the primary closure in the apical triangle, philtrum, superior vermilion, and lower cutaneous lip.

In wounds involving more than one perioral subunit (n=35), the method most used for reconstruction was flaps (n=17) (Figure 6), followed by primary closure (n=15), and grafts (n= 2). Among these 35 cases, four required the association of more than two methods (Figure 7).

TABLE 1: Demographic and surgical data of 103 patients and 108 cases

Age (years)	Gender		Skin phototype		Antiplatelet agents	Preoperative antibiotic use	Postoperative antibiotic use
64 (32 to 91)	Men	33 (32%)	I	8 (7.8%)	18 (17.4%)	27 (26.2%)	51 (49.5%)
			II	55 (53.4%)			
	Women	70 (68%)	III	38 (36.9%)			
			IV	2 (1.9%)			

Histologic types		Primary	Tumor size (mm)	Defect size (mm)	Number of surgical stages	Reconstruction with a single method	
BCC	86 (76.6%)	97 (89.8%)	11.5 (2 to 50)	16.3 (4 to 70)	1.40 (1 to 4)	77 (71.3%)	
SCC	18 (16.7%)					Primary closure	47
						Flaps	28
						Rotation	8
						Unilateral advancement	6
SCC *in situ*	2 (1.9%)					V-Y	6
						Double advancement	2
Atypical fibroxanthoma	1 (0.9%)					Transposition	2
						Tunneled	1
Merkell cell carcinoma	1 (0.9%)					Healing by secondary intention	3
						Full-thickness skin graft	2

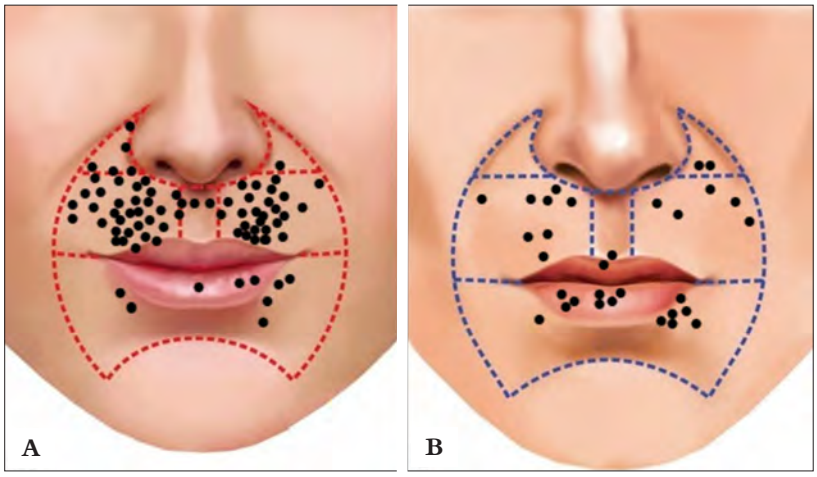

FIGURE 1: Perioral region and its anatomical subunits. The markings indicate the tumor location in women **(A)** and men **(B)**

Preoperative prophylactic antibiotics were used in 27 patients and postoperatively in 51. Complications occurred in four cases: two trapdoors treated with intralesional steroids, one partial dehiscence, and one infection with graft necrosis (Figure 8). The latter case culminated in a partial loss of suction capacity due to partial removal of the orbicularis muscle. The other complications evolved with a satisfactory resolution.

DISCUSSION

Surgical reconstruction of the perioral region can influence mouth function, aesthetics and impact patients' social interactions.[2] Tumors treated with wide local excision can lead to unnecessary defects of considerable size and thickness when "sacrificing healthy skin". They may require complex flaps and sometimes a multidisciplinary approach. Furthermore, wide local excision can cause significant morbidity.[6,7] Conversely, MMS preserves the healthy skin, allowing the complete examination of surgical margins during the intraoperative period, leading to reconstructions with less morbidity and lower risk of complications. Also, MMS enables complex reconstruction methods by assuring that the tumor has been completely removed.[2] The present study demonstrated the variety of reconstruction options for the perioral region.

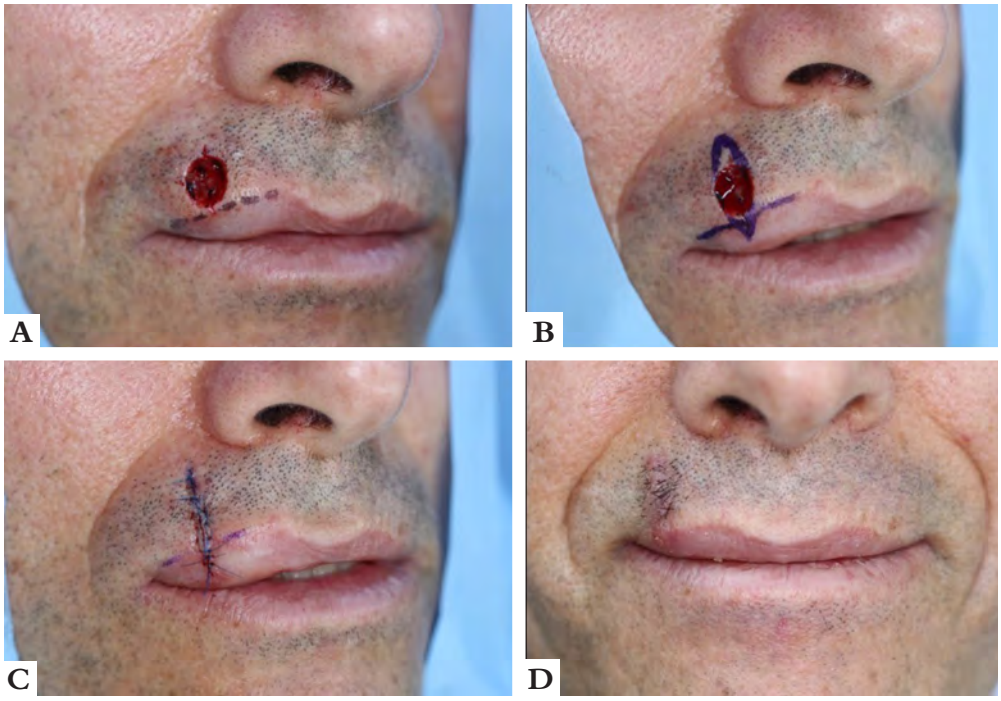

Figure 2: Primary closure.
A - Surgical defect involving the right UCL.
B - Design of the primary closure. Note the pen mark on the vermilion border to orient its approximation.
C - Immediate postoperative period.
D - 2 weeks postoperative

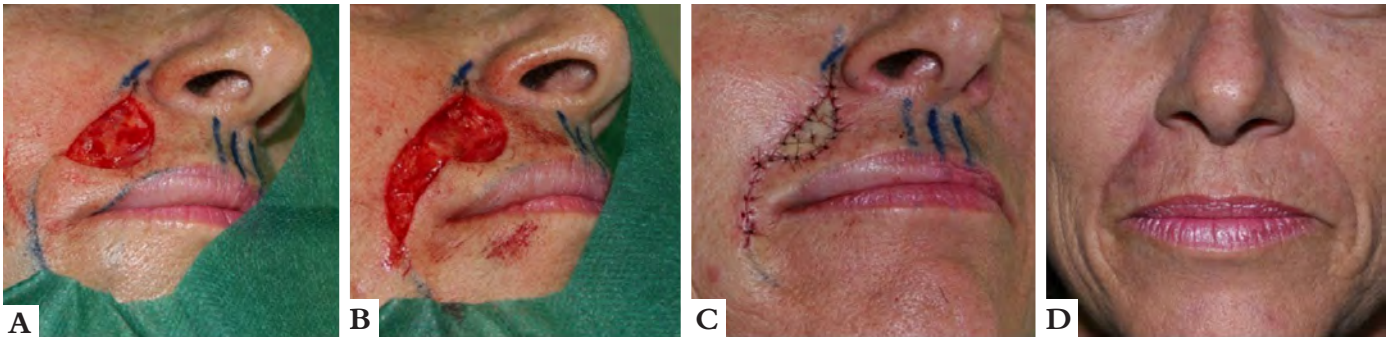

Figure 3: Burow's graft. **A -** Surgical defect of the right UCL. **B -** Inferior Burow's triangle removed on the right NLF. **C -** Immediate postoperative period after primary closure and inferior Burow's triangle as a full-thickness skin graft. **D -** Late postoperative

Like previous publications, BCC was the most prevalent malignant tumor in the cutaneous portion of the lip, while SCC was the most common (and the only one) in the vermilion.[1] In 32% of cases (n=35), the tumor extended through more than one perioral subunit, and in 11%, the extension reached another facial unit (mainly the malar). This demonstrates the complexity of repairs in the perioral region. The involvement of sites beyond the nasolabial fold (NLF) is important because, in some cases, it is preferable to combine reconstruction methods for better results.

After tumor removal from the perioral region, surgical wounds can be divided according to thickness, size, and location. These factors help to guide the choice of the reconstruction method.[8] According to a 2009 literature review, the most common method for reconstructing the perioral region was primary closure.[9] In the present study, 77 reconstructions used a single repair method, mainly primary closure (n=47) (Figure 2), followed by flaps (n=25). In reconstructions using combined techniques (n=31), the most associated secondary method was grafts (n=14) (Figure 3), followed by flaps (n=9), secondary intention healing (n=7), and primary closure (n=1). These data demonstrate the importance of knowing several surgical techniques for proper restoration of the perioral region. It is vital to keep in mind that wounds in the mucosa without the involvement of the orbicularis muscle can be left to heal by secondary intention, obtaining excellent results as described in the literature.[10-12] Also, it is noteworthy that this option is usually only possible when performing MMS since wide local excision removes deeper margins due to postoperative margin examination of 1-2% of the margins.[5]

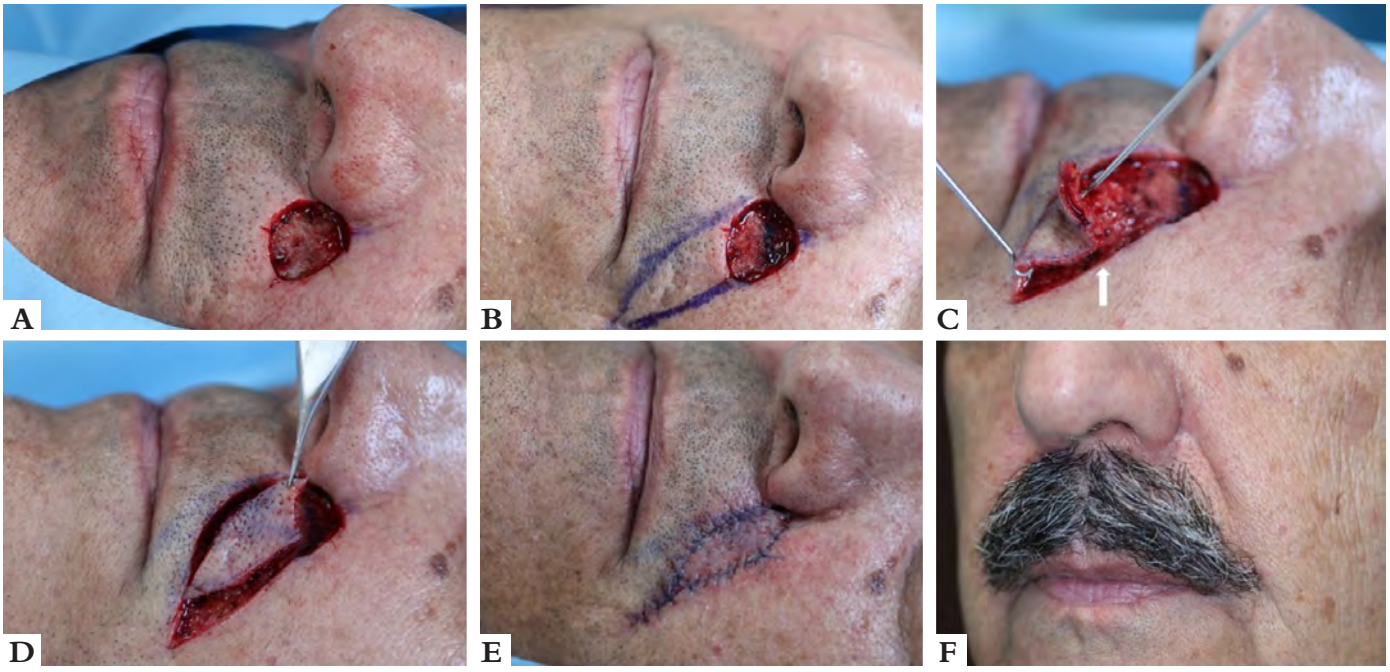

Figure 4: V-Y flap. **A** - Surgical defect of the left UCL and apical triangle adjacent to the NLF. **B -** Design of the flap. **C -** Flap undermined. The white arrow indicates its pedicle. **D -** Flap movement. **E -** Immediate postoperative. **F -** Four-month postoperative

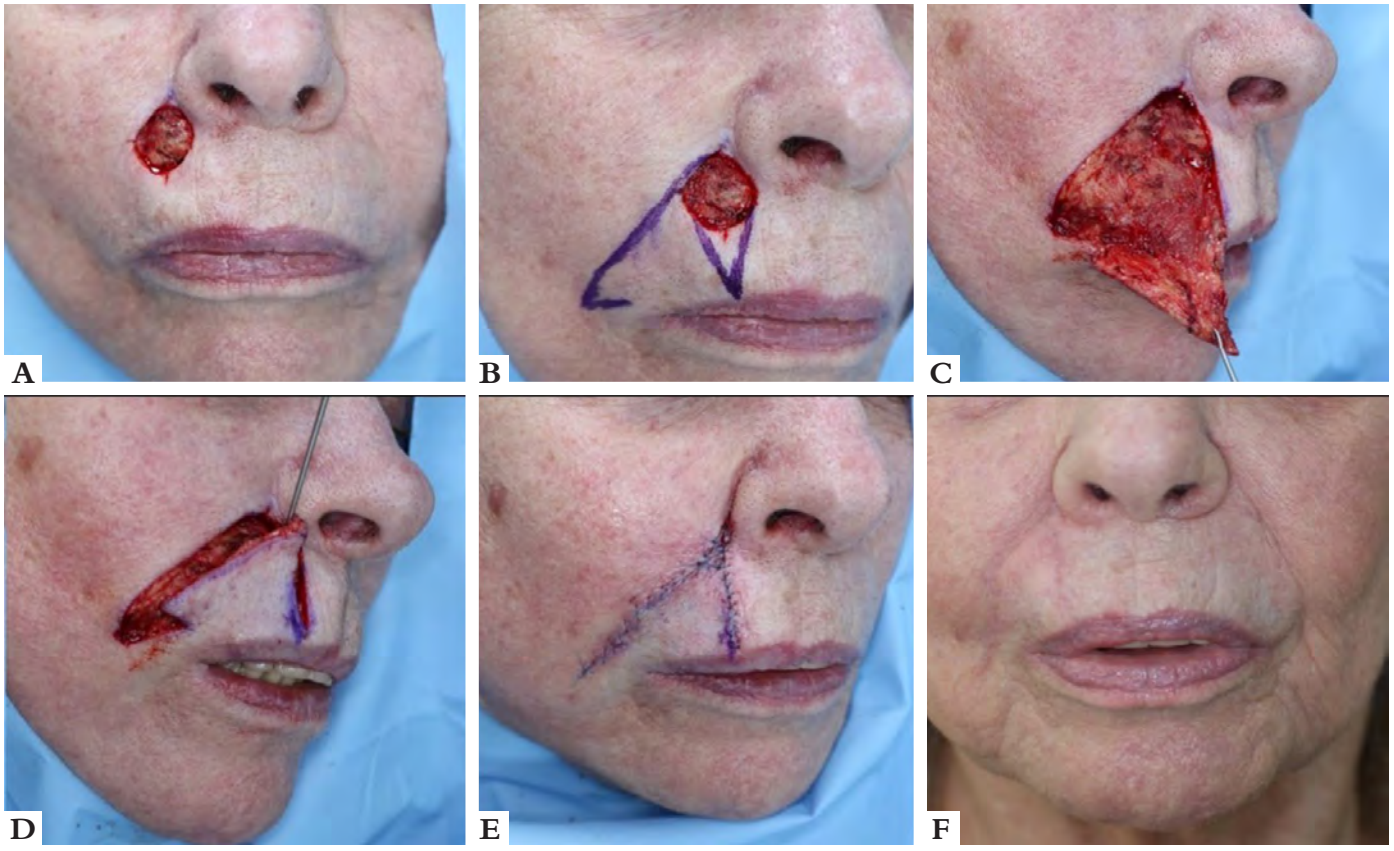

Figure 5: Rotation flap of the NLF. **A -** Surgical defect of the right UCL and apical triangle adjacent to the NLF. **B -** Design of the flap. **C -** Flap undermined in the supramuscular plane. **D -** Flap movement. **E -** Immediate postoperative. Note the rotation arch in the NLF. **F -** Six-month postoperative

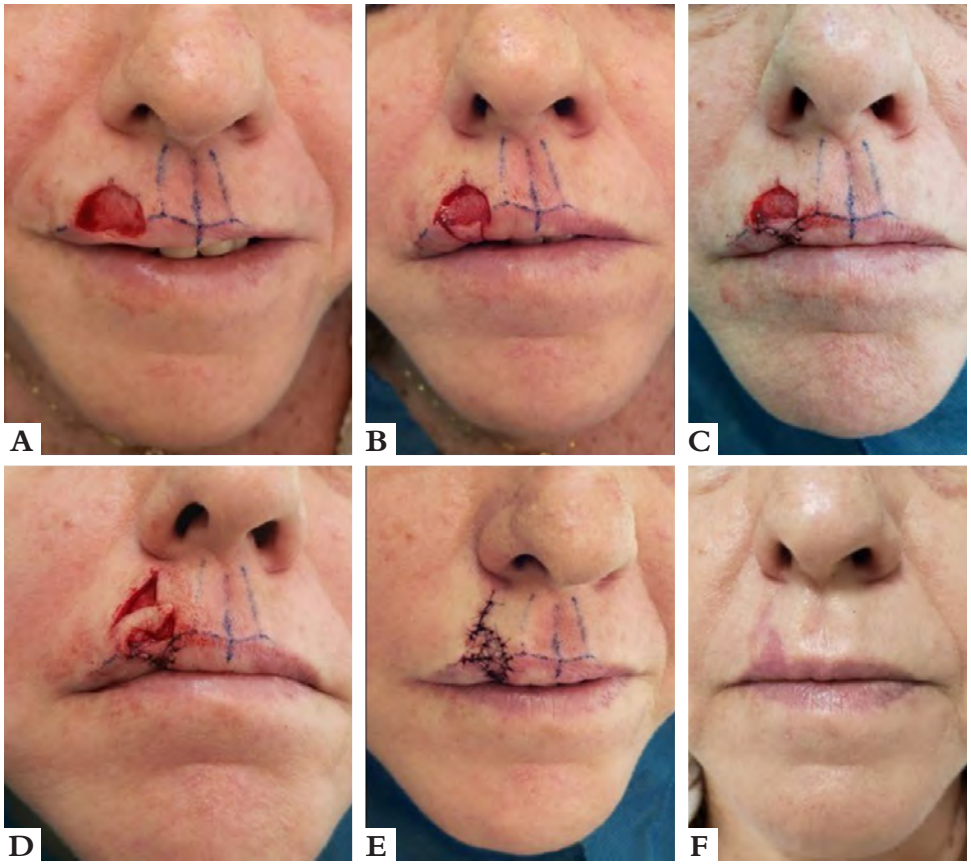

Figure 6: Cutaneous transposition flap combined with mucosal V-Y flap.
A - Surgical defect involving the right UCL and vermilion.
B - V-Y mucosal flap incised.
C - Mucosal flap sutured into place.
D - Cutaneous transposition flap movement towards the UCL defect.
E - Immediate postoperative.
F - Late postoperative. The flap erythema faded over time

In the UCL, the most affected subunit, 37 cases were restored by primary closure. Thirty-three cases by flaps, mainly V-Y (Figure 4), advancement (Figure 9), and rotation (Figure 5). When adequately performed advancement and rotation flaps yield good results in the perioral region, allowing maintenance of function, sensitivity, and symmetry of the lips, in addition to avoiding microstomy.[13] These flaps aesthetic result is satisfactory as they maintain the color and texture of the tissues around the surgical defect, and camouflage the scars in between the boundaries of the facial anatomical units.[14,15] For the advancement flap, it is essential to position the incisions between the anatomical subunits (vermilion/UCL, UCL/alar base) whenever possible.[16] For the rotation flap, the arch should be positioned in the NLF, thus remaining hidden after the healing. Cases requiring greater mobility of the rotation flap can receive a back cut in the distal portion of the arch.[15]

The V-Y island pedicle flap is better indicated when one of the incisions can be camouflaged in the NLF. For extensive cases, adjacent to the philtrum and affecting almost the entire area between the nasal vestibule and vermilion, one should consider removing the remaining skin to camouflage both incisions: one between vermilion and UCL, the other between nose and UCL.[17] In addition to the oblique/lateral design, the V-Y island pedicle flap can be performed vertically for wounds in the philtrum or adjacent to it. The island flap can also recruit tissue beyond the NLF. However, blunting of the NLF can cause visible asymmetry. Few options do not lead to some NLF asymmetry degree in these cases. As with all island flaps, its proximal portion must be "thinned' according to the surgical wound thickness to reduce the risk of the trapdoor effect.[17]

With the preservation of healthy tissue due to MMS, the defects are smaller and thinner than those from wide local excision, often reducing the need for more complex reconstruction.[18] In addition to V-Y, advancement, and rotation flaps, transposition (Figure 6) and tunneled flaps were used. We did not need to perform flaps indicated for extensive full-thickness wounds, such as the Abbé or Karapandzic flap, as the three full-thickness cases were relatively small and managed with less complex reconstructions.[7]

It is important to emphasize that the National Comprehensive Cancer Network (NCCN) does not recommend the use of flaps in cases that the surgical margins were not completely assessed. [19] This limits the reconstructive options, affecting the functional and esthetic restoration. Therefore, MMS, in addition to having the highest cure rates to treat cutaneous carcinomas, allows the Mohs surgeon to safely restore the wound using flaps, often necessary for better outcomes.[5]

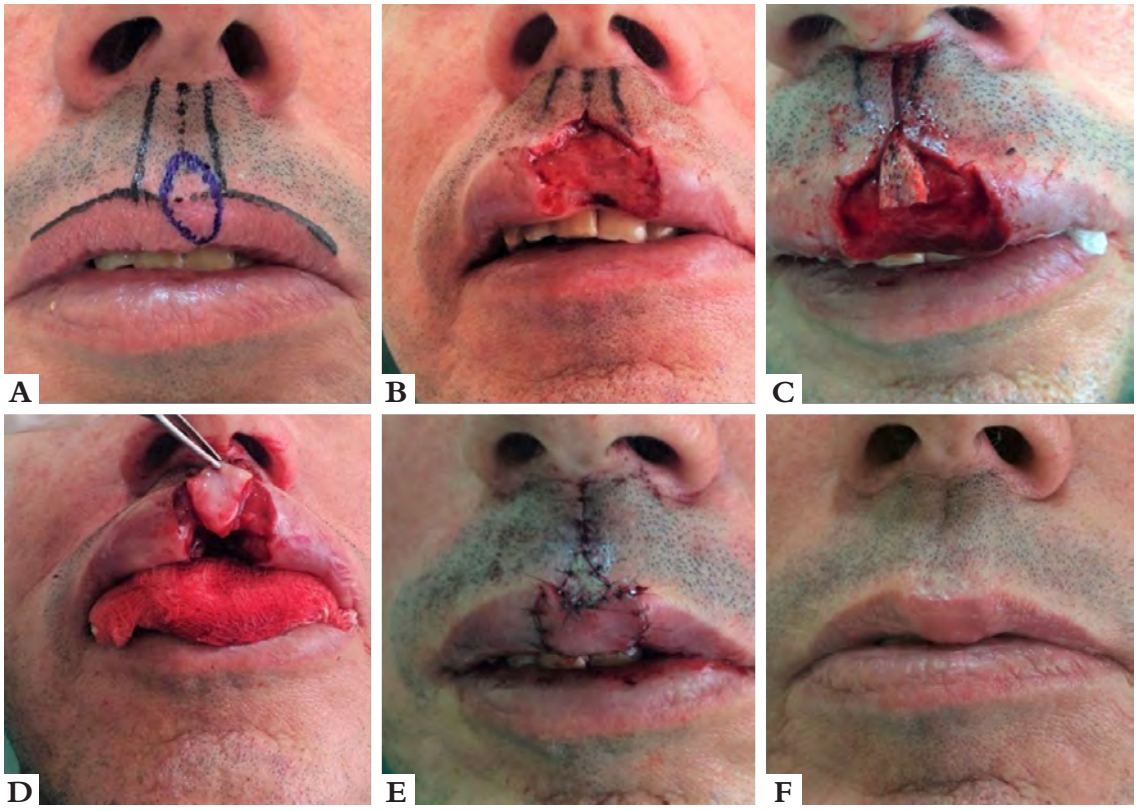

Figure 7: V-Y flap combined with Burow's graft.
A - Ill-defined BCC
B - Surgical defect involving philtrum and vermilion.
C - Burow's graft sutured to restore the philtrum.
D - Mucosal V-Y flap to restore the vermilion.
E - Immediate postoperative.
F - Late postoperative. Note the proper recreation of the Cupid's bow

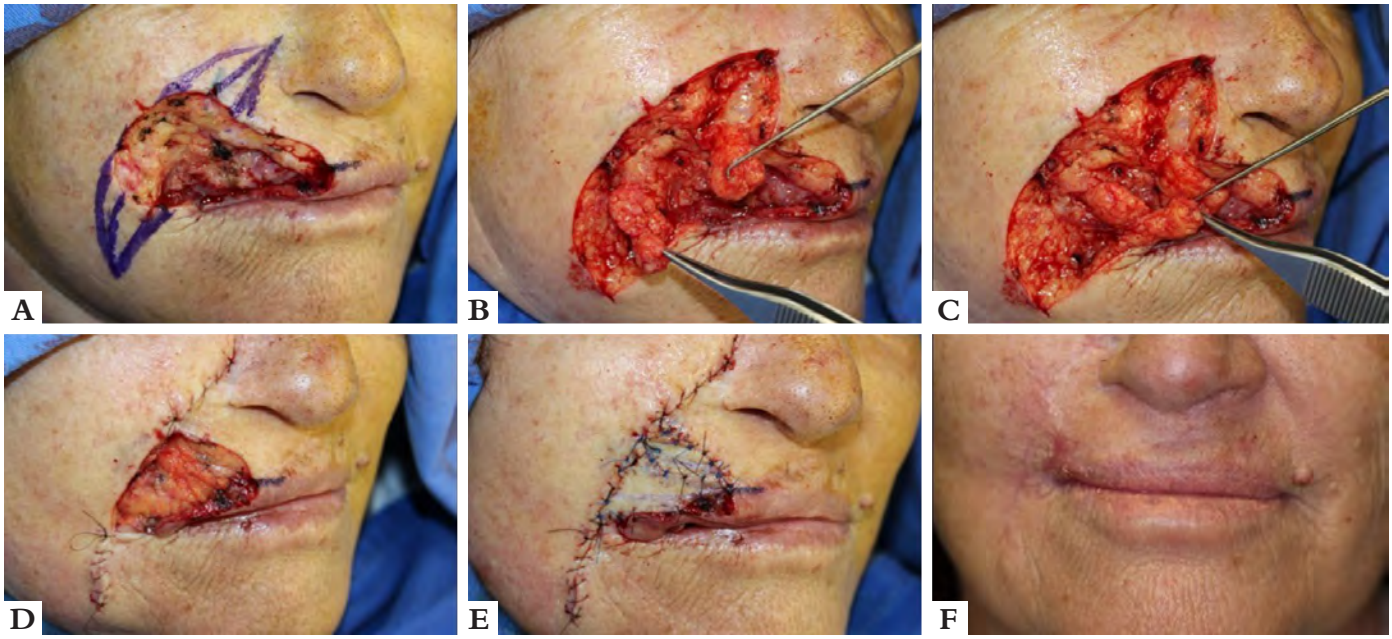

Figure 8: Double hinge flap, combined with Burow's grafts and secondary intention healing.
A - Extensive and deep operative wound. Design of the primary closure in the malar region. **B** and **C -** Subcutaneous hinge flaps from the cheek used to restore the UCL. **D -** Note replacement of the UCL volume after suturing the hinge flaps. **E -** Immediate postoperative. Burow's grafts sutured. Small area in the vermilion left to heal by secondary intention. **F -** Four-month postoperative. The nasal asimmetry is from a previous surgery performed in a different hospital

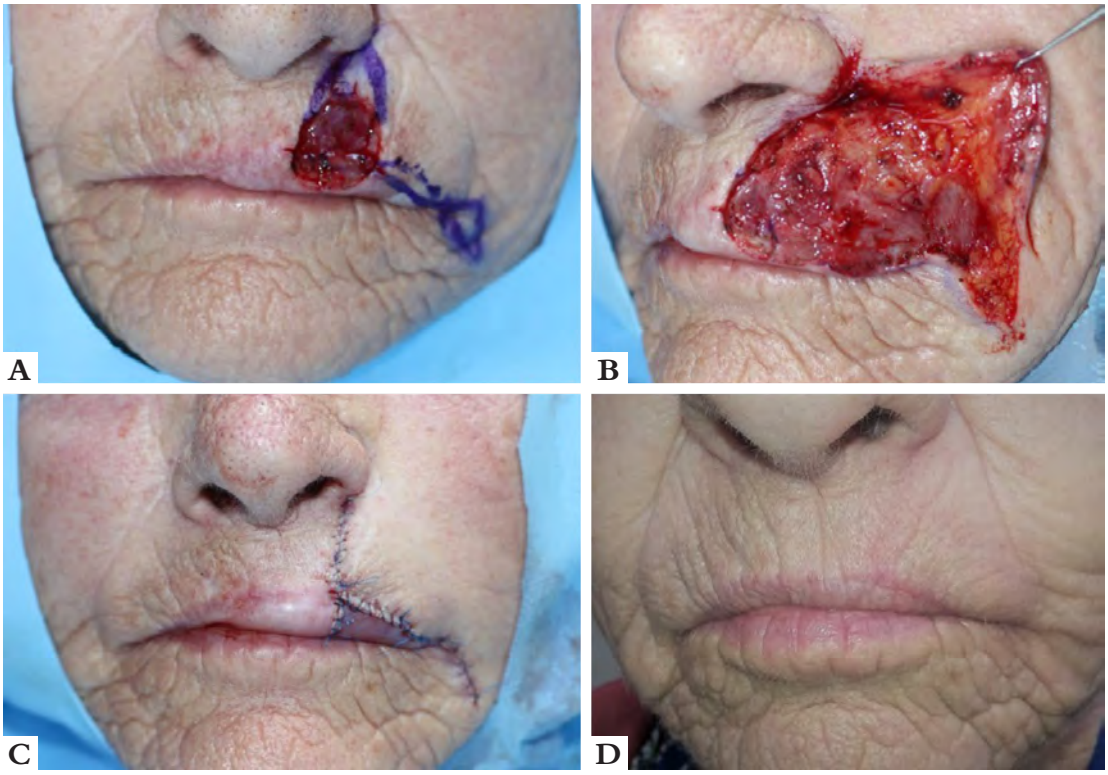

FIGURE 9: Lateral advancement flap.
A - Surgical defect involving the left UCL and vermilion after removing an atypical fibroxanthoma. Flap design.
B - Flap undermined. At the UCL region, the undermining plane is supramuscular, while beyond the NLF, it is in the subcutaneous tissue. Care must be taken not to deepen the undermining in this region.
C - Immediate postoperative.
D - Four-month postoperative

The use of pre and postoperative antibiotics is a controversial topic in dermatologic surgery.[20-23] Cutaneous surgeries are considered clean, but the proximity to the oral cavity makes the perioral region a site with a significant chance of potentially contaminated surgeries.[24] This study used preoperative prophylactic antibiotic therapy in 26.2% of cases and postoperative in 49.5%, reflecting the difficulty in anticipating the wound size and the reconstruction method to be performed. With a low mean of surgical stages (which reduces the surgical time) and appropriate indication for antibiotic therapy, there was only one case of postoperative infection of a recurrent morpheaform BCC (treated by wide local excision eight years earlier). The tumor extended from the UCL to the upper vermilion and philtrum, leading to a 48 mm surgical defect repaired with a hinge flap combined with full-thickness skin graft and secondary intention. In this case, despite the use of pre and postoperative antibiotics, there was infection and graft necrosis. However, post-operative care and additional antibiotics led to a satisfactory outcome, except for the slight functional impairment (suction) secondary to a significant loss of orbicularis muscle due to tumor's aggressiveness (Figure 8).

Other complications were two cases of trapdoor, one after a V-Y flap and the other secondary to a tunneled flap both in the UCL. Both had a good response with intralesional steroids (triamcinolone acetonide 20 mg/ml). There was one case of partial dehiscence in the apical triangle following primary closure.

Preserving the function and volume of the perioral region is challenging because even minor defects can impair the lips' movement, competence, and symmetry. The surgeons must invest all their efforts in resolving the disease with a satisfactory aesthetic-functional surgical outcome. As recommended by the NCCN, reconstructions, especially in cosmetic sensitive areas, should ideally be performed after complete tumor resection confirmed by histological analysis of 100% of the surgical margins perioperatively as in MMS.[19] The Mohs surgeon should be able to perform complex and straightforward reconstructions in the perioral region. More challenging cases may require a multidisciplinary approach.

CONCLUSIONS

Primary closure was the most used technique for reconstruction, followed by flaps (mainly V-Y, unilateral advancement, and rotation). Combined methods were performed in 28.7% of cases. A combined approach is better indicated for wounds involving cutaneous and mucosal subunit, such as UCL and vermilion.

Knowing the reconstruction strategies and possibilities of associations is essential for the proper reconstruction of the perioral region, maintaining its functionality, sensation and aesthetics. ●

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Prevalence of pathological diagnoses and epidemiological profile of patients with non-melanoma skin cancer suspicious lesions

Prevalência dos diagnósticos anatomopatológicos e perfil epidemiológico dos pacientes com lesões suspeitas de câncer de pele não melanoma

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ABSTRACT

Introduction: Cutaneous cancer has a high incidence, can be screened with dermatological clinical examination and confirmed by cutaneous biopsy.

Objective: To verify the prevalence of pathological diagnoses for suspected non-melanoma skin cancer (NMSC) lesions in a Reference Service.

Methods: Observational and cross-sectional study. Patients with indication of skin biopsy for suspected NMSC were included. Variables analyzed: age, gender, personal history of skin cancer, number of biopsies, biopsy site, and pathological outcome, divided into Group 1 (neoplastic lesions); Group 2 (premalignant lesions), and Group 3 (benign lesions).

Results: A total of 287 patients, with an average of 1.33 biopsies per patient. The median age in the sample was 71 years, and 56.1% were women. Personal history of skin cancer: 44.95%. General sample: group 1: 62%; group 2: 21% and group 3: 17%. Neoplasms found: 68% were BCC, 30% were SCC, and other neoplasms: 2%. In the group of premalignant lesions: mainly actinic keratosis; in the group of benign lesions: diagnostic variety. The cephalic segment was the most frequently biopsied topography (58%).

Conclusions: In this study, we showed a higher incidence of skin cancer in women, with the majority of elderly patients being the most frequent diagnosis of BCC.

Keywords: Basal Cell; Biopsy; Carcinoma; Neoplasms; Skin neoplasms; Squamous cell.

RESUMO

Introdução: *o câncer cutâneo apresenta alta incidência, pode ser rastreado com exame clínico dermatológico e confirmado por biópsia cutânea.*

Objetivo: *verificar a prevalência dos diagnósticos anatomopatológicos por lesões suspeitas de câncer de pele não melanoma (CPNM) em um Serviço de Referência.*

Métodos: *estudo observacional e transversal. Inclusos pacientes com indicação de biópsia cutânea por suspeita de CPNM. Variáveis analisadas: idade, gênero, história pessoal de câncer de pele, número de biópsias, local da biópsia e resultado anatomopatológico, este dividido em grupo 1 (lesões neoplásicas); grupo 2 (lesões pré-malignas) e grupo 3 (lesões benignas).*

Resultados: *um total de 287 pacientes, com média de 1,33 biópsia por paciente. A idade mediana na amostra foi 71 anos, sendo que 56,1% eram mulheres. História pessoal de câncer de pele: 44,95%. Amostra geral: grupo 1: 62%; grupo 2: 21% e grupo 3: 17%. Neoplasias encontradas: 68% eram CBC, 30% eram CEC; e 2%, outras neoplasias. No grupo de lesões pré-malignas: principalmente queratoses actínicas; no grupo de lesões benignas: variedade diagnóstica. O segmento cefálico foi a topografia mais frequentemente biopsiada (58%).*

Conclusões: *neste estudo, evidenciamos uma maior incidência de câncer de pele em mulheres, sendo a maioria dos pacientes idosos, e o diagnóstico mais frequente o CBC.*

Palavras-chave: *Biópsia; Carcinoma basocelular; Carcinoma de células escamosas; Neoplasias cutâneas*

Original Article

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INTRODUCTION

Skin cancer has gained special significance in recent decades due to its increasing incidence. It is considered a public health problem in geographic areas of intense exposure to ultraviolet radiation.[1,2,3] Non-melanoma skin cancer (NMSC), represented by basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), corresponds to 30% of all malignant tumors registered in the country. BCC accounts for 70% of skin cancer diagnoses, followed by SCC, diagnosed in 25% of cases.[1]

It is believed that 90% of NMSC can be attributed to sun exposure,[4] and BCC is associated with cumulative exposure. This fact reinforces the importance of photoprotection, which should be introduced from childhood and is considered the measure of choice worldwide to prevent NMSC.[5] Other causes related to the development of skin cancer are family history, exposure to chemicals, radiotherapies, phenotypic factors, immunosuppression, and some hereditary genetic syndromes.[6]

Diagnosis of skin cancer mainly involves clinical examination, conducted through visual inspection of the patient's skin, and histopathological analysis after the lesion's biopsy, which is indicated when a clinical study shows suspicion of NMSC or melanoma.[7] A specialized professional must perform a thorough physical examination, identifying suspected malignant lesions through their clinical characteristics. Advances in dermoscopic studies of these lesions allowed higher precision in indicating skin biopsies for diagnostic confirmation.[8,9,10]

When detected early, BCC presents high cure rates.[2,6] According to the National Comprehensive Cancer Network (NCCN), NMSC treatment should prioritize the complete cure of the tumor. The NCCN recommends the biopsy of all NMSCs before any procedure, allowing the most appropriate treatment choice.[11] Despite the low mortality rate, this type of tumor has high morbidity because it causes disfigurement, resulting in physical and psychological disability.[12] However, in some cases, there is tumor recurrence after excision. Among the reasons for occurrence, some studies highlight the relationship with the location, lesion extension, compromised surgical margins, and others. Considering this, it is of paramount importance to screen patients who have already had skin tumors to monitor the recurrence or persistence of tumors and detect new lesions.[14]

Assuming that there is considerable underreporting due to underdiagnosis, and also because it is a neoplasm with good prognosis if treated in an appropriate and timely manner, this study aims to verify the prevalence of anatomopathological results and epidemiological/clinical profile of patients who underwent biopsy for NMSC suspicious lesions in the Dermatology Service of Complexo Hospitalar Padre Bento de Guarulhos-SP (CHPBG), between June and December 2019, promoting further discussion and analysis on this subject.

METHODS

We conducted a cross-sectional and retrospective observational study by analyzing medical records of patients who underwent skin biopsies for NMSC suspicion lesions in the Dermatology Service of CHPBG, from June to December 2019. This study was submitted to the CHPBG Research Ethics Committee (CEP 245/2025) through Plataforma Brasil and it was approved under the number 3,929,819.

The variables analyzed in the study were: age, gender, personal history of skin cancer, number of biopsies, biopsy site, and anatomopathological results. After completing data collection, the general epidemiological profile of the sample was designed (total number of patients in the study) by observing the mean, maximum, and minimum age and gender, in addition to following the frequency of the personal history of skin cancer.

Then, the patients were grouped according to the anatomopathological result, forming three distinct groups: Group 1, comprising patients with confirmed neoplastic lesions in the anatomopathological analysis; Group 2, including individuals with premalignant lesions in the anatomopathological analysis; and Group 3, with patients with benign lesions in the anatomopathological examination. The epidemiological profile of each group was analyzed later. We subdivided Group 1 into BCC, SCC, and other neoplasms to enable the individual assessment of each histological type of neoplasm found, allowing the analysis of the topographic location in each of these subgroups.

The study included the medical records of patients with skin lesions suggestive of NMSC, whose biopsies already had a histopathological result. The biopsies were performed at the CHPBG Dermatology Service from June to December 2019. We excluded the medical records of patients with requests for biopsy of cutaneous lesions not suggestive of malignancy, in addition to patients with cutaneous lesions suggestive of malignancy that had already been surgically addressed, even those with an indication for a new biopsy. Likewise, patients who did not attend or did not have the anatomopathological report during the research period and individuals with a previous diagnosis of NMSC known as Gorlin Syndrome, xeroderma pigmentosum, or mycosis fungoid, or those treated outside the established period, were excluded.

RESULTS

This study included all skin biopsy samples indicated by clinical suspicion of NMSC, totaling 382 points of skin biopsies in a total of 287 patients, corresponding to a mean of 1.33 biopsies per patient, with a maximum number of seven biopsies in the same patient.

The overall sample (287 patients) comprised 126 (43.9%) men and 161 (56.1%) women, and the patients' age ranged between 20 and 97 years, with a median of 71 years. Among the assessed patients, 129 (44.95%) had a personal history of skin cancer and 158 (55.05%) did not.

We formed three large groups according to the anatomopathological results obtained from the samples to know the diagnoses of suspicious lesions in the general sample:

- Group 1: comprising samples with anatomopathological results that confirmed neoplastic lesions;
- Group 2: including samples with anatomopathological results of premalignant lesions;
- Group 3: encompassing samples with anatomopathological results of benign lesions.

Group 1 comprised 62% (238 cases) of the general sample, most of them (52%) women. This group had a median age of 71 years, with a minimum age of 40 years and a maximum of 97 years. Group 2 corresponded to 21% (81 cases, 64% women and 36% men) and Group 3 to 17% (63 cases, 52% women and 48% men) of the total sample. The median age was 72 years, with a minimum age of 43 years and a maximum of 94 years, and 67 years, with a minimum age of 20 years and a maximum of 90 years, for Groups 2 and 3, respectively (Table 1).

Regarding the personal history of skin cancer, we found it in 45% (n=107) of positive biopsies for skin cancer (238 samples). For the group of positive biopsies for premalignant lesions (81 samples), 54% (n=44) already had a previous skin cancer diagnosis. In the group of positive biopsies for benign lesions (63 samples), 37% (n=23) had a previous history of skin cancer (Table 2).

After this initial classification into three large groups, we subdivided the samples from Group 1 according to the histological type of skin cancer. We found 163 cases of BCC (68%), 71 cases of SCC (30%), and 4 cases of other neoplasms (2%). In the latter, the neoplasms found were melanoma (1), undifferentiated carcinoma (1), epithelioid neoplasm (1), and adenocarcinoma (1) (Figure 1).

The anatomopathological results compatible with the diagnosis of actinic keratoses (81 samples) justified the formation of Group 2 since they comprise the spectrum of premalignant skin lesions not classified as neoplastic or benign.

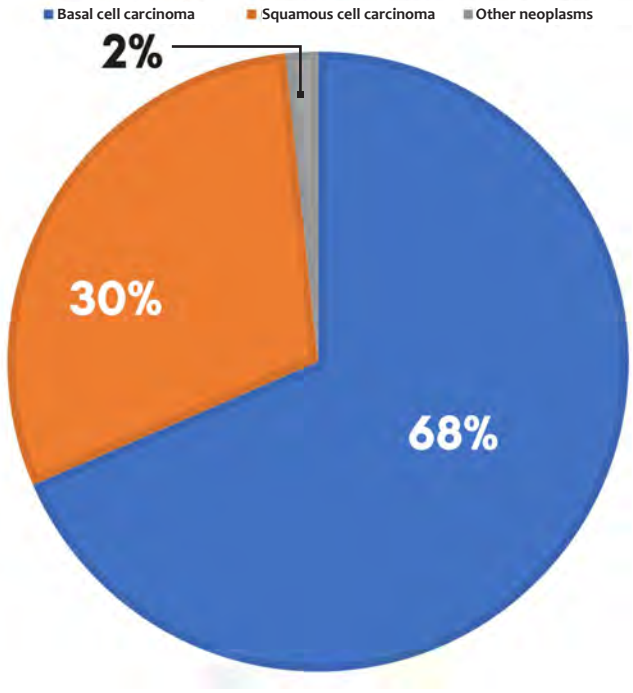

FIGURE 1: Neoplasms

Regarding Group 3, most benign lesions found were nonspecific inflammatory process (15), followed by seborrheic keratosis (11), and intradermal and compound melanocytic nevus (9), in addition to the viral wart (7), among others with lower frequency.

We also assessed the frequencies of the topographic locations of the biopsies performed. The cephalic segment was prevalent with 221 samples (58%), followed by 161 samples (42%) in the trunk and limbs. Regarding the topographic loca-

Table 1: Epidemiological profile of the general sample and groups formed regarding anatomopathological results

	Group 1 Neoplastic lesions n=238		Group 2 Premalignant lesions n=81		Group 3 Benign lesions n=63		General sample N=382	
Age	71 years (40-97 years)		72 years (43-94 years)		67 years (20-90 years)		70 years (20-97 years)	
Sex	**Women** 124 (52%)	**Men** 114 (48%)	**Women** 52 (64%)	**Men** 29 (36%)	**Women** 33 (52%)	**Men** 30 (48%)	**Women** 161 (56,1%)	**Men** 126 (43,9%)

Table 2: Personal history of skin cancer in the general sample and in each group regarding anatomopathological result

	Group 1 Neoplastic lesions n=238		Group 2 Premalignant lesions n=81		Group 3 Benign lesions n=63		General sample N=382	
Skin cancer history	**Positive** 107 (45%)	**Negative** 131 (55%)	**Positive** 44 (54%)	**Negative** 37 (46%)	**Positive** 23 (37%)	**Negative** 40 (63%)	**Positive** 129 (44.95%)	**Negative** 158 (55.05%)

tion of biopsied lesions, in the individual analysis of each group, we noticed that Group 1 presented 61% of the samples in the cephalic segment, as well as Group 2 (53%) and Group 3 (54%) (Table 3).

Concerning the topographic locations of the neoplastic lesions (Group 1), in the different histological types, we observed that most of the biopsies for BCC (71%) were in the cephalic segment. On the other hand, SCC was more biopsied in the trunk and limbs (63%) (Table 4).

Finally, due to the prognostic importance that the cephalic segment's risk zones (zone H and zone M) can pose, this region was subdivided into nose, periauricular/temporal, periorbital, forehead, cheeks, jaw, chin, lips, and scalp. Thus, it was possible to identify the frequencies of biopsies in each of these anatomical subunits.

This study showed that the prevalent anatomical subunits of the cephalic segment in Group 1 were the periauricular/temporal (42% - 29.1%) and nose (40% - 27.7%). Regarding Group 2, the most frequent anatomical subunits of the cephalic segment were cheek (25.5%), periauricular/temporal (23.2%), nose (18.6%), and periorbital (13, 9%). There were no biopsies in the chin region resulting in pre-malignant lesions. In Group 3, the cheek (29.4%), nose (23.5%), and periorbital (14.7%) areas were the most biopsied anatomical subunits. It is noteworthy that there were no biopsies in the chin and lips regions represen-ting benign lesions (Table 5).

When we assessed only the frequency of biopsies location in the anatomical subunits of the cephalic segment that obtained BCC results, we observed that the most frequent were the nose (32%) and periauricular/temporal regions (29%). Likewise, regarding SCC in the cephalic segment, when we analyzed this frequency, we noticed that the most frequent locations were the periauricular/temporal and cheek areas, both with the same incidence (30.7%) followed by the frontal region (4%-15.3%). It should be noted that, in the entire sample, the jaw and lips regions did not present reports compatible with SCC (Table 6).

DISCUSSION

This study evaluated the anatomopathological results of all skin lesions indicated for biopsy due to suspicious malignancy over seven months (June to December 2019) in the Dermatology Service of the CHPBG. We obtained 382 biopsies from a total of 271 patients, of which 62% had a diagnosis of skin cancer, 21% indicated premalignant lesions, and only 17% excluded neoplasia. A study conducted in a Reference Service in Southern Brazil found a similarity in the order of frequency of diagnoses. It evaluated 531 anatomopathological results of skin cancer and actinic keratoses, in which 39.74% were BCC, 18.27% were SCC, 4.89% were melanoma, and 31.1% were actinic keratosis.[15]

According to the data from this study, the mean age of the general sample of patients with suspected skin cancer was 70 years and, for the group with confirmed skin cancer, it was 71 years – similar to those found in other studies. It indicates a higher prevalence of skin cancer in patients over 40 years of age due to greater sun exposure throughout life, the most important risk factor.[1,8,9,16,17]

Table 3: Topographic location of biopsies performed on the general sample and on the groups formed regarding the pathological results

	Group 1 Neoplastic lesions N=238	**Group 2** Premalignant lesions N=81	**Group 3** Benign lesions N=63	**General sample** N=382
Cephalic segment	144 (61%)	43 (53%)	34 (54%)	221 (58%)
Trunk/Members	94 (39%)	38 (47%)	29 (46%)	161 (42%)

Table 4. Frequency of topographic locations of biopsies from Group 1 and subgroups with different histological diagnoses

	Group 1 n=238	**Basal cell carcinoma n=163**	**Squamous cell carcinoma n=71**	**Other neoplasms n=4**
Cephalic segment	144 (61%)	116 (71%)	26 (37%)	2 (50%)
Trunk/Members	94 (39%)	47 (29%)	45 (63%)	2 (50%)

In Brazil, approximately 176,930 new cases of skin cancer were estimated in 2020. The state of São Paulo estimated an incidence rate of non-melanoma skin cancer in 2020 higher for women (101.84 per 100,000 women) and lower for men (72.31 per 100,000 men).[1] According to this study's findings, the prevalence was also increased for women, as they had more indication for biopsy (56.1%). The increased prevalence among women was also verified when we evaluated only patients with confirmed skin cancer (52% were women).

The patient with skin cancer becomes a matter of concern due to the risk of developing other skin cancers such as BCC, SCC, and melanoma. Evidence from cohort studies and case registries shows that the patient with skin cancer has a relative risk of 1.12-1.49 times higher for developing a new skin tumor.[18] Thus, it is worth noting that, in our study, 45% of patients with skin cancer confirmed by the anatomopathological examination (Group 1) had a second diagnosis of skin cancer in their lifetime.

Among the neoplasms confirmed by the anatomopathological examination, BCC presented the highest prevalence, with 68% of the total diagnosed neoplasms. This percentage agrees with the literature data that shows that this histological type is the most frequent, with rates reaching up to 70% of all skin neoplasms.[8,16,17] According to the order of prevalence of neoplasms, we also emphasize that SCC ranked second, representing 30% of diagnoses. These values are very close to those of the 2015 European Consensus, where SCC represents approximately 20% of skin neoplasms.[18]

The anatomopathological results compatible with the diagnosis of actinic keratoses represented 21% of the total cases in our study. These lesions comprise a classic spectrum of premalignant cutaneous lesions not categorized as malignant or benign. However, some authors classify them as "in situ" neoplasms since they derive from clonal modifications of keratinocyte DNA.[9] Although the diagnosis of actinic keratosis is clinical, some criteria may justify the need for biopsy due to the possibility of neoplastic transformation, such as lesions larger than 1 cm, bleeding, ulceration, induration, rapid growth, and intense erythema.[9]

NMSC is typically found in the cephalic and cervical segment, upper trunk, and arms.[8,9,18,19] In our study, more than half (58%) of the biopsies were performed in the cephalic segment, in accordance with what was found in another Reference Hospital, where the authors showed that most biopsies were performed in the cephalic segment (50.47% of cases).[20]

A study that epidemiologically assessed patients who obtained skin biopsies compatible with BCC observed that 67% of them were identified in the cephalic segment. The three prevalent anatomical subunits were the nose (47.4%), ear (16.3%), and forehead (14.9%).[18] Our study showed that, for patients diagnosed with BCC, the three anatomical subunits most frequently biopsied were the nose (32%), periauricular/temporal region (29%), as reported in the study mentioned above, and the cheek(12%), differing from the previous research.

Most conclusive SCC biopsies occurred in the trunk and limbs (63%), and face (37%). It differs from the literature, which

Table 5: Frequency of biopsies location in the anatomical subunits of the cephalic segment in general sample and in groups formed regarding the anatomopathological results

	Group 1 Neoplastic lesions n=144	**Group 2** Premalignant lesions n=43	**Group 3** Benign lesions n=34	**General sample** N= 221
Nose	40 (27.7%)	8 (18.6%)	8 (23.5%)	56 (25.3%)
Periauricular/Temporal	42 (29.1%)	10 (23.2%)	4 (11.7%)	56 (25.3%)
Periorbital	9 (6.2%)	6 (13.9%)	5 (14.7%)	20 (9%)
Forehead	13 (9%)	2 (4.6%)	4 (11.7%)	19 (8.6%)
Malar	23 (16%)	11 (25.5%)	10 (29,4%)	44 (19.9%)
Mandibular	3 (2.1%)	2 (4.6%)	1 (2.9%)	6 (2.7%)
Mentonian	3 (2.1%)	-	-	3 (1.3%)
Lips	5 (3.4%)	2 (4.6%)	-	7 (3.1%)
Scalp	6 (4.1%)	2 (4.6%)	2 (5.8%)	10 (4.5%)

Table 6. Frequency of biopsies localization in the anatomical subunits of the cephalic segment for the histological results of basal cell carcinoma and squamous cell carcinoma

	Basal cell carcinoma n=116	Squamous cell carcinoma n=26
Nose	38 (32%)	2 (7.6%)
Periauricular/Temporal	34 (29%)	8 (30.7%)
Periorbital	8 (6.8%)	1 (3.8%)
Forehead	9 (7.7%)	4 (15.3%)
Malar	14 (12%)	8 (30.7%)
Mandibular	2 (1.7%)	1 (3.8%)
Mentonian	3 (2.5%)	-
Lips	5 (4.3%)	-
Scalp	3 (2.5%)	2 (7.6%)

indicates a higher frequency of these tumors also in the cephalic segment. According to the European Consensus (2015), 90% of SCCs are in photoexposed areas, such as the head, neck, back of the hands, and forearms.[19] An epidemiological assessment conducted in 2012 identified that 25.9% of SCC biopsies were performed in trunk and limbs and 32.6% on the face, but 41.5% of the reports did not disclose this information.[12]

According to a literature review about actinic keratoses, these lesions are predominantly located in sun-exposed areas, such as the face, scalp (mainly of bald heads), cervical region, shoulders, forearms, and back of the hands.[9] Although the diagnosis of actinic keratosis is clinical, some criteria may justify the need for biopsy due to the possibility of neoplastic transformation, such as lesions larger than 1 cm, bleeding, ulceration, induration, rapid growth, and intense erythema.[9] In our study, the biopsied lesions were mainly distributed in the cephalic segment, representing 53% of the sample, and the malar subunit was the most biopsied. Also, 47% of the biopsies were performed in the trunk and limbs. Another relevant factor concerns the potential for malignant actinic keratosis. Though it presents a relatively low percentage (about 10% in immunocompetent patients and 20% in immunocompromised patients, considering only one lesion in 10 years), patients with this type of lesion have a history of intense and prolonged sun exposure. Thus, they almost always have a diagnosis of more than one lesion – which increases the chance of having some malignant transformation.[9]

When we face a possible clinical diagnosis, together, a range of possible differential diagnoses opens up. With non-melanoma skin cancer it is no different. Thus, other neoplastic diseases of varying cell lineages, such as melanocytes, spindle cells, muscle fibers, gland cells, and non-neoplastic lesions of different inflammatory and even infectious origins, are part of these diagnostic options.[21] It justifies the finding of other neoplasms (melanoma, undifferentiated carcinoma, epithelioid neoplasm, and adenocarcinoma) and the different benign lesions as anatomopathological results of some patients in our study.

CONCLUSIONS

Due to the epidemiological importance of NMSC and its growing incidence in the world population, its consideration as a public health problem is imperative. In this study, we evidenced a higher incidence of skin cancer among women and elderly patients, and the most frequent diagnosis was basal cell carcinoma. Therefore, better understanding the epidemiological profile of skin cancer in patients treated at a Reference Hospital and knowledge of the accuracy of the biopsies performed allowed a better assessment of the prevalence and possible risk factors associated with this type of neoplasm in this sample of the population. Thus, we emphasize the need for conducting more studies to establish better prevention strategies, with emphasis on early diagnosis and treatment.

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Treatment of hook nails using the Bakhach's technique: a retrospective study

Tratamento da unha em gancho com a técnica de Bakhach: estudo retrospectivo

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ABSTRACT

Introduction: The cause of the hook nail is the trauma of the hyponychium. The nail plate presents longitudinal hypercurvature of volar concavity, causing functional loss, aesthetics concerns, and pain.

Objective: To evaluate the research results of 20 medical records of patients submitted to hook nail correction surgeries of traumatic etiologies.

Methods: Epidemiological, cross-sectional, retrospective study of patients' medical records who were submitted to Bakhach's surgical technique, from 2010 to 2018, in the Hand Surgery Outpatient Clinic of the Hospital do Servidor Público Municipal de São Paulo.

Results: We analyzed 20 affected fingers: 7 were victims of accidents with sharp objects, 5 with press machines, 5 with doors, 1 with window, 1 with motorcycle, and 1 due to a dog bite. The finger with the highest incidence was the middle finger (n=12), followed by the index finger (n=5), and ring finger (n=3). The main complaint was aesthetics (n=11); pain (n=6), and functional (n=3). All cases had type II distal digital transverse amputations and underwent surgical treatment. The reconstruction surgery occurred between 4 and 25 months after the trauma.

Conclusion: 15 patients were satisfied and two felt pain: one in the distal interphalangeal joint and the other in the hyponychium. The follow-up ranged from 6 months to 2 years.

Keywords: Finger injuries; Hand injuries; Nail diseases; Nails malformed

RESUMO

Introdução: *a causa da unha em gancho é o trauma do hiponíquio. A lâmina ungueal se apresenta com hipercurvatura longitudinal de concavidade volar, causando perda funcional, comprometimento estético e dor.*

Objetivo: *avaliar os resultados na pesquisa de 20 prontuários de pacientes submetidos a cirurgias de correções de unhas em gancho de etiologias traumáticas.*

Métodos: *estudo retrospectivo transversal epidemiológico, de 2010 a 2018, de prontuários de pacientes submetidos à técnica cirúrgica de Bakhach, no ambulatório de Cirurgia da Mão do Hospital do Servidor Público Municipal de São Paulo.*

Resultados: *20 dedos acometidos. Sete vítimas de acidente com objetos cortantes, cinco com máquinas tipo prensa, cinco com portas, um com janela, um com motocicleta e um por mordida de cachorro. O dedo com maior incidência foi o médio (12 casos); seguido do indicador (cinco casos) e do anelar (três casos). A queixa principal foi estética (11); dor (seis) e funcional (três). Todos tiveram amputações digitais distais transversas do tipo II e foram submetidos a tratamento cirúrgico. A cirurgia de reconstrução ocorreu entre quatro e 25 meses pós-trauma.*

Conclusão: *15 ficaram satisfeitos, embora dois destes tenham relatado dor: um na articulação interfalângica distal e o outro no hiponíquio. O acompanhamento variou de seis meses a dois anos.*

Palavras-chave: *Doenças da unha; Traumatismos dos dedos; Traumatismos da mão; Unhas malformadas*

Original Article

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INTRODUCTION

Amputations of the end of the distal phalanx can result in bone and tissue loss, making it difficult to close the wound. The hook nail is a deformity caused by traumatic injury to the hyponychium, and the nail plate presents a longitudinal hypercurvature with volar concavity. The patient complains of functional incapacity, aesthetic impairment, and pain.[1-5]

This study aims to demonstrate the necessity of Bakhach's surgical technique for the functional rehabilitation of the affected finger of the hook nail with the esthetic satisfaction of the patient.

MATERIAL AND METHODS

We assessed 20 medical records of patients treated at the Hand Surgery Outpatient Clinic of the Hospital do Servidor Público Municipal of São Paulo between 2010 and 2018. All patients presented hook nails with traumatic etiology. The Informed Consent Form (ICF) was not applied, considering the current coronavirus pandemic and the fact pointed out by the researchers that some surgeries were performed many years ago. Once the researchers explicitly committed to the secrecy and care with the confidentiality of the data, the research ethics committee considered the waiver of the informed consent pertinent.

According to the medical records, surgeries were performed under anesthesia, with an injection of 3 ml 2% lidocaine without epinephrine in the flexor tendon sheath. The tourniquet was performed using the finger of a glove. The nail plate was removed, and two lateral incisions were made on each side of the paronychia. Between these incisions, a rectangular skin graft was taken from the region proximal to the eponychium.[4] The nail matrix was carefully separated from the phalanx, preserving the irrigation of the proximal portion. The nail matrix was reinserted proximally, with the distal interphalangeal joint as a limit. We used the "V-Y" flap, popularized by Atasoy,[3] to reconstruct the hyponychium. Weekly dressings were performed, and the stitches were removed within 14 days (Figures 1 to 5).

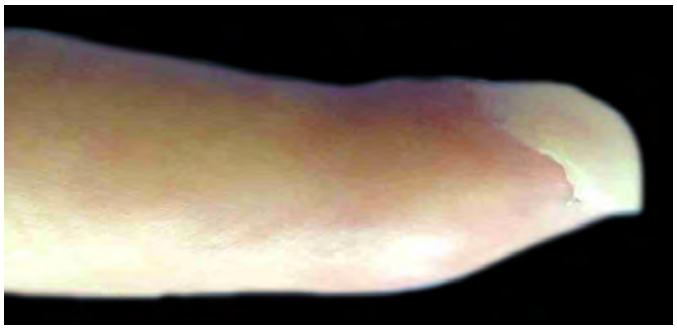

Figure 1: MLOS, 29-year-old woman, teacher, amputation III finger (qd) due to crushing caused by a door nine months ago

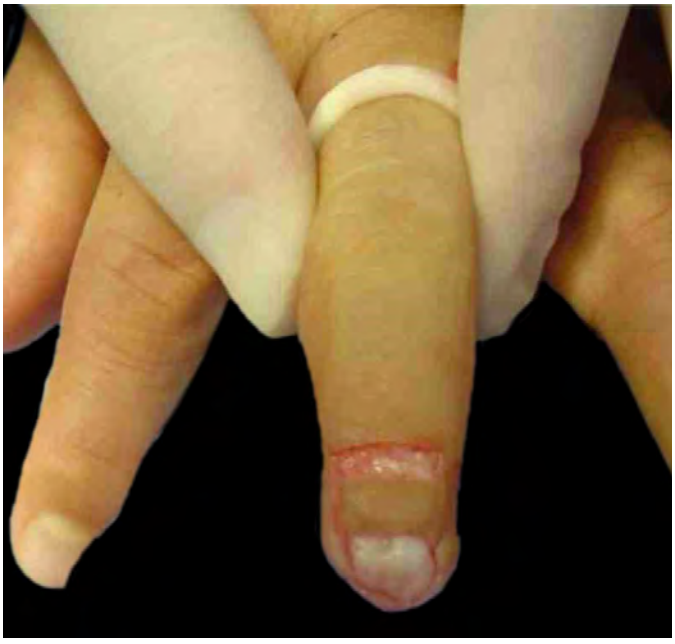

Figure 2: Tourniquet - incision on the side of the paronychium - donor area - rectangular skin graft from the region proximal to the eponychium

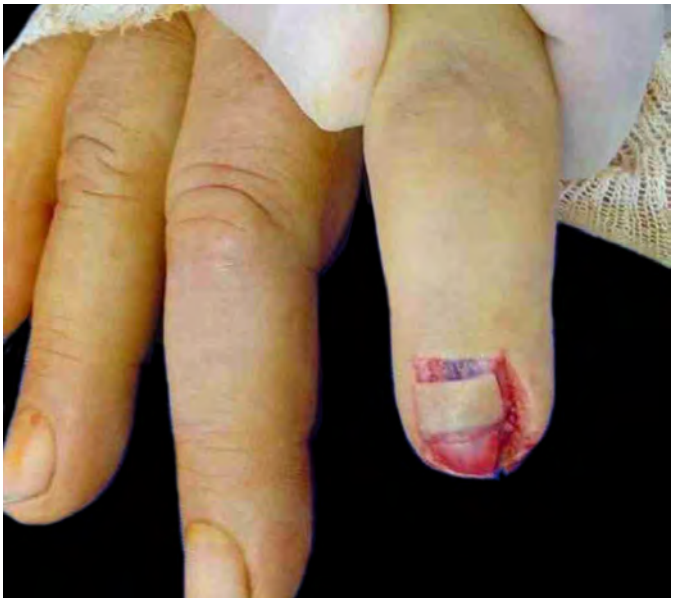

Figure 3: Arterial branches originating from the distal dorsal digital arch allowing the elevation of the dermal-hypodermal flap. The arrow indicates an irrigation tunnel

RESULTS

Of the 20 fingers affected, 15 belonged to male patients and five to female patients. Seven patients were victims of accidents with sharp objects, five with press machines, five with doors, one with a window, one with a motorcycle, and one due to a dog bite (Chart 1).

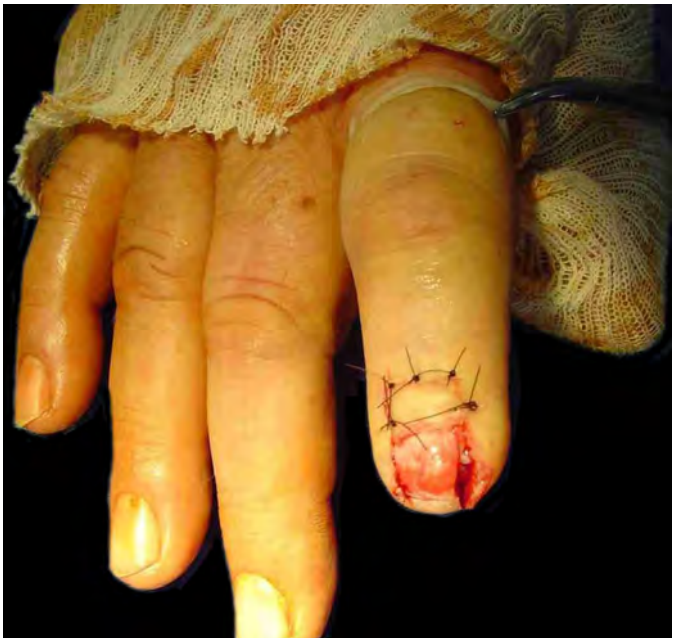

Figure 4: Final operative aspect

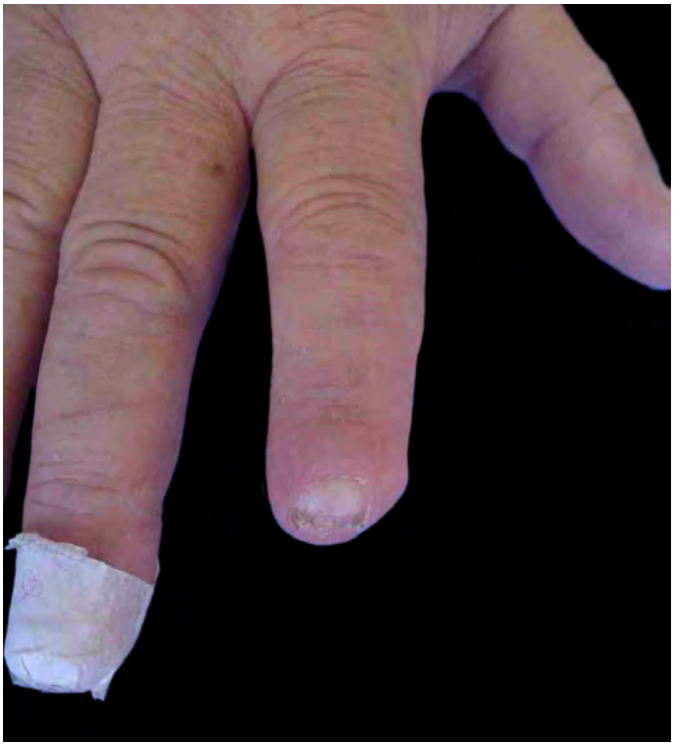

Figure 5: Six months postoperative

The most affected finger was the middle (12), followed by the index (5) and the ring (3) (Chart 2).

The main complaint of patients was aesthetic (11), followed by pain (6), and function (3). Shows these results (Chart 3).

All patients had undergone type II transverse digital amputations and underwent urgent surgical treatment at different hospitals. Reconstructive surgery took place between four and 25 months post-trauma. We obtained a proximal repositioning of the nail bed ranging from 3 mm to 5 mm (10 patients with 5 mm, five with 4 mm, and five with 3 mm). No flap showed necrosis. The surgical time ranged between 30 and 55 minutes. Fifteen patients were satisfied with the result, although two remained in pain, one in the distal interphalangeal joint and the other in the hyponychium. Follow-up time ranged from six months to two years, and all patients returned to their normal activities (Chart 4).

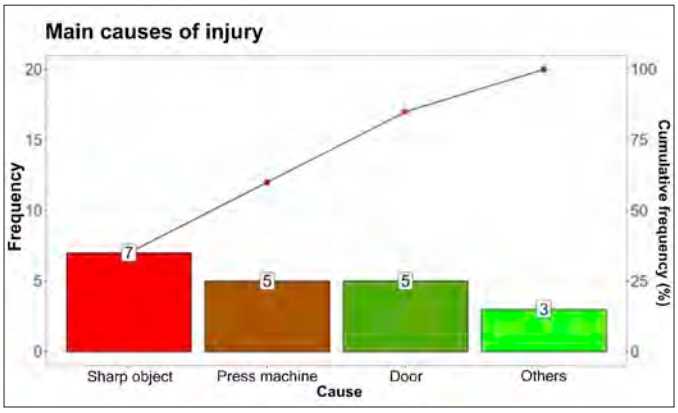

Chart 1: Causes of injury

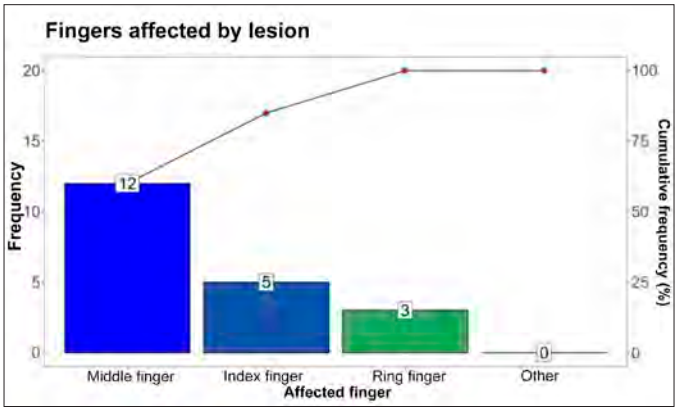

Chart 2: Fingers affected

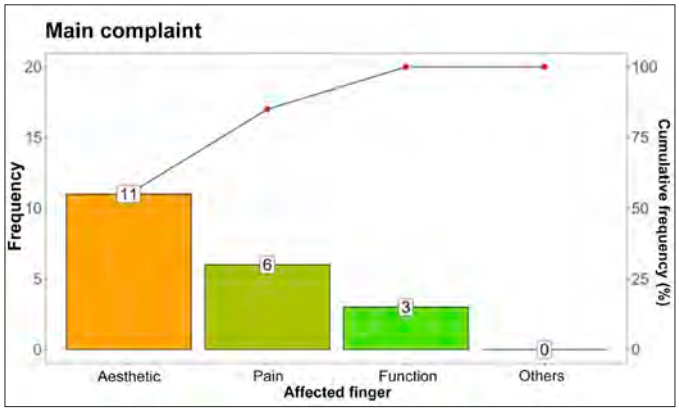

Chart 3: Main complaint

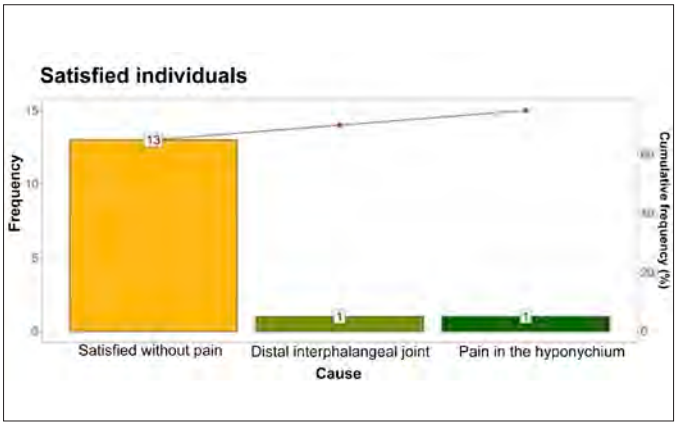

Chart 4: Result of follow-up

DISCUSSION

Acute nail bed injuries must be cared for urgently and adequately, as established deformities are challenging to treat.[1,6] The attempt to obtain coverage of the shortened bone of the distal phalanx by traction of the nail bed towards the digital pulp generates the deformity known as a hook nail. Some authors have described techniques with variable aesthetic results[6,7,8] and/or that require sophistication for microsurgical reconstruction with tissue donated from the first or second toe.[9,10] The method described by Bakhach[1,2] proved to be efficient precisely for its practicality, low complication rate, and good clinical and aesthetic improvement in acute cases or its long evolution, as demonstrated in our series.

Numerous arterial branches originating from the distal dorsal digital arch irrigate the eponychium flap,[1,2] allowing the safe elevation of the dermal-hypodermal flap. We obtained the replacement of the nail in a more proximal position (3 mm to 5 mm) similar to that obtained by Bakhach et al.[2] This repositioning increases the area supported by the phalanx, favoring the growth of a nail plate with greater length and without longitudinal curvature. The V-Y advancement flap3 favored the reconstruction of the hyponychium and a better quality digital pulp.[3, 10-13]

CONCLUSION

The hook nails surgical treatment using the Bakhach technique is a safe surgical option, with good aesthetic and functional results. ●

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Use of botulinum toxin in hidradenitis suppurativa

Uso da toxina botulínica na hidradenite supurativa

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ABSTRACT

Introduction: Hidradenitis suppurativa (HS) is an inflamatory, chronic, recurrent, and debilitating condition. There is a lack of consensus about its treatment.

Objective: We conducted a review of the national and international literature, searching for articles that addressed the use of botulinum toxin in HS, in addition to describing the doses and techniques used.

Methods: A bibliographic search was performed in LILACS, Medline, and SciELO.

Results: Botulinum toxin can be an effective therapy in patients with HS, especially in cases of concomitant hyperhidrosis and traditional therapies fail. It offers the possibility of conducting treatment with minimal adverse events, reproducible over time without loss of effectiveness, in addition to reducing pain.

Conclusions: Patients will likely need more than one treatment over time, as the lesions tend to recur after 6 to 10 months. The technique used has been the standard for hyperhidrosis. Further research is needed to understand its role in the management of HS, including the ideal dosage and frequency of administration.

Keywords: Hidradenitis suppurativa; Hidradenitis; Botulinum toxins; Botulinum toxins, type A

RESUMO

Introdução: *hidradenite supurativa (HS) é uma condição inflamatória, crônica, recorrente e debilitante. Há uma falta de consenso sobre o seu tratamento.*

Objetivo: *foi realizada revisão da literatura nacional e internacional, buscando-se artigos que abordassem o uso da toxina botulínica na HS, além de descrever as doses e técnicas utilizadas.*

Métodos: *foi realizada busca bibliográfica nas bases LILACS, Medline e SciELO.*

Resultados: *considera-se que a toxina botulínica pode ser eficaz em pacientes com HS, principalmente se houver hiperidrose concomitante e quando as terapias tradicionais falham. Oferece a possibilidade de realizar um tratamento com efeitos colaterais mínimos, repetíveis ao longo do tempo sem perda de eficácia, além de diminuir a dor.*

Conclusões: *é provável que os pacientes precisem de mais de um tratamento com o tempo, pois as lesões tendem a se repetir após uma média de seis a 10 meses. Utiliza-se a técnica padrão para hiperidrose. Mais pesquisas são necessárias para entender o seu papel no gerenciamento da HS, incluindo dosagem e frequência ideais de administração.*

Palavras-chave: *Hidradenite supurativa; Hidradenite; Toxinas botulínicas; Toxinas botulínicas tipo A Rotação*

Original article

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INTRODUCTION

Hidradenitis suppurativa (HS) is also known as acne inversa or Verneuil's disease. It is an inflammatory condition of a chronicle character, recurrent and debilitant. Its pathogenesis results from chronic obstruction of the follicular portions of the pilosebaceous units.[1,2] Its prevalence ranges from 1% to 4% of the world's population, but it is believed to be underestimated.[2]

The proposed pathogenic HS sequence starts with a follicular occlusion, causing dilation of the pilosebaceous unit, rupture, and exit of the follicular content (keratin, corneocytes, bacteria, sebaceous matter) in the dermis. The secondary inflammatory process involves deregulation in both innate and adaptive immunity.[3,4] Extensive fibrosis is often seen as a late result of this inflammation. We still don't know whether this mechanism comes from environmental and/or genetic factors.[5] Among the risk factors, we can identify family history, obesity, smoking, and drug use (oral and injectable contraceptives containing medroxyprogesterone acetate or levonorgestrel).[6]

HS may occur sporadically, but genetic studies have identified susceptibility genes involved in the gamma-secretase expression. However, mutations were found only in a minority of HS patients.[7] Currently, 23 pathogenic sequences are identified in HS. Still, these findings are probably significant only in the familial HS.[8] Hessam et al. showed that the expression of IL36α, β, γ, and IL36Ra was significantly higher in HS lesional skin compared to healthy controls.[9]

The most common sites of HS involvement are intertriginous skin areas, including armpits, groins, perianal, perineal, and inframammary regions.[10] The symptoms begin after puberty and at age 40, being more common in women, with a proportion of 3,6:1 reported in a retrospective French observational study.[6,11] Lesions start as inflamed nodules and may evolve into fistulized and interconnected abscesses, forming scars, with pain as their main characteristic.[12]

It is noteworthy that the pain, associated with foul odor due to the secretion and scar formation, significantly impacts the patients' quality of life. Even though it is a prevalent disease with limited therapeutic options, it is necessary to correctly treat HS patients due to the higher presence of depression and sexual dysfunction among them.[13] Thus, due to its chronic character and its impact on the patients' quality of life, its correct management, although complex, is essential.[14]

The initial approach of these patients depends on their classification using Hurley's clinical staging:[15] stage I - abscess(es) formation, no fistulization, and no scarring; stage II - recurrent abscesses, with sinus tracts formation and scarring; stage III - diffuse abscesses or interconnected sinus tracts and multiple abscesses.

In all patients, conservative management with weight loss and smoking cessation is recommended, and psychosocial support and analgesia if necessary. Antibiotics are effective in mild to moderate cases. In women, antiandrogenic therapy reduces the severity of the disease in some cases. Systemic immunosuppression, including cyclosporine and infliximab, led to a significant improvement in moderate to severe disease. In advanced disease, or where medical therapy has failed, surgical treatment may involve radical excision of affected apocrine glands. LASER (light amplification by stimulated emission of radiation) therapy and external beam radiation have also demonstrated efficacy and may be helpful in selected patients.[16]

Recently, the multiple uses of botulinum toxin (BT) in dermatological conditions have been reviewed, especially those called "Fold (intertriginous) dermatoses".[17] Among these is HS, which involves precisely these areas of the body.[5]

The exact mechanism by which BT affects the disease process in HS is unclear. The moist environment resulting from the sweat retained in the armpit and groin provides ideal conditions for bacteria to flourish. The presence of apocrine glandular secretions can aggravate it, forming a rich substrate for bacterial growth. The antiperspirant effect of BT reduces the skin flora population, consequently decreasing the inflammatory stimulus for HS. A second possibility is that BT shuts down the function of the whole pilosebaceous unit and apocrine secretion, preventing the rupture and dissemination of follicular material through the dermis, which usually results in more inflammation.[18]

Currently, there is a lack of consensus on the ideal treatment for HS. Despite the advent of biological drugs, the disease remains a therapeutic challenge. Many therapies are available, but the benefits of these treatments should be weighed against the adverse events. BT represents a new and promising treatment option for this complex disease. However, a shared treatment regimen is necessary to define the potential of this treatment in HS, and mainly, a change in the quality of life of these patients. Given this context, it is relevant to conduct studies seeking to relate such information and subsidize new and more efficient approaches. The present study aimed at reviewing the use of botulinum toxin in hidradenitis suppurativa in the national and international literature, besides describing the doses and techniques used to treat the disease.

METHOD

This study is a narrative literature review. We conducted a bibliographic search on the electronic databases Latin American & Caribbean Health Sciences Literature (LILACS), Medical Literature Analysis and Retrieval System Online (Medline), and Scientific Electronic Library Online (SciELO), published from 2009 to 2019.

The descriptors used were: Hidradenitis Suppurativa, Hidradenitis, Botulinum Toxins and Botulinum Toxins, Type A. All descriptors are found in the Health Sciences Descriptors (DeCS). We identified nine articles in the databases mentioned above and selected six of them for this study after reading their title and abstract.

RESULTS

The first case of HS treated with botulinum toxin type A (BTXA) dates back to 2005. The 38-year-old patient (patient A) had the disease for more than ten years and was submitted to therapy with lymecycline and flucloxacillin without clinical improvement. She received then 250 U of Dysport® in both armpits. The toxin was delivered with intradermal papules, the standard technique for hyperhidrosis. After 15 days of the administration, there was no evidence of active inflammation. The patient had complete remission of symptoms until approximately ten months later when the first symptoms of mild inflammation reappeared.[19]

Feito-Rodriguez et al. described the first case of application of botulinum toxin A in a prepubertal child to treat HS (patient B). At six years of age, the child was diagnosed with HS, presenting erythematous papules and painful nodules only in the groin, symmetrically. Topical and oral antibacterials were prescribed, in addition to isotretinoin, which was discontinued due to adverse events. At the age of 7 years and 5 months, a total dose of 40 U of Botox® was applied under sedation, distributed in 10 to 12 points on an elliptical area on each side of the groin. She had complete remission until six months later when the first lesions reappeared. A new, similar application was made with a good therapeutic response.[20]

Khoo & Burova reported the third case in the literature, using BTXA to treat HS in three patients. The authors reported the most successful case in a 46-year-old patient (patient C) who had the disease for 11 years (Hurley II). She had already been submitted to systemic antibiotics, without improvement, and surgical drainage of the abscesses. The patient received 50 U of BTXA in each armpit. There was a good clinical response within three months after the first treatment, and after the second treatment, there was clinical remission, which lasted for more than a year. The other two patients presented a disease-free period from 5 to 6 months.[18]

Reilly et al. described another case of success in a 23-year-old woman (patient D), diagnosed with HS for four years. She had performed eight surgical incisions in the groins, buttocks, and inner part of the thighs, with slight improvement. The patient received 100 U of BTXA (Botox®) in the groin and inner thighs and 130 U in the buttocks. There was a complete resolution of the symptoms for three months. In the following 18 months, the patient received five more BTXA applications, each consisting of 200 U (100 U in the anterior region and 100 in the posterior). There was a four-month interval between treatments, and in the last month of this interval, there was an exacerbation of the lesions, requiring surgical intervention.[16]

Shi et al. also reported a case of successful treatment of HS in stage III with BTXA. The 40-year-old patient (patient E) presented HS in the groin and armpits with chronic pain and had failed therapy with oral and topical antibiotics and surgical treatment. She then received a total of 400 U of BTXA – 100 U for each site (bilateral and inframammary axillary region). The study used intradermal injection in parallel lines with 1 cm of distance between the points, with approximately 20 injections per area. There was an excellent response with a significant reduction in drainage and inflammation, as well as pain relief of 50%. In subsequent administration, the dose was reduced to 50 U per area, in addition to injection at other areas such as groins and perineal regions. However, the symptoms returned earlier with the dose reduction. Thus, the subsequent applications resumed the dose of 100 U for each site. The patient received no other treatment during BTXA therapy.[10]

In 2019, Campanati et al. described two cases of HS treated with BTXA. Case 1 was a 23-year-old young woman (patient F) who presented HS in the armpits (Hurley II) refractory to topical and oral therapies. The area was treated with BTXA (Vistabex®), with a technique similar to axillary hyperhidrosis' procedure, using 50 U per armpit diluted in 2.5 ml of 0.9% saline solution. She received an intradermal injection, with the administration of 4 U in each square of 1.5 cm^2. Case 2 was a 50-year-old man (patient G) with HS in the groin and inner thigh region (Hurley II) who had failed other topical and systemic therapies. He received BTXA (Botox®) in the same dilution and technique described above, but 100 U on each side. Both patients were reassessed after one, three, and six months. They experienced real improvement with the disappearance of inflammatory lesions in case 1 and reduction of fistulas in the groin in case 2. The patient of case 1 decided to undergo therapy again after ten months with an optimal response[5] (Table 1).

DISCUSSION

Botulinum toxin type A can be an effective therapy in patients with HS, especially if there is concomitant hyperhidrosis and when traditional therapies fail.

The BTXA blocks the release of acetylcholine and other pre-synaptic vesicle neurotransmitters by deactivating SNARE proteins. It has been used for hyperhidrosis blocking the cholinergic nerve fibers of the sweat glands. The US Food and Drug Administration (FDA) approved it in 2004 to treat severe primary axillary hyperhidrosis refractory to the use of antiperspirants.[10]

It is not clear how BTXA can improve HS. The first hypothesis is that local factors such as humidity can create an ideal environment for bacterial growth, a known pro-inflammatory element. In fact, bacteria are not promoters of the disease, but they among the main contributors to a vicious inflammatory circle.[21] Thus, reducing sweat production could reduce the skin flora population and its potential pro-inflammatory effect.

The other hypothesis about the BTXA therapeutic effect is that it shuts down the function of the entire pilosebaceous unit and apocrine secretions, preventing the rupture and spread of follicular material through the dermis, which usually results in more inflammation and formation of the sinus tract.[17]

Patient A, treated with 250 U of Dysport® in both armpits, presented condition improvement attributed to reducing

Table 1 - Botulinum toxin type A (BTXA) injection therapy in patients with hidradenitis suppurativa (HS)

First author	N	Hurley	BTNA – dose	Follow-up	Results
O'Reilly (2005)	1	–	250 U – armpits	10 months	Remission
Feito-Rodriguez (2009)	1		40 U – inguinal regions	6 months	Remission
Khoo (2014)	3*	II	100 U – armpits	3 years	Remission
Reilly (2015)	1	-	100U – groins/thigh 130 U - buttock	18 months	Remission
Shi (2018)	1	III	200U - armpits 200U - inframammary	–	Remission
Campanati (2019)	2	II II	100 U – armpits 200 U - groins	10 months 6 months	Remission

*Only one case described.

Source: Clinical research

apocrine sweat, thus decreasing the tendency of follicular rupture. The study didn't report how the dilution was made. The technique used was similar to that of hyperhidrosis, but the remission period was ten months, superior to that of hyperhidrosis – 6 to 8 months.[19]

Patient B received 40 U of Botox®, distributed in 10 to 12 intradermal points in the groin. No dilution was described. She had complete remission within six months, responding satisfactorily to a second treatment. BTXA therapy can be a safe, well-tolerated, and effective method for young patients who develop mild to moderate HS, refractory to other therapies.

Patient C received 50 U of BTXA in each axilla (100 U diluted in 4 ml of 0.9% SS). The study didn't report the technique used. She presented clinical remission after the second treatment and periodically continued to perform the toxin application.

Patient D underwent application of 100 U of Botox® in the groin and thighs and 130 U in the buttocks. Neither technique nor dilution was reported. She presented a complete resolution of the symptoms for three months but required subsequent treatments (five treatments of 200 U), with intervals of four months. Nevertheless, the patient developed infectious exacerbation demanding surgical treatment.

Patient E received 400 U of BTXA, 100 U in each area: right/left inframammary and right/left axilla. The dilution was 100 U of toxin in 2 ml saline solution, and the technique used intradermal injection in parallel lines with a distance of 1 cm between the points. At each point, 0.1 ml of the dilution was injected. Here, we obtained the first complete description of the doses, dilution, and technique. The patient obtained an excellent response to treatment beyond pain relief. Shi et al. also reported that subsequent applications with lower BTXA dosages (50 U per area) led to a faster return of symptoms, resuming the higher doses. The authors pointed out that BTXA seems to work best in the inflammatory state of the disease and that the toxin can be an economical treatment for HS, even in the Hurley III.[10]

Patient F underwent application of 50 U of Vistabex® in each axilla, in a technique similar to that of axillary hyperhidrosis (50 U diluted in 2.5 ml 0.9% SS). Each 1.5 cm^2 square received 4 U. Patient G received 100 U of Botox® in each groin, with the same dilution and technique described above. In both, efficacy was similar to hyperhidrosis treatment (6-12 months) with a slow recovery from the disease.

It is worth mentioning that most of the off-label uses of BTXA are for chronic diseases. However, a question remains: how long can we use this treatment in patients with HS without risks or sequelae? We found that all patients needed subsequent doses to control the disease better. Another topic to be discussed is that the botulinum toxin has an immunogenic potential related to the dose injected and injection frequency. Therefore, it is reasonable to extend the application intervals by balancing the dose with the expected duration of the clinical effect. A well-defined dosage regimen is required, as well as injection and dilution techniques for standardization of these protocols.

CONSIDERATIONS

BTXA is a new and promising treatment option. Further research is needed to understand its role in HS management, including optimal dosing and administration frequency. Patients are likely to need more than one treatment over time, as lesions tend to recur after an average of six to ten months. The technique used has been the standard one for hyperhidrosis.

It is a safe, well-tolerated, and effective method for young patients who develop mild to moderate HS without improvement after several therapeutic modalities. Also, it offers the possibility to perform a treatment dedicated to some patients providing minimal, reproducible adverse events over time without loss of effectiveness, in addition to reducing pain. ●

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Use of botulinum toxin for rosacea: a pilot study

Uso da toxina botulínica para rosácea: estudo-piloto

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ABSTRACT

Introduction: Rosacea is a chronic inflammatory skin disease. The intradermal application of botulinum toxin (BT) has been studied as a therapeutic option for patients who struggle to manage flushing and/or persistent facial erythema. There is no standard protocol for BT application in rosacea.

Objective: To evaluate the effectiveness of botulinum toxin application on erythematotelangiectatic rosacea.

Methods: Pilot study with case series. We applied intradermal BT in 10 patients with a diagnosis of rosacea and symptoms of persistent erythema and/or facial flushing. Patients received 10 to 15 injections per hemiface (1 unit of onabotulinum BT per injection) and 0 to 5 injections in the nasal region, totaling 25 to 35 units per patient.

Results: Seventy-five percent of the patients presented a reduction in flush and erythema intensity. The follow-up time was three months, and no serious adverse events were observed.

Conclusions: The therapeutic arsenal to control erythema and facial flushing of rosacea, especially refractory to the usual treatment, should consider the intradermal application of BT type A.

Keywords: Erythema; Rosacea; Flushing; Botulinum toxins

RESUMO

Introdução: rosácea é uma doença inflamatória crônica da pele, e a aplicação intradérmica de toxina botulínica (TB) tem sido estudada como uma opção terapêutica aos pacientes de difícil manejo do flushing *e/ou eritema facial persistente. Ainda não há protocolo-padrão para aplicação da TB na rosácea.*

Objetivo: *avaliar o efeito da aplicação de toxina botulínica na rosácea eritêmato-telangiectásica.*

Métodos: *estudo-piloto com série de casos. Foi realizada a aplicação intradérmica da TB em 10 pacientes com diagnóstico de rosácea e sintomas de eritema persistente e/ou flushing facial. Os pacientes foram submetidos a 10 a 15 injeções por hemiface (1 unidade de TB onabotulínica por injeção) e 0 a 5 injeções na região nasal, totalizando 25 a 35 unidades por paciente.*

Resultados: *apresentaram redução na intensidade do* flush *e do eritema 75% dos pacientes. O tempo de acompanhamento foi de três meses e nenhum evento adverso grave foi observado.*

Conclusões: *a aplicação intradérmica de TB tipo A deve ser considerada no arsenal terapêutico para controle do eritema e flushing facial da rosácea, especialmente em casos refratários ao tratamento habitual.*

Palavras-chave: *Eritema; Rosácea; Rubor; Toxinas botulínicas*

Original Article

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INTRODUCTION

Rosacea is a chronic inflammatory skin condition that predominantly affects the midfacial region. It is characterized by recurrent episodes of flushing, transient or persistent erythema, papules, pustules, and telangiectasias.[1,2] Its prevalence ranges from 1% to 22%, according to different studies and populations.[3]

Although its pathophysiology has not yet been fully understood, the literature shows that innate immune deregulation and commensal skin microbiota imbalance occur. Triggering factors include mite *Demodex folliculorum* infection, ultraviolet radiation exposure, alcohol, heat, exercise, and spicy foods, which support the role of neurogenic inflammation in disease development.[4,5] It is assumed that activating the peripheral sensory neurons of transient receptor potential vanilloid type 1 (TRPV1) and transient receptor potential ankyrin 1 (TRPA1) receptors stimulates the release of vasoactive neuropeptides that cause the disease exacerbation.[5] In addition to vascular hyperreactivity, innate immune system deregulation through cathelicidin abnormal levels (antimicrobial peptides from human skin) also plays a central role in the pathogenesis of rosacea.[5]

Rosacea can be classified into four clinical presentations: erythematotelangiectatic, papulopustular, phymatous, and ocular. According to the 2017 ROSCO panel, this classification is shifting, and one or more characteristics may be present simultaneously in the same patient. The phymatous changes can be individually diagnostic for rosacea, and persistent centrofacial erythema, associated with periodic intensification by potential aggravating factors, is a feature of this condition. In their absence, the diagnosis can also be established by two or more main characteristics: papules and/or pustules, facial flushing, telangiectasia, and specific ocular manifestations.[1,4]

Management regimens aim to suppress inflammatory lesions, erythema, and, to a lesser degree, telangiectasia involved with rosacea.[2] Treatment is based on the phenotype of each patient, and they often overlap. Topical agents such as metronidazole, azelaic acid, ivermectin, brimonidine, and oral agents such as tetracyclines are widely used. Technologies like intense pulsed light and off-label oral medications, such as antihypertensive beta-blockers and adrenergic agonists, can be used to control flushing. However, oral medications often have adverse events and, even with optimized treatment, it can be challenging to treat persistent erythema and flushing in refractory rosacea cases. The intradermal application of botulinum toxin (BT) has been studied as a therapeutic option in patients in whom flushing and/or erythema compromise the quality of life.[6]

This study aims to evaluate the effect of botulinum toxin type A (Botox®) application on rosacea erythema in a series of patients.

METHODS

This is a pilot study with a series of cases. We selected ten patients from the Cosmiatry Clinic of the University Hospital Pedro Ernesto of the State University of Rio de Janeiro (UERJ). Patients of both genders diagnosed with erythematotelangiectatic rosacea (persistent facial erythema and episodes of facial flushing) were enrolled. All individuals agreed to participate in the research and signed the informed consent form (ICF).

We turned off the air conditioner and exposed the skin to the LED red light mask for five minutes to stimulate the erythema. Antisepsis of the face was performed with an alcoholic 2% chlorhexidine solution, followed by delimitation of the erythema region. Erythema was classified into: (1) absence of erythema; (2) erythema and/or mild flushing; (3) erythema and/or moderate flushing; (4) erythema and/or intense flushing; (5) very intense erythema and/or flushing.

We marked 10-15 application points per hemiface and 0-5 application points in the nasal region, with a distance of 1cm between them (Figure 1). Onabotulinum toxin (Botox®Allergan Inc., Irvine, CA, USA) was used, reconstituting the 100 U vial in 1 ml of 0.9% saline solution (1 U per 0.01 ml) and applying intradermally 1 U per marked point.

Clinical evaluation, photographic documentation, and quantification of erythema intensity were performed after 30 and 90 days.

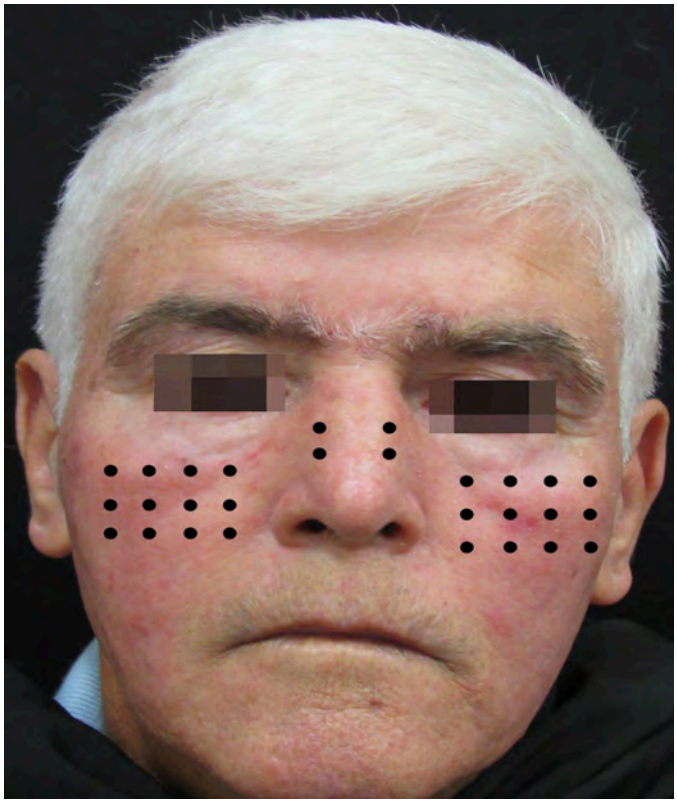


Figure 1: 10 to 15 points were performed in each hemiface and 0 to 5 points in the nasal region

RESULTS

We conducted the treatment in eight women and two men. Age ranged from 19 to 60 years, and skin phototypes, from I to III. Among the triggering factors for erythema and flushing, sun exposure was the most reported, followed by exposure to heat, emotional stress, and physical activity (Table 1).

Of the 10 treated patients (P1 to P10), eight returned for reassessment on the scheduled dates (P1, P2, P3, P4, P7, and P10 showed up in 30 days; P1, P2, P3, P4, P5, and P6 showed up in 90 days).

Of the eight reassessed patients, five reported improvement in erythema and flushing symptoms within 30 days, one reported improvement within 90 days, and two subjects reported no improvement in symptoms. All patients who described enhancement within 30 days maintained the same positive report within 90 days (Figures 2 and 3).

Regarding the analysis and clinical classification of facial erythema and flushing intensity after exposure to LED light, 63% of patients (n=5) decreased their intensity stage, 25% (n=2) remained in the same stage, and 12% (n=1) increased one intensity stage (Graph 1).

Statistical analyzes with non-parametric tests were performed, assessing the results at 30 and 90 days. For the D0-D90 test, the p-value was 0.035 (<0.05), rejecting the null hypothesis. Thus, we can say that there is a reduction in erythema after treatment, with statistical significance.

Adverse events were observed in only two patients: one presented ecchymosis at the BT application site with resolution within five days, and another presented mild asymmetrical smile (not perceived by the patient), corrected with the application of 1U of BT in the region of the contralateral zygomaticus major muscle.

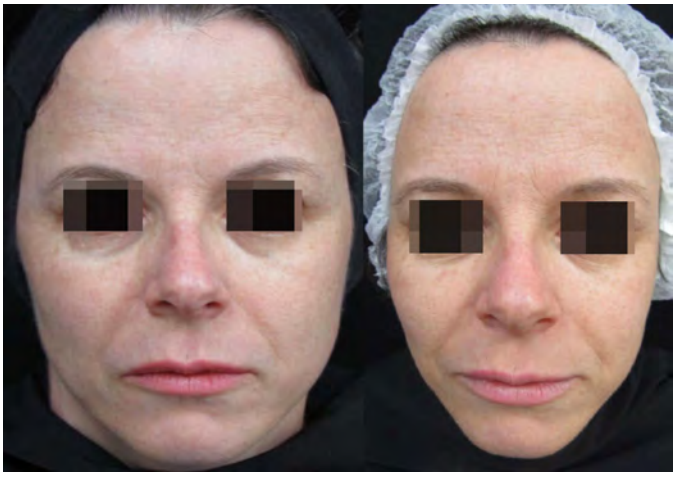


Figure 2: Before BT application and after 30 days

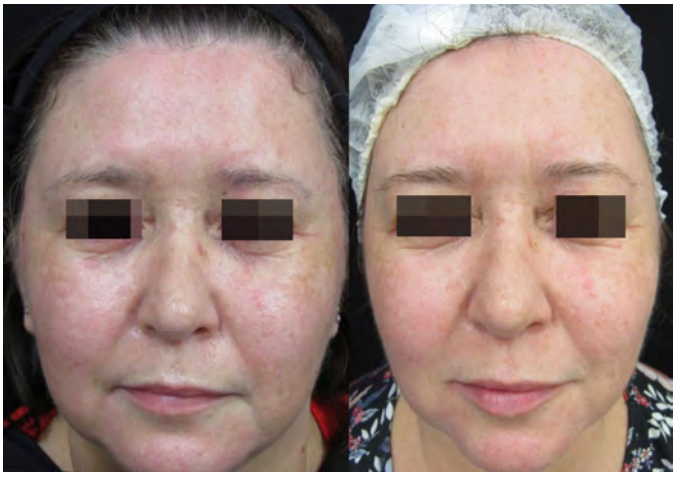
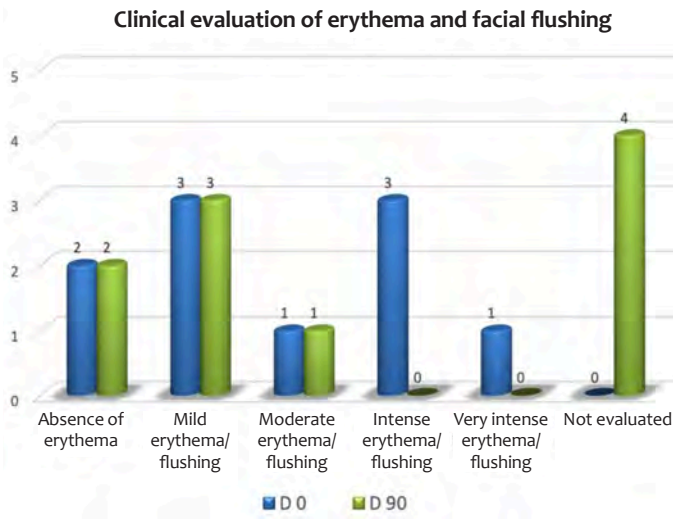


Figure 3: Before BT application and after 30 days

Table 1: Facial flushing triggers

Flushing triggers	Patients	
	Yes (%)	No (%)
Heat	80	20
Cold	60	40
Physical activity practice	60	40
Consumption of hot drinks	20	80
Consumption of alcoholic beverages	40	60
Emotional stress	70	30
Consumption of spicy foods	20	80
Sun exposure	90	10
Use of medications	20	80
Use of cosmetics	60	40
Premenstrual period	10	90
Others	10	90

Facial flushing triggers



Graphic 1: Clinical evaluation of erythema and facial flushing before TB application and after 90 days

Table 2: Studies that used BT to treat flushing and persistent facial erythema

Author	N.	Country	Treated area	Toxin used	Dilution / final concentration	N of points per area	Distance between points	Dose per point/ total dose	Results (erythema improvement)	Complications	Duration of effect	Follow up
Yuraitis M *et al.*, 2004[12]	1	USA	Malar	BT type A	100U in 5ml SF 0.9%/ 2U/0.1ml	⋆	1cm	⋆/ 10U (per area)	Satisfactory (after 2 weeks)	⋆	⋆	2 weeks /1 month
Kranendonk SK *et al.*, 2005[15]	1	USA	Unilateral malar	BT type A	⋆/ 4U/0.1ml	4 points	1cm	2U/ 8U total	Unsatisfactory	Yes (upper lip drop one week after application)	⋆	⋆
Alexandroff AB et al., 2006[16]	2	UK	Unilateral face	BT type A (ONA)	100U in 5ml SF 0.9%/ (2U/0.1ml)	⋆	1cm	⋆/ 10U total	Unsatisfactory (no improvement after 6 weeks)	⋆	⋆	⋆
Oh YJ *et al.*, 2011[13]	15	Korea	Unilateral face	BT type B	1ml BT-B in 0.1ml de NaHCO 8.4%	10-15 points	1cm	⋆/ 682U	Unsatisfactory (after 1, 4 e 8 weeks)	No	-	1, 4 and 8 months
Dayan SH *et al.*, 2012[17]	13	USA	Malar	BT type A (ONA)	100U in 7ml SF 0,9%/ (1.4U/0.1ml)	⋆	0,5cm	0,7U/ 8-12U per area	Satisfactory (after 1 week)	No	3 months	⋆
Park KY *et al.*, 2015[18]	2	South Korea	Malar, chin and forehead	BT type A (ONA)	50U in 2,5ml SF 0.9%/ (2U/0/1ml)	⋆	1cm	⋆/ 40-50U total ⋆⋆	Satisfactory (after 1 week)	No	4 months	1 week/3 months
Bloom BS *et al.*, 2015[19]	25	USA	Forehead, nose, malar and chin	BT type A (ABO)	300U in 3ml SF 0.9%	⋆	⋆	⋆/ 15-45U (mean dose: 25U)	Satisfactory ⋆⋆⋆	No	3 months	1, 2, 3 months
Eshghi G *et al.*, 2016[20]	24	Iran	Malar	BT type A	⋆	⋆	1cm	1U / 30U per area	Satisfactory (between week 2 e 3)	No	⋆	1 month
Bharti J *et al.*, 2018[11]	⋆	India	⋆	BT (type ⋆)	⋆/ 1U/0.1ml	⋆	0,5cm	0,5U/ ⋆	Satisfactory (after 1 a 2 weeks)	⋆	3-4 months	4-5 months
Antonio CR *et al.*, 2018[3]	1	Brazil	Forehead, nose, malar and chin	BT type A (ONA)	100U in 8ml SF 0,9%/ (1.25U/0.1ml)	10 points	0,5cm	0,625U /5-7,5U per area	Satisfactory (after 2 weeks and performed a second application)	⋆	⋆	14 days/24 days/ 2 months
Silva LC *et al.*, 2018[21]	6	Brazil	Malar	BT type A	100U in 5ml SF 0.9%/ (2U/0.1ml)	⋆	0,5cm	0,2-0,5U / 6-15U per area	Satisfactory (in the first 3 months)	⋆	6 months	1, 2, 3, 6 months
Kim MJ *et al.*, 2019[22]	23	South Korea	Unilateral malar	BT type A ⋆⋆⋆⋆	⋆/ 1U/0.1ml	30 points	1cm	0,5U/ 15U	Satisfactory (after 4 e 8 weeks)	No	⋆	2, 4, 8, 12 weeks
Al-Niaimi F *et al.*, 2020[23]	20	England, Denmark and Russia	Bilateral malar	Pulsed dye laser + BT type A (ABO or ONA) ⋆⋆⋆⋆⋆	500U in 5ml (ABO)/ 10U/0.1ml and 100U/ 2.5ml (ONA)/ 4U/0.1ml	⋆	⋆	⋆/2050U per area (ABO) and 10-20U per area (ONA)	Satisfactory	Yes (Moderate purpura in a patient lasting 10 days)	⋆	2 weeks/3 and 9 months

SF 0,9% - sodium chloride at 0,9%; NaHCO 8,4% - sodium bicarbonate at 8,4%

⋆ Not reported; ⋆⋆ Two BT applications were performed one week apart; ⋆⋆⋆ 15/25 patients had improvement in erythema scores at 1, 2 and 3 months after treatment; ⋆⋆⋆⋆ Prabotulinumtoxin A; ⋆⋆⋆⋆⋆ Three pulsed dye laser sessions were performed, followed by the application of BT at intervals of four to six weeks

DISCUSSION

The therapeutic arsenal to treat rosacea aims at controlling vascular inflammation. Topical medications such as metronidazole, azelaic acid, and, more recently, ivermectin reduce erythema related to vascular inflammation, as well as the group of oral cyclins. However, they have minor effects on erythema caused by permanently dilated superficial vessels.[7] Vasoconstrictor drugs, such as brimonidine, which acts as an alpha-adrenergic agonist, promote transient effects on facial erythema (9 to 12 hours) with reports of a rebound effect.[8] Some oral drugs, such as non-steroidal anti-inflammatory drugs, antihistamines, clonidine, and beta-blockers, have off-label use to control flushing in rosacea, with variable results and presence of adverse events.[9] According to the ROSCO 2019 panel, topical alpha-adrenergic modulating agents and oral beta-blockers were discouraged due to limited scientific evidence to treat flushing.[10]

BT use was suggested in the search for other alternatives to treat flushing and facial erythema. Its mechanism of action is not yet fully understood. Among the hypotheses is the inhibition of the release of the neuropeptides associated with vasodilation and inflammation, such as substance P (SP), calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), and acetylcholine (ACh) from the presynaptic vesicle.[5]

In a recent study, Choi et al. demonstrated through in vivo tests that the mechanism of botulinum toxin in rosacea treatment involves blocking the mast cells degranulation through the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins cleavage. Therefore, it proposed that BT targets the rosacea's neurogenic inflammatory component and also has direct inhibitory effects on mast cells.[5] Its effect in reducing the size of noticeable pores has also been reported. Its therapeutic benefit is possibly explained by blocking acetylcholine directed to the hair's erector muscles, decreasing pore size, and muscarinic receptors located in the sebaceous glands.[11]

Yuraitis and Jacob published the first report on intradermal BT type A as an effective treatment for facial erythema in 2004.[12] The authors reconstituted BT-A with 5 ml of isotonic saline for a final dilution of 2 IU by 0.1 ml. The application was performed at points 1 cm apart, in a total of 10 UI of BT in each treated region. The study observed a satisfactory result within two weeks after application, and the patient returned one month later to continue treatment in other areas. However, not all BT serotypes are effective in treating rosacea. An open, double-blind, split-face study, conducted in 2011 in Korea, aimed to assess BT-B's effectiveness in treating facial flushing. Fifteen individuals participated in the study, receiving the application of 682 units of BT-B on one side of the face, and saline solution on the other side, as a control. However, after evaluating the erythema index between the two treated sides, the BT-B injection side showed no significant decrease in erythema compared with the control side.[13]

According to the literature, there are no explicit criteria for treatment dilution, dose, and frequency, considering the different presentations of BT and each author's experience. A 2019 review analyzed 30 articles on the use of BT to treat facial flushing and rosacea. The dose of BT applied ranged from 1 UI to 6 UI for each cm^2 of treated area, and the number of sessions varied from 1 to 3 with different time intervals between them. All articles had satisfactory results.[14] Table 2 presents a literature review on the studies that used BT to treat flushing and persistent facial erythema with dilutions, doses, complications, duration, follow-up time, and results.[3,11-13, 15-23] In the present study, we opted for clinical observation of erythema after exposure to a LED red light mask (with heat emission) to standardize the stimulus since the heat was one of the triggers most reported by patients. Our series found satisfactory results, with few adverse events in the 1:1 BT dilution and a total dose ranging from 25 U to 35 U per patient.

Our limitations include the small sample size, the lack of a control group to compare the results and a long-term follow-up, and the fact that this was an open-label study. More extensive, randomized, blinded, placebo-group studies are needed for standardization and consensus on the ideal dose, technique, and treatment duration.

CONCLUSION

The intradermal application of BT can be considered a therapeutic alternative to control rosacea's erythema and facial flushing without a rebound effect or systemic repercussion. There is no consensus in the literature regarding the best dilution, number of points, dose, and frequency of application in these cases. The protocol performed (standard dilution 1:1 [1 U per 0.01ml]) generated good clinical results without significant adverse events. ●

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Intralesional vitamin D in multiple recurrent plantar warts - A single, blind, prospective, placebo-controlled study

Vitamina D intralesional em múltiplas verrugas plantares recorrentes - Um estudo cego, prospectivo e controlado por placebo

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.2021130050

ABSTRACT

Introduction: Warts or verrucae, caused by the human papillomavirus (HPV), are a benign epidermal proliferation of the skin. Most patients seek medical advice as warts are cosmetically unacceptable and can be painful. Plantar warts, in particular, are typically refractory to treatment requiring multiple treatment sessions. High recurrence rates, pain, and scarring limit the available therapeutic modalities. In contrast, immunotherapeutic approaches stimulate the host immune system by enhancing cellular immunity to eliminate the virus.

Objective: To assess the safety and efficacy of intralesional vitamin D3 injection to treat multiple recurrent plantar warts.

Methods: 60 patients with multiple recurrent warts were divided into two groups of 30 each. Group 1 received 0.5 ml intralesional vitamin D in the base of the largest wart, and Group 2 received 0.5 ml of normal saline. The sessions were repeated every two weeks for a maximum of four sessions, and patients were followed up for 12 months to detect any recurrences.

Results: The study group showed complete clearance in 73.3% (22) individuals, while most controls (70%) showed no response.

Conclusion: Intralesional vitamin D3 is a safe and effective treatment option for multiple recurrent plantar warts.

Keywords: Cellular immunity; Injections, intralesional; Warts

RESUMO

Introdução: *As verrugas, são proliferações epidérmicas benignas da pele. A maioria dos pacientes procura orientação médica, pois as verrugas são cosmeticamente inaceitáveis e podem ser dolorosas. As verrugas plantares, em particular, são tipicamente refratárias ao tratamento que requer várias sessões. As modalidades terapêuticas disponíveis são limitadas pela alta taxa de recorrência, dor e cicatrizes. Em contraste, as abordagens imunoterapêuticas estimulam o sistema imunológico do hospedeiro, aumentando a imunidade celular para eliminar o vírus.*

Objetivo: *Avaliar a segurança e eficácia da injeção intralesional de vitamina D3 no tratamento de múltiplas verrugas plantares recorrentes.*

Métodos: *Um total de 60 pacientes com verrugas plantares múltiplas recorrentes, foram divididos em dois grupos de 30. No grupo 1, 0,5ml de vitamina D intralesional foi injetado na base da maior verruga e no grupo 2, injetou-se 0,5ml de solução salina normal. As sessões foram repetidas a cada 2 semanas por no máximo 4 sessões e os pacientes foram acompanhados por um período de 12 meses.*

Resultados: *No grupo de estudo, a eliminação completa foi observada em 73,3% (22) e nos controles, 70% dos pacientes não apresentaram resposta.*

Conclusão: *A vitamina D3 intralesional é uma opção de tratamento segura e eficaz em verrugas plantares.*

Palavras-chave: *Imunidade celular; Injeções; Verrugas*

Original Article

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INTRODUCTION

Warts or verrucae are a benign epidermal proliferation of the skin caused by the human papillomavirus (HPV). As it is highly infectious, some people experience HPV infection at some point in their life.[1,2] Based on their form and site, warts are classified into verruca vulgaris, verruca plana, verruca plantaris, filiform/digitate warts, myrmecia, subungal/periungal warts, anogenital warts, and mosaic warts.[3]

Although 60-65% of warts resolve spontaneously by two years, most patients seek medical advice as warts are cosmetically unacceptable and can be painful at specific sites, such as plantar warts.[1] Plantar warts, in particular, are typically refractory to treatment requiring multiple treatment sessions.[4] Several therapeutic modalities are available such as medical agents (5-fluorouracil, podophyllotoxin, salicylic acid, oral zinc and ranitidine, cytodestructive methods (electrocautery, cryotherapy, photodynamic therapy), and surgical excision. High recurrence rates, pain, and scarring limit these modalities. Also, they are not suitable for multiple refractory warts.[5,6] In contrast, immunotherapeutic approaches stimulate the host immune system by enhancing cell-mediated immunity to eliminate the virus rather than only clearing the lesions.[6,7] Immunotherapy leads to warts clearance without scarring or physical changes and augments the host response against the causative agent.[8] Various antigens have been tried, such as measles, mumps, and rubella vaccine (MMR), also purified protein derivative (PPD) and candida antigen. Few studies used topical vitamin D.[9-12]

The effect of vitamin D derivatives on warts is speculated to be derived from its potential to regulate epidermal cell proliferation and differentiation and modulate cytokine production. Upregulation of vitamin D receptors (VDR) in the skin leads to the induction of antimicrobial peptides.[9-12]

Our study aims to evaluate the safety and efficacy of intralesional vitamin D3 injection in multiple recurrent plantar warts.

METHODS

Study design

It is a hospital-based, single-blind, comparative, interventional study conducted in the Department of Dermatology outpatient clinic of the Medical Sciences and Research Centre, Bengaluru - Karnataka - India from June 2018 to January 2020, after obtaining approval from our institutional ethics committee.

Sample size

A total of 60 patients with multiple recurrent plantar warts were included in the study. Informed written consent was taken from each participant in the study.

Inclusion criteria

Patients with multiple recurrent plantar warts of different sizes and duration with/out distant warts willing to provide informed written consent were included in the study.

Exclusion criteria

Children <12 years, pregnant and lactating women, and patients with keloidal tendency, any evidence of immunosuppression, systemic or dermatological disorder, or prior hypersensitivity to vitamin D3 or any drug, were excluded from the study.

Study intervention

We randomly assigned patients into two groups of 30 each using the "chit box" method.

All the patients were subjected to a standard protocol that included complete history and systemic and cutaneous examination.

Complete history included demographic data (name, age, gender, address, occupation), and present history (disease duration, presence or absence of distant warts, drug intake, or systemic illness).

Cutaneous examination comprised assessing number and size of plantar warts, as well as presence or absence of distant warts. Dermoscopy was performed to diagnose plantar warts in doubtful cases.

We conducted a thorough general and systemic examination to exclude any systemic diseases.

Group 1 (cases)

Under asepsis, 0.5 ml of vitamin D3 (6lakh IU) was injected intralesionally into the base of the largest wart with an insulin syringe.

Group 2 (controls)

Under asepsis, 0.5 ml of normal saline was injected into the base of the largest wart.

Treatment procedure

The lesions were cleaned with povidone-iodine and spirit. We applied the injections into the base of the largest wart using a 40U insulin syringe. The syringe was held parallel to the skin surface, and the needle was held with the bevel facing upwards while injecting. The injection was repeated into the same wart every session. The session was repeated every two weeks in both groups, similarly, until complete clearance or for a maximum of four sessions. Patients were followed up for 12 months after the last dose to detect recurrences. We assessed patients for warts clearance and adverse events.

Post-treatment care

After each session, patients were advised to avoid using other lines of treatment during the study and follow-up period.

Assessment of improvement

We assessed the clinical improvement using color photographs at baseline, at each session, and after 12 months of the last session.

The clinical improvement was graded as complete clearance (complete resolution of warts), partial response (reduction

in size/ number of warts but not complete clearance), no response (no change in size or number).

Statistical analysis

Data was analyzed using SPSS version 22 and represented as frequency and percentage for categorical variables, mean and standard deviation for quantitative variables. T-test and chi-square tests were used. P<0.05 was considered statistically significant.

RESULTS

All 60 patients completed the study. Patients were comparable regarding age and sex distribution (p>0.05). The mean age in the study group was 32.1±7.48, and in controls, it was 29.6±7.55. In our study, we noticed a men predominance in both study (53.3%) and control groups (60%). Table 1 presents the demographic data of the study participants.

In the study group, we observed complete clearance in 73.3% (22) (Figure 1), partial clearance in 20% (6), and no improvement in 6.7% (2) of patients. In the control group, 70% (21) of patients showed no improvement, 26.7% (8) showed partial response, and 3.3% (1) showed complete response (Chart 1). The difference in improvement was statistically significant (p<0.01). We observed complete resolution of distant warts in all the patients who showed complete response (Table 2).

Adverse events

We noted pain during injection in all the patients in the study group and in 40% in the control group.

Persistent erythema and edema were observed in 3.3% of patients in the study group, which decreased spontaneously within 7-10 days. We followed patients for 12 months, and we observed recurrence in 6.7% (2) subjects in Group 1 during this period.

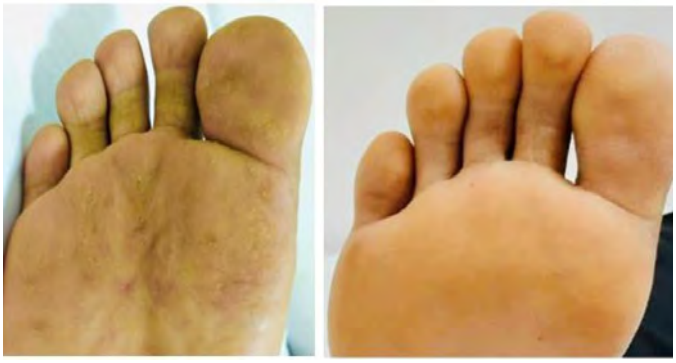
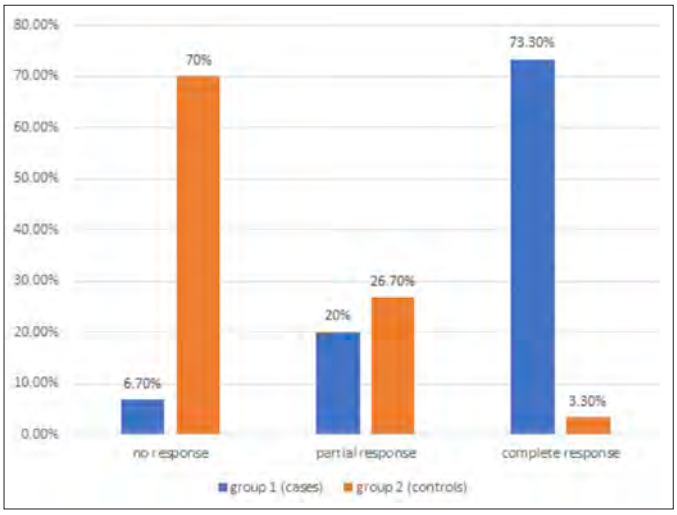


Figure 1: 32-year-old man showing complete response after 4 session



Graph 1: Clinical improvement in cases and controls

Table 1: Demographic data of the participants

CLINICAL DATA	CASES	CONTROLS
Age (Mean± SD) years	32.07±7.48	29.63±7.55
Gender		
Men	16(53.3%)	18(60%)
Women	14(46.7%)	12(40%)
Duration		
<6 months	5(16.7%)	5(16.7%)
6-12 months	10(33.3%)	14(46.7%)
>12 months	15(50%)	11(36.7%)
Number of warts Median (Q1,Q3)	4.50(2.0,10.25)	5.50(3.0,9.50)

DISCUSSION

Recurrent multiple plantar warts constitute a frustrating disorder to patients and a challenge to practitioners, as no single therapy is completely effective in all patients, especially when it presents multiple lesions. Immunotherapy has been used as a preferred treatment as it is known to cause resolution of both treated and distant warts by inducing HPV targeted immunity.[13] The exact mechanism of vitamin D activity against warts remains to be elucidated.[14] However, it is known to control cell proliferation and differentiation and as is known to have immunoregulatory activities. Its effects are mediated via vitamin D receptor (VDR), which is present in the keratinocytes, fibroblasts, melanocytes and other skin's immune cells.[15] Upregulation of VDR leads to activation of Toll-like receptors of human macrophages and induction of antimicrobial peptide

Table 2: Clinical improvement in cases and controls

Clinical Improvement	Group 1 (cases) % (n)	Group 2 (controls)
No response	6.7% (2)	70% (21)
Partial response	20% (6)	26.7% (8)
Complete response	73.3% (22)	3.3% (1)

expressions as thymic stromal, lymphopoietin, and cathelicidin. It also acts as an anti-inflammatory by reducing the synthesis of IL1alpha and IL6.[16]

Our study revealed that intralesional vitamin D3 is an effective therapy for multiple recurrent plantar warts with a success rate of 73.3%, as 22 out of 30 patients had complete clearance of plantar warts. This was in concordance with a study by Aktas et al.,[4] who reported total clearance in 80% (16 out of 20) of plantar warts patients. Another study, by Raghukumar et al.,[13] evaluated the effect of intralesional injection of vitamin D3 in 60 patients with various extragenital warts, showing complete response in 90% of cases.

During the follow-up period of 12 months, we observed recurrence in 6.7% of our study group. It agreed with Raghukumar et al.,[13] who reported a recurrence rate of 3.33% during the six-month follow-up.

A randomized controlled trial by El-Sayed et al.[17] compared the effectiveness of 0.2 ml intralesional vitamin D3 and 0.2 ml intralesional zinc sulfate every two weeks for a maximum of four sessions. It showed complete response of 62.9% with vitamin D and 71.4% with zinc sulfate.

A placebo-controlled study by Abdel Azim *et al.*[14] showed total clearance of warts in 56.25% (18 out of 32) of patients with intralesional vitamin D3 in cutaneous warts. But our study showed a better response in plantar warts.

Another placebo-controlled study by Kareem et al.[16] used 0.2 ml intralesional vitamin D once monthly for two sessions for common warts. It showed complete clearance in 45% of the patients. Our study presented better results, probably due to the increased number of sessions (four sessions) and the use of a higher dose (0.5 ml) of vitamin D3.

There were no significant adverse events observed in our study. The limitation of our study is the relatively small sample size.

CONCLUSION

Our study shows a beneficial role of intralesional vitamin D3 in multiple recurrent plantar warts. It is a simple, safe, cost-effective treatment modality with a low recurrence rate. However, larger case-control studies as well as in-vitro/in-vivo studies are needed to elucidate the exact mechanism of action of vitamin D3 in warts.

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The importance of interaction between hyaluronic acid and CD44 receptor

A importância da interação entre o ácido hialurônico e o receptor CD44

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ABSTRACT

Hyaluronic acid is one of the most used substances in dermatology. It presents structural roles in the extracellular matrix, binding to cells and biological components through specific and nonspecific interactions. The native ligand for hyaluronic acid is the transmembrane CD44 receptor, which interacts not only with hyaluronic acid but also with different growth factors, cytokines, and extracellular matrix proteins. We seek to review the interaction of the CD44 receptor with the various forms of hyaluronic acid in the skin to better understand its action and fully explore its use in dermatology.

Keywords: Rejuvenation; Hyaluronic acid; Skin

RESUMO

Ácido hialurônico é uma das substâncias mais utilizadas na Dermatologia. Apresenta tarefas estruturais na matriz extracelular, ligando-se às células e a componentes biológicos por interações específicas e inespecíficas. O ligante nativo para o ácido hialurônico é o receptor transmembrânico CD44, que interage não apenas com o ácido hialurônico, mas também com diferentes fatores de crescimento, citocinas e proteínas da matriz extracelular. Buscamos revisar a interação entre o receptor CD44 e as diversas formas de ácido hialurônico na pele, a fim de compreender melhor sua ação e explorar seu uso de forma mais completa na Dermatologia.

Palavras-chave: *Rejuvenescimento; Ácido hialurônico; Pele*

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INTRODUCTION

Hyaluronic acid (HA) is a natural biodegradable polymer. It is a non-sulfated, non-branched glycosaminoglycan composed of repeating disaccharide units (1.4 β-D-glucuronic acid and 1.3 N-acetyl-β-D-glucosamine). HA is a polyanion that can bind to each other and water molecules, forming a rigid and viscous structure similar to gelatin. HA is one of the main extracellular matrix (ECM) elements of vertebrate tissues, available in almost all body fluids and tissues. This biopolymer has a structural function, binding extracellular matrix molecules. Also, it is involved in several essential biological processes, such as regulation of cell adhesion and motility, in addition to acting in cell differentiation and proliferation and the mechanical properties of tissues.[1]

The HA characteristics, such as consistency, biocompatibility, and hydrophilicity, make it ideal for use in Aesthetic Dermatology. Also, its unique viscoelasticity and limited immunogenicity led to its use in various medical applications, such as osteoarthritis treatment (OA), eye surgery aid, and wound regeneration.[2] We will discuss the use of injectable hyaluronic acid as a dermal filler and its interactions with its primary receptor, CD44, to understand how it can promote rejuvenation through its biological interactions.

Hyaluronic acid metabolism in the skin

In the epidermis, HA content is especially high in the proliferating basal regions. It is in line with maintaining the undifferentiated and proliferative state of basal cells and corresponding observations during embryogenic development.[3] Histological findings suggest that basal layer keratinocytes contain intracellular HA, whereas extracellular HA prevails in the upper epidermal layers.[4] Extracellular HA is believed to maintain diffusion and open spaces to facilitate cell migration.[5]

HA's primary source in the dermis is fibroblasts, with higher HA synthesis activity in the papillary dermis. HA structures' high flexibility and hydrophilicity allow these molecules to fill any gaps in the ECM.[6] The multiple hydrogen bonds between adjacent disaccharides especially explain HA's large hydrodynamic volume, but these may also depend on the close interaction of HA with highly glycosylated proteoglycans. The viscoelastic properties resulting from HA in the dermis are responsible for supporting the dermal tissue architecture. Dermal HA has access to the lymphatic system, probably regulating the water content in the dermis. Both free HA crosslinked by proteins or proteoglycans and HA associated with the cell membrane facilitate cell migration, proliferation, and communication by interacting with cell receptors, grouping receptors, and subsequent signaling cascades.[7]

Specific enzymes called HA-synthase (HAS) synthesize the HA. They are membrane-binding enzymes that synthesize HA on the inner surface of the plasma membrane and then eliminate it through pore-like structures into the extracellular space. Three enzymes are responsible for HA synthesis: HAS-1, 2, and 3, which exhibit distinct enzymatic properties and synthesize HA chains of various lengths.[7,8]

HA degradation is a gradual process that can occur through enzymatic or non-enzymatic reactions. Three types of enzymes (hyaluronidase, β-D-glucuronides, and β-N-acetylhexosaminidase) are involved in the enzymatic degradation of HA. These enzymes are found in several forms, in the intercellular space and serum. Hyaluronidase breaks high molecular weight HA into smaller fragments, while the other two enzymes degrade the fragments by removing non-reducing terminal sugars. In addition to the enzymatic mechanisms of HA degradation, it can be degraded by shear stress, heat, and chemical reactions, such as acid/alkaline hydrolysis and degradation by oxidants. These types of degradation occur at random, often resulting in disaccharide fragments.[1,9]

Skin aging and hyaluronic acid

The most dramatic histochemical change observed with aging skin is the marked disappearance of hyaluronic acid in the epidermis, while HA is still present in the dermis.[11] The reasons for the changes in HA homeostasis with aging are unknown, but it is known that the underlying dermis influences epidermal HA synthesis. A progressive reduction in the size of HA polymers in the skin due to aging has also been reported. Thus, the epidermis loses the main molecule responsible for binding and retaining water molecules, resulting in the loss of moisture from the skin. In the dermis, the main age-related change is the increasing avidity of HA for tissue structures and loss of HA extraction capacity. Also, there is progressive collagen crosslinking and loss of collagen extraction capacity with age. All of the above age-related phenomena contribute to the apparent dehydration, atrophy, and loss of elasticity that characterizes aging skin.[10]

The premature skin aging due to repeated and prolonged exposure to radiation results in an abnormal content of glycosaminoglycans and distribution compared to that found in scars, with decreased HA and increased chondroitin sulfate proteoglycans levels.[12] In dermal fibroblasts, this reduction in HA synthesis was attributed to collagen fragments, which activate αvβ3 integrins, resulting in reduced HA synthase expression (enzymes responsible for HA production).[12]

Injectable Hyaluronic Acid in Dermatology

Hyaluronic acid-based dermal fillers are currently one of the most commonly performed aesthetic procedures. HA injections into the skin promote a volume-filling effect and induce collagen synthesis, reversing the signs of aging skin.[13]

Compositional properties and rheological properties characterize the compositions of HA formulations used for tissue filling. The design of fillers includes concentration, size, and crosslinking particles (substances that generate intermolecular bonds that increase the stability and clinical durability of the filler). In contrast, rheological properties include elasticity (G') and viscosity (N'). Crosslinked HA (crosslinking particles) can be made with several chemicals (butanediol diglycidyl ether, divinyl sulfone, etc.). The increase in crosslinking particles and

concentration strengthens the fillers' resistance to enzymatic degradation. The polymerization of glycosaminoglycan chains and tension determine the particle size, which optimizes tissue lifting capacity. Elasticity and viscosity guarantee fillers the ability to resist compression and shear force, respectively. Another critical feature is hydrophilicity, that is, the filler's ability to attract water and expand.[14,15]

Each product consists of a unique combination of different characteristics, and understanding these differences allows treating appropriately other areas of the face. Softness and less viscosity are characteristics that make the filler ideal for surface wrinkles, lips, and eyelids. In contrast, denser and heavier fillers are better for deeper plane injection to increase volume.[16] Duration of corrective effect of HA fillers ranges from three to 24 months, predominantly depending on HA concentration, cross-linking (degree and type), treated area, and individual.[17]

In addition to replenishing volume, injectable HA acts as a skin remodeler because the filling effect persists for a time much longer than the filler's bioavailability. Studies have shown that HA can induce an increase in the production of collagen and elastic fibers, restoring the extracellular matrix by direct stimulation and/or mechanical stretching of fibroblasts.[18]

HA performs several structural tasks of ECM, as it binds to cells and other biological components through specific and non-specific interactions. Binding to HA stabilizes several ECM proteins. Specific molecules and receptors that interact with HA are involved in cellular signal transduction, such as the aggrecan, versican, and neurocan molecules, and the cellular receptors CD44, RHAMM, TSG6, GHAP, ICAM-1, and LYVE-1.[19] Among these receptors, CD44 (cell surface glycoprotein) deserves more attention as, due to its wide distribution and based on current knowledge, it is considered the primary HA receptor on most cell types.[1,20] We will address the importance of the CD44 receptor and its interactions with HA to promote rejuvenation.

CD44 receptor and hyaluronic acid

The native ligand for HA is the transmembrane receptor CD44.[21] HA binds to the N-terminal of CD44, which functions as a coupling site and is coated by a mixture of predominantly essential and hydrophobic amino acids.[22] The CD44 gene contains 20 exons, 10 of which can be regulated by alternative binding, leading to the generation of other variants (variant exons or 'v'), which are translated to a polypeptide of molecular weight 80-90kDa, depending on the binding. Biological functions, such as cell migration, adhesion, and structural integrity during anti-inflammatory processes, depend on the HA-CD44 interaction. The smallest CD44 isoform, standard CD44 (CD44s), is ubiquitous, whereas variant isoforms are expressed only in some epithelial tissues and cancers.[23,24]

The different forms of hyaluronic acid synthesized for medical use have common and distinct interactions with the CD44 receptor. Generally, HA-CD44 interactions can be altered according to HA extent modification, chemical group type used for that modification, and HA location where the alteration was made. Regardless of the peculiarities involving the different types of synthetic hyaluronic acid and CD44 receptor, we will globally address this receptor role in allowing HA action to go beyond simply filling tissues, mainly acting in tissue biomodulation.[25]

CD44 can also interact with different growth factors, cytokines, and extracellular matrix proteins, such as fibronectin.[26] The intracellular CD44 domain interacts with the cytoskeleton. Consequently, when its extracellular domain binds to the ECM's HA, it creates a link between the cytoskeleton structures and the polymer.27 Several intracellular signaling pathways are involved in the HA-CD44 interaction, and they act by controlling cellular biological processes: HA degradation and internalization, angiogenesis, cell migration, proliferation, aggregation, and adhesion to ECM components.[27,28,29]

HA concentration manipulations or HA-CD44 interactions can alter signaling pathways of many regulatory and adapter molecules, such as SRC kinases, Rho-GTPases, VAV2, and GAB1.[30] The binding of CD44 to hyaluronic acid can alter cell survival or proliferation by altering intracellular protein binding.[31] Also, HA can activate several receptor tyrosine kinases, and HA binding to CD44 can group and cooperate with growth factors.[32] It has also been shown that the CD44 receptor is involved in cellular uptake of extracellular HA.[33]

Kaya *et al.* (1992) demonstrated that CD44 is associated with the regulation of HA homeostasis in keratinocytes. The authors developed transgenic mice expressing an antisense CD44 cDNA triggered by the keratin-5 promoter. These mice do not show detectable CD44 expression on skin keratinocytes and corneal epithelium and exhibit abnormal HA accumulation in the superficial dermis and stroma of the cornea, morphological changes distinct from basal keratinocytes and cornea, and defective proliferation of keratinocytes in response to mitogen and growth factors. A decrease in skin elasticity, poor local inflammatory response and tissue repair, delayed capillary growth, and epidermal failure to undergo hyperplasia in response to the carcinogen reflect these changes. Therefore, they observed two main functions of CD44 in the skin: the regulation of keratinocyte proliferation in response to extracellular stimuli and the maintenance of local HA homeostasis.[34]

Vistejinova *et al.* (2014) conducted a study to compare the ability of high molecular weight (HMW) with low molecular weight (LMW) HA to stimulate the production of cytokines and chemokines by human dermal fibroblasts, associated with the importance of the CD44 receptor in this process. The study showed that dermal fibroblasts and their primary function of producing the extracellular matrix could respond to low molecular weight HA fragments via interaction with CD44 through the production of cytokines, suggesting that the LMW HA is implicated in an inflammatory signal that stimulates stromal fibroblasts.[35]

Studies have demonstrated that HA and CD44 on the outer surface of dermal fibroblasts act by regulating the physio-

logy of fibroblasts and stimulating the production of extracellular matrix.[36] Thus, it may be possible to alter the skin's collagen production by increasing or reducing the amount of HA.[37] In Wang *et al.* study (2007), 11 volunteers received injections of HA filler or vehicle and underwent biopsy at four and 13 weeks after the procedure. The results demonstrated that, compared to controls, skin treated with crosslinked hyaluronic acid injections revealed increased collagen deposition around the filler material, gene expression for types I and III procollagens, and various growth factors profibrotic, was also regulated between four and 13 weeks compared to controls. The authors concluded that the injection of crosslinked hyaluronic acid stimulates collagen synthesis, partially restoring the dermal matrix components lost in photoaged skin.[13]

Bhattacharya *et al.* (2017) demonstrated that alterations in HA structures modify its interaction with the CD44 receptor. They observed that both sulfation and deacetylation of HA in individuals are associated with lower interaction with CD44; thus, both modifications are necessary to reduce the HA-CD44 interaction. Therefore, the study suggests that it would be possible in future studies to regulate cell activation pathways through different forms of HA.[38]

Wang *et al.* (2019) assessed how different types of HA influence the binding of CD44 to HA hydrogels. HA-CD44 interactions can be altered when HA is modified to synthesize HA macromers, depending on the modification extent, chemical group type used for transformation, and the site used with HA for alteration. These effects are observable when HA macromers are presented to CD44 in soluble form and after crosslinking in hydrogels. Gene expression and long-term biochemical and histological analyzes of mesenchymal stromal cells encapsulated in HA hydrogels strongly suggest that levels of HA macromer modification influence cell-hydrogel interactions and chondrogenic differentiation. Notably, low and moderately modified HA hydrogels promote significantly higher binding to CD44 compared with inert molecules. Also, chondrogenesis and cartilage formation are regulated with HA hydrogels compared to inert polyethylene glycol hydrogel controls.[39]

Gruber, Holtz, and Riemer (2021) performed an in vitro evaluation on the influence of different molecular weights of HA on its binding to CD44. They showed that low molecular weight HA and a commercial complex with HA of three molecular weights (high, medium, and low) increased the CD44 protein expression in human epidermal keratinocytes. In contrast, medium and high molecular weight HA fractions didn't. Therefore, they concluded that HA can influence the expression of the CD44 protein and that this influence seems to be dependent on the molecular weight.[40]

CD44 receptor and carcinogenesis

It is known that the abnormal activation of the CD44 signaling cascade by HA and the CD44 overexpression and upregulation can result in the development of pathological lesions and malignant transformation since the HA-CD44 interaction is involved in cell processes such as cell proliferation and angiogenesis.[29,41] Therefore, CD44 is overexpressed in several solid tumors, such as pancreas, breast, and lung tumors.[42]

There is a complex communication between cancer cells and their microenvironment. Evidence indicates that the tumor microenvironment may regulate the capacity for tumor growth and metastasis.[43] HA provides cell support and hydrophilic matrix and also regulates cell-cell adhesion, cell migration, growth, and differentiation.[44] Thus, these properties make it a suitable candidate for involvement in pathological processes such as cancer. Furthermore, by forming pericellular layers, HA can protect tumor cells from immune attack.[45] Several tumor cells produce increased amounts of HA or induce the production of HA by releasing growth factors and cytokines. Likewise, fragmented HA induced by reactive oxygen species (ROS) also contributes to HA overproduction.[46] Tumor and stromal cells express HA isoforms and produce HA in the ECM, which accumulates in the tumor parenchyma and peritumoral stromal tissues, contributing to metastatic spread.[47] Also, HA overproduction in tumor cells can induce cancer cell-like epithelial changes toward a migratory fibroblastic phenotype.[48] HA-rich ECM can also mediate mesenchymal stem cells recruitment, which are progenitors of tumor-associated fibroblasts.[49]

HA interaction with CD44 could explain many HA tumor-promoting activities. There are three ways in which CD44 can interact with HA: binding with soluble extracellular HA molecules and ECM, interacting with receptor tyrosine kinases for anti-apoptosis and drug resistance, and binding of CD44 to actin cytoskeleton.[50]

Activated CD44 is overexpressed in solid tumors, but much less or almost none, in its non-tumorigenic counterparts. Adhesion of CD44 to HA induces upregulation of integrins that strengthen stem cell adhesion.[51] Tumor-derived cells express CD44 in a high-affinity state that can bind to and internalize HA. The binding affinity of CD44 to HA is essential for cell migration allowing CD44 to be incorporated into the leading edge of cells. CD44 can also react with other molecules, including collagen, fibronectin, osteopontin, growth factors, and metalloproteinases on tumor cells, but the functional roles of such interactions are less known.[50]

Receptor tyrosine kinases (RTKs) are a subclass of cell surface growth factor (GFR) receptors with an intrinsic tyrosine kinase activity controlled by ligands. The HA-CD44 interaction has a general effect on activating anti-apoptotic cell survival proteins, initiated by association with the activation of tyrosine kinase receptors. Also, CD44 binds to cytoskeletal proteins, and this interface is modulated by the HA-CD44 interaction.[50]

Thus, given that HA levels and their interactions with CD44 can regulate cell differentiation (such as epidermal keratinocyte cornification and fibroblast differentiation), the modulatory capacity of regulated cell differentiation through the HA route could be used therapeutically, especially in Oncology. The fact that HA binding to CD44 can interact with several recep-

tor systems is very intriguing. If HA and CD44 interactions are necessary to lead to carcinogenesis and metastasis, then it is believed that manipulation of these interactions can be performed therapeutically.[37]

Since the first reports of HA liposomes targeting CD44 in 2001, researchers have devoted a great effort to using HA-mediated CD44 targets for disease and drug-delivery applications. Then, studies of HA nanomaterials have emerged as an effective way to improve drug delivery. In the future, it is believed that the straightforward structure and easy manufacturing process for HA nanomaterials may increase the possibility of success in clinical practice.[51]

CONCLUSION

There are numerous interactions between HA and its primary receptor, CD44. We know that they depend on several factors, including the type of HA involved. Studies show that HA-CD44 interactions occur not only with endogenous HA but also with topical and injectable HA. Therefore, we can conclude that exogenous HA acts with CD44 to cause cellular and molecular modulation in the site where it is applied, thus bringing results beyond the simple fact of filling the treated place. It mainly alters the environment through local interactions and improves skin quality. Also, several studies report the involvement of the CD44 receptor in carcinogenesis. Although further studies on this subject are needed, a better understanding of the role of the CD44 receptor can also positively influence the treatment of cancer in the future. ●

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Advanced squamous cell carcinoma and immunotherapy: new therapeutic perspectives

Carcinoma espinocelular avançado e imunoterápicos: novas perspectivas terapêuticas

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ABSTRACT

Squamous cell carcinoma (SCC) has the second highest incidence rate among non-melanoma skin cancers. About 5% of cases progress to locally advanced and/or metastatic lesions, making the surgical approach often unfeasible. Based on this, we performed a literature review on the use of immunotherapy drugs to treat advanced SCC. The results showed that immunotherapy is a potential therapeutic strategy due to the antitumor activity promotion through the individual immune response, reducing the adverse events of surgeries, chemotherapy, and radiotherapy.

Keywords: Squamous cell carcinoma; Tumor Evasion; Immunotherapy; Skin neoplasms

RESUMO

O carcinoma espinocelular (CEC) apresenta a segunda maior taxa de incidência entre os cânceres de pele não melanoma. Cerca de 5% desses casos evoluem para lesões localmente avançadas e/ou metastáticas, tornando a abordagem cirúrgica muitas vezes inviável. Com base nisso, foi realizada uma revisão na literatura sobre o uso de imunoterápicos no tratamento do CEC avançado. Observou-se, então, que a imunoterapia é uma potencial estratégia terapêutica devido à promoção da atividade antitumoral por meio da própria resposta imunológica individual, o que contribui para a redução dos efeitos colaterais de cirurgias, quimioterapias e radioterapias.

Palavras-chave: Carcinoma de células escamosas; Evasão tumoral; Imunoterapia; Neoplasias cutâneas

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INTRODUCTION

Non-melanoma skin cancers (NMSCs) represent one of the most prevalent groups of malignancies in the world. Worldwide, an estimated 18 million new cancer cases occurred in 2018, causing around 100,000 deaths. Of these, approximately 1 million were NMSCs.[1-3] In Brazil, the National Cancer Institute estimates near 625,000 cancer cases in the country, of which 177,000 are NMSCs. Thus, this is the group of malignant neoplasms with the highest incidence.[3]

NMSCs include several malignant neoplasms, including basal cell carcinoma (BCC), the most common skin cancer, and squamous cell carcinoma (SCC), the second most frequent skin malignancy.[3] BCCs and SCCs originate from the neoplastic proliferation of epidermal keratinocytes exposed to carcinogenic factors, including exposure to ultraviolet (UV) radiation, chronic immunosuppression, burn scars, contact to ionizing radiation, among others.[1,2]

UV radiation stands out among the carcinogenic factors. It is recognized for its high mutagenic potential, providing BCCs and SCCs with the highest mutation load among all types of cancer. However, SCCs are a matter of greater concern given their more aggressive behavior: about 5% of cases evolve to locally advanced or metastatic conditions, with uncontrollable growth and substantial disfigurement.[4–6]

Regarding treatment, early surgical excision is considered the therapeutic option of choice, allowing the tumor type confirmation, histological differentiation degree, and free margins analysis. Nevertheless, some SCC cases are diagnosed in elderly patients with comorbidities that limit the adoption of more invasive therapeutic alternatives.[5,6] The tumors' location and size can also restrict surgical therapies, such as lesions with a diameter greater than 20 mm in periocular, auricular, labial, and temporal regions, as well as in cases of metastatic diseases.[7,8]

Locally advanced cutaneous SCC represents a significant therapeutic challenge. For unresectable, unsuitable for radiotherapy SCC, standard systemic treatment options include chemotherapy (usually platinum or fluoropyrimidine-based) or targeted therapy with epidermal growth factor receptor inhibitors.[6] The responses often have a short life and may be associated with significant adverse events in an elderly and frail population.

Despite the relevance of the surgical approach in advanced SCCs, cases of greater clinical complexity can adopt therapeutic alternatives. These alternatives include radiotherapy and chemotherapy with cisplatin, 5-fluorouracil, paclitaxel, and methotrexate (often used in inoperable and advanced lesions).[5,6]

Improved understanding of the immunological control mechanisms involved in skin cancer pathogenesis led to the development of specific immunotherapeutic treatments to promote antitumor activity. In this sense, immunotherapy provides individualized treatment to patients, with minimal adverse events, as it acts in the tumor microenvironment through molecular and cellular mechanisms.[9,10]

Given the new therapeutic approach proposed by immunotherapy for malignant skin neoplasms, this study aimed to conduct an integrative review of immunotherapy drugs to treat advanced squamous cell carcinomas and/or in patients with comorbidities that limit other therapies.

METHODS

The study aimed to overview the current scientific production on the use of immunomodulators to treat advanced cutaneous squamous cell carcinoma and/or in patients with comorbidities that limit conventional therapies. It adopted the integrative review as a research method. Integrative reviews consist of research methods that aim to provide a synthesis of knowledge about a particular subject or field to integrate concepts, ideas, and results from original and/or secondary studies.[11,12]

We conducted the literature review in three databases: Medline (Medical Literature Analysis and Retrieval System Online), Lilacs (Latin American and Caribbean Center on Health Sciences Information), and Scopus (SciVerse Scopus - Elsevier) adopting as search strategy the keywords: "cutaneous squamous cell carcinoma" AND "immunotherapy". The search used the filters "10 years" - to select studies published from 2010 to 2020 – and "full text" – to retrieve articles with the full version available.

From the results obtained with the search strategy, we started the article selection process, using as inclusion criteria studies on the use of immunomodulators to treat cutaneous squamous cell carcinoma (SCC), with text in Portuguese or English available, and primary focus related to cutaneous immunology in SCCs and/or the use of immunotherapy drugs in SCC treatment. The exclusion criteria adopted were: studies addressing SCC systemic treatments generically or broadly, with full texts not available, and relating immunotherapeutic treatment with other therapeutic alternatives. Such standards aimed to allow the data synthesis to be more targeted and specific to the study objectives.

We assessed the selected studies separately, dividing them into two thematic areas: "Immune system and immunotherapy in cutaneous squamous cell carcinoma" and "Immunotherapy drugs in cutaneous squamous cell carcinoma". Then, the articles' contents were analyzed and summarized through a conceptual synthesis.

RESULTS

The search in the databases identified a total of 123 publications. The titles and abstracts preliminary assessment through eligibility criteria allowed the selection of 59 studies, from which 24 were excluded due to duplicity. Thus, 35 publications comprised the sample analyzed in the review and conceptual synthesis (Figure 1).

We distributed the assessed studies in two thematic areas: 17 studies in "Immune system and immunotherapy in cutaneous squamous cell carcinoma" and 18 studies in "Immunotherapy drugs in cutaneous squamous cell carcinomas". Most of these

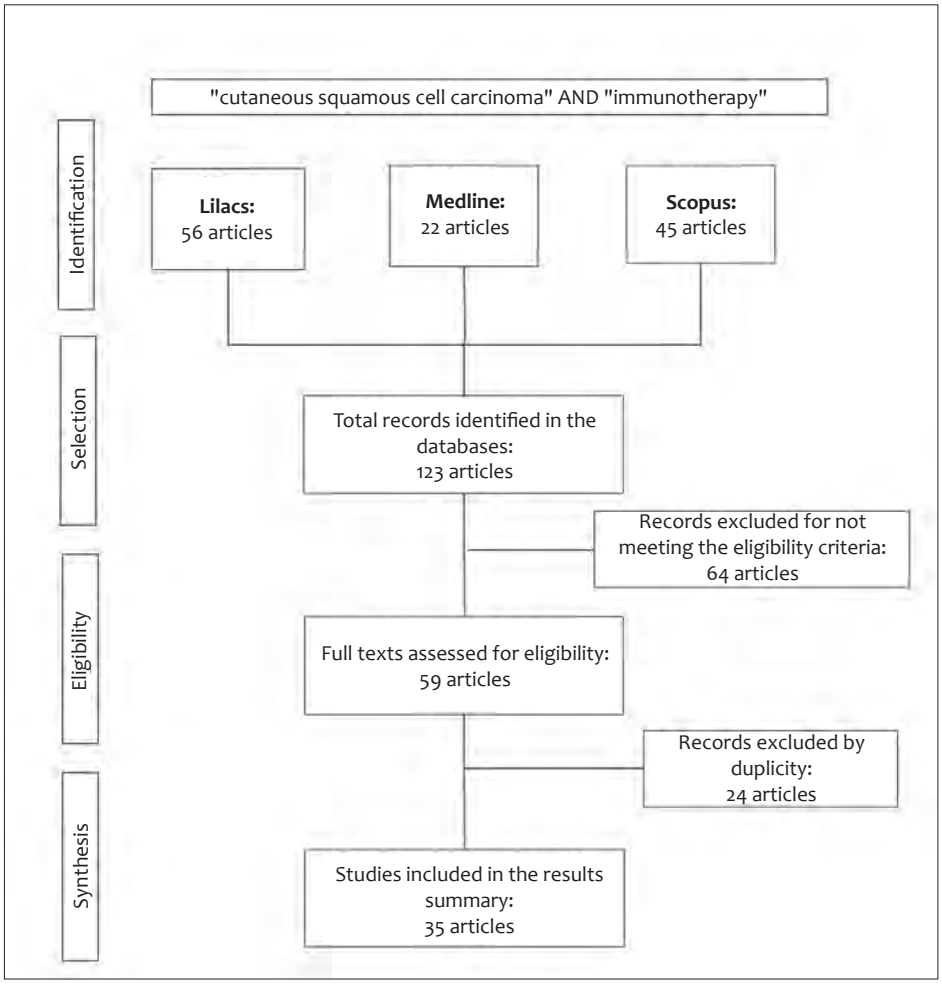

Figure 1: Search in three databases

studies were composed of narrative reviews (16 articles) and case reports (five studies), and the year 2019 had the highest number of publications, with 13 studies (Table 1).

DISCUSSION

Cutaneous squamous cell carcinoma (SCC) is the second most frequent among non-melanoma skin cancers (NMSC). More than 90% of SCCs have a favorable prognosis, and early surgical treatment can cure it through the excision of the lesions. However, the disease progresses locally in about 4-5% of cases, becoming unresectable and/or metastatic and requiring alternative therapeutic approaches such as radiotherapy, chemotherapy, and, more recently, immunotherapy.[5,18,31]

The use of immunomodulators to treat squamous cell carcinomas is based on the ability of the immune system to control the carcinogenesis process.[39] The high NMSC incidence among immunocompromised individuals, such as in HIV infection cases, or immunosuppressed patients, condition of solid organ transplant recipients, supports this perspective. Thus, the immunological surveillance role to control neoplasms is highlighted, making it relevant to understand the relationship between the immune system and cutaneous carcinogenesis.[2]

THE IMMUNE SYSTEM AND SKIN CANCERS

The skin plays essential roles in the homeostasis of the human body, acting to maintain body temperature, protect against environmental agents (physical and chemical), and produce nervous and endocrine stimuli, in addition to working in the body's immune defense. Such defense can occur in the form of innate immunity, characterized by the absence of immunological memory, represented by neutrophils, eosinophils, natural killer (NK) cells, mast cells, cytokines, complement, and antibacterial peptides; or in the form of adaptive immunity, through antigen-presenting cells (dendritic cells), T-lymphocytes (regulators, CD8 and CD4) and B-lymphocytes.[8]

The immune system, under physiological conditions, can recognize and destroy antigens from infectious agents and/or neoantigens from neoplastic cells, acting through innate and adaptive immunities. The neoantigens formation results from the cell mutation process, through which unrepaired damage to cellular DNA sequences promote mutations that lead to changes in cell functions and carcinogenesis.[2,8,27,30]

Cutaneous squamous cell carcinomas (SCCs) originate from mutations in keratinocytes of the epidermal squamous

Table 1: Synthesis of studies analyzed by the systematic review

Authors	Year	Title	Journal	Type of study	Subject Area
Ascierto PA, Garbe C.[5]	2020	Updates and new perspectives in nonmelanoma skin cancer therapy: highlights from 'Immunotherapy Bridge'	Immunotherapy	Narrative review	Immune system and immunotherapy
Hall ET *et al.*[2]	2020	Immunologic Characteristics of Nonmelanoma Skin Cancers: Implications for Immunotherapy	American Society of Clinical Oncology Educational Book	Narrative review	Immune system and immunotherapy
Choi FD *et al.*[13]	2020	Programmed cell death 1 protein and programmed death-ligand 1 inhibitors in the treatment of non-melanoma skin cancer: A systematic review	Journal of the American Academy of Dermatology	Systematic review	Immune system and immunotherapy
Lima PO *et al.*[4]	2020	Epidermal Growth Factor Receptor's Function in Cutaneous Squamous Cell Carcinoma and Its Role as a Therapeutic Target in the Age of Immunotherapies	Current Treatment Options in Oncology	Narrative review	Immune system and immunotherapy
Salzmann M *et al.*[14]	2020	Programmed cell death protein 1 inhibitors in advanced cutaneous squamous cell carcinoma: real-world data of a retrospective, multicenter study	European Journal of Cancer,	Retrospective cohort study	Immunotherapy drugs in SCC
Hanna GJ *et al.*[15]	2020	Real-world outcomes treating patients with advanced cutaneous squamous cell carcinoma with immune checkpoint inhibitors	British Journal of Cancer	Prospective cohort study	Immunotherapy drugs in SCC
Pezeshki S *et al.*[16]	2020	Novel treatments using PD1 inhibitors for advanced and metastatic cutaneous squamous cell carcinoma	Journal Expert Review of Anticancer Therapy	Narrative review	Immune system and immunotherapy
Rischin D *et al.*[17]	2020	Phase 2 study of cemiplimab in patients with metastatic cutaneous squamous cell carcinoma: primary analysis of fixed-dosing, long-term outcome of weight-based dosing	Journal for Immunotherapy of Cancer	Clinical trial	Immunotherapy drugs in SCC
Barrios DM *et al.*[18]	2020	Immune checkpoint inhibitors to treat cutaneous malignancies	Journal of the American Academy of Dermatology	Narrative review	Immune system and immunotherapy
Desilets A *et al.*[19]	2020	Safety evaluation of pembrolizumab for treating recurrent head and neck squamous cell carcinoma	Expert Opinion on Drug Safety	Narrative review	Immunotherapy drugs in SCC
Lee A *et al.*[20]	2020	Cemiplimab: A Review in Advanced Cutaneous Squamous Cell Carcinoma	Drugs	Systematic review	Immunotherapy drugs in SCC
Ferris RL[21]	2019	Nivolumab in Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck: Efficacy and Safety in CheckMate 141 by Prior Cetuximab Use	Clinical Cancer Research	Clinical trial	Immunotherapy drugs in SCC
Habib LA *et al.*[8]	2019	Advances in Immunotherapy and Periocular Malignancy	Seminars in Ophthalmology	Systematic review	Immune system and immunotherapy
Guminski A, Stein B[9]	2019	Immunotherapy and other systemic therapies for cutaneous SCC	Oral Oncology	Narrative review	Immune system and immunotherapy
Liebl MC, Hofmann TG[22]	2019	Identification of responders to immune checkpoint therapy: which biomarkers have the highest value?	Journal of the European Academy of Dermatology and Venereology	Narrative review	Immune system and immunotherapy
Ahmed SR *et al.*[23]	2019	Cemiplimab-rwlc as first and only treatment for advanced cutaneous squamous cell carcinoma	Expert Review of Clinical Pharmacology	Narrative review	Immunotherapy drugs in SCC
van Baar MLM *et al.*[24]	2019	Pembrolizumab for cutaneous squamous cell carcinoma: Report of a case of inoperable squamous cell carcinoma with complete response to pembrolizumab complicated by granulomatous inflammation	JAAD Case Reports	Case report	Immunotherapy drugs in SCC
Kacew AJ *et al.*[25]	2019	Chromosome 3q arm gain linked to immunotherapy response in advanced cutaneous squamous cell carcinoma	European Journal of Cancer	Retrospective cohort study	Immunotherapy drugs in SCC
Ogata D, Tsuchida T[26]	2019	Systemic Immunotherapy for Advanced Cutaneous Squamous Cell Carcinoma	Current Treatment Options in Oncology	Narrative review	Immunotherapy drugs in SCC

Continuation…

Table 1: Synthesis of studies analyzed by the systematic review

Authors	Year	Title	Journal	Type of study	Subject Area
Paulson KG *et al.*[27]	2019	Immunotherapy for skin cancer	International Immunology	Narrative review	Immune system and immunotherapy
Liu Y *et al.*[28]	2019	Prolonged Response to Pembrolizumab in Spindle Cell Squamous Cell Carcinoma Metastatic to the Central Nervous System	Journal of Investigative Medicine High Impact Case Reports	Case report	Immunotherapy drugs in SCC
Di Nardo L *et al.*[29]	2019	Molecular genetics of cutaneous squamous cell carcinoma: perspective for treatment strategies	Journal of the European Academy of Dermatology and Venereology	Narrative review	Immune system and immunotherapy
Barber BR[30]	2019	Immune Status and Immunotherapy in Advanced Cutaneous Squamous Cell Carcinoma-What Are Our Next Steps?	JAMA Otolaryngology-Head & Neck Surgery	Letter to the editor	Immune system and immunotherapy
Bottomley *et al.*[31]	2019	The Role of the Immune System in Cutaneous Squamous Cell Carcinoma	International Journal of Molecular Sciences	Narrative review	Immune system and immunotherapy
Chen A *et al.*[7]	2018	Clinical Remission of Cutaneous Squamous Cell Carcinoma of the Auricle with Cetuximab and Nivolumab.	Journal of Clinical Medicine	Case report	Immunotherapy drugs in SCC
Amoils M *et al.*[32]	2018	PD-L1 Expression and Tumor-Infiltrating Lymphocytes in High-Risk and Metastatic Cutaneous Squamous Cell Carcinoma	Head and Neck Surgery	Cross-sectional study	Immunotherapy drugs in SCC
Migden MR *et al.*[33]	2018	PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma	New England Journal of Medicine	Clinical trial	Immunotherapy drugs in SCC
Degache E *et al.*[34]	2018	Major response to pembrolizumab in two patients with locally advanced cutaneous squamous cell carcinoma	Journal of the European Academy of Dermatology and Venereology	Letter to the editor	Immunotherapy drugs in SCC
Yanagi T, Kitamura S, Hata H[35]	2018	Novel therapeutic targets in cutaneous squamous cell carcinoma	Frontiers in Oncology	Narrative review	Immune system and immunotherapy
Ilyas M, Costello CM, Sharma A[36]	2017	Exploring the relationship between natural killer cells and cutaneous squamous cell carcinoma development	JAAD Case Reports	Case report	Immunotherapy drugs in SCC
Falchook GS *et al.*[37]	2016	Responses of metastatic basal cell and cutaneous squamous cell carcinomas to anti-PD1 monoclonal antibody REGN2810	Journal for Immunotherapy of Cancer	Case report	Immunotherapy drugs in SCC
Chang ALS *et al.*[38]	2016	A case report of unresectable cutaneous squamous cell carcinoma responsive to pembrolizumab, a programmed cell death protein 1 inhibitor	JAMA Dermatology	Letter to the editor	Immunotherapy drugs in SCC
Macdonald JB *et al.*[39]	2015	Cutaneous adverse effects of targeted therapies: Part II: Inhibitors of intracellular molecular signaling pathways	Journal of the American Academy of Dermatology	Narrative review	Immune system and immunotherapy
Yanofsky VR *et al.*[40]	2013	Understanding dendritic cells and their role in cutaneous carcinoma and cancer immunotherapy	Clinical and Developmental Immunology	Narrative review	Immune system and immunotherapy
Fujita H *et al.*[41]	2012	Langerhans cells from human cutaneous squamous cell carcinoma induce strong type 1 immunity	Journal of Investigative Dermatology	Experimental study	Immune system and immunotherapy

cell layer, which expand into tissues through neoplastic clones. Tumor promoters stimulate clonal tumor expansion. They can be exogenous, such as ultraviolet radiation (UVR), chemical agents, medications, and infections, or endogenous, such as diet and immune suppression. SCCs carry one of the highest tumor mutation loads among all types of cancer, which increases their immunogenicity due to the expression of tumor neoantigens, mutations, and/or viral gene expression.[2,27,30]

Natural killer (NK) cells represent one of the main cell lines of innate immunity, and they're found mainly in the dermis.[31] NK cells are responsible for the neoantigens immunosurveillance, controlling tumor progression through cytolytic response.[36] Tissue

macrophages also constitute another crucial lineage in the anti-tumor immune response, identifying damaged keratinocytes and promoting leukocyte recruitment and pro-inflammatory mediator in the neoplastic site to eradicate cancer cells. However, when infiltrated into neoplastic tissue, tumor associated macrophages act as stimulating agents for tumor development by secreting pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMP).[31,36]

Dendritic cells (DCs) also promote antigens recognition in peripheral tissues, and they're differentiated into six subtypes of cutaneous dendritic cells. The Langerhans cells, present in the corneal and granular layers of the epidermis, and the dermal myeloid dendritic cells, found in the dermis, can be highlighted. Dendritic cells recognize neoplastic neoantigens in the cutaneous tissue, introducing them to CD8+ and CD4+ naive T-lymphocytes located in regional lymph nodes .[31,40,41]

T cells make up about 10% of the cellular infiltrate of skin tumors, thus playing an essential role in neoplastic immunological control. Dendric cells introduce tumor neoantigens through the major histocompatibility complex (MHC). They promote the activation of naive T cells into effector T cells and the polarization of T cell responses into Th1, Th2, Th9, and Th17.[31, 40] The T response pattern is crucial to prevent the development of cutaneous malignancy and metastases. The Th1 pattern (cytotoxic response) is the main responsible for controlling tumor progression, and the Th2 pattern is generally associated with neoplastic development.[31,40]

In addition to cellular immunity, the humoral response of effector B cells is also an essential component of neoplastic control. B cells act through the immunoglobulins and cytokines production, contributing to the T-lymphocyte responses polarization, and to pro-inflammatory mechanisms chemotaxis and activation that will lead to carcinogenesis failure.[31]

Despite the immune control mechanisms, some neoplasms can evade the immune system, proliferating and invading adjacent structures and spreading to other tissues.[8] The neoplastic evasion process is strongly influenced by the tumor microenvironment through its cellular, molecular, and environmental characteristics.

The tumor microenvironment and the immune escape

The tumor microenvironment comprises several malignant and non-malignant cell types that establish complex and dynamic interactions through chemotactic agents, such as cytokines, growth factors, and inflammatory enzymes.[31] In this perspective, the balance or imbalance between such biological interactions will determine tumor progression or suppression through mechanisms intrinsic or extrinsic to neoplastic cells (Figure 2).

Among the intrinsic factors is the tumor's surface proteins expression, hindering recognition and phagocytosis by DCs, and the cytokines secretion, promoting DC dysfunction and inhibiting specific tumor T cells activation. It results in an increased SCCs tumor burden.[31,40,41]

The immune status is one of the extrinsic factors that influence the tumor microenvironment.[27] It can also affect the Th1 and Th2 immunity patterns. Immunocompetent individuals tend to demonstrate gene expressions associated with Th1 and Th2 responses, while immunosuppressed individuals show a Th2 immunity predominance, an immune response more related to cell infiltration and tumor progression.[27,31]

Another extrinsic factor is ultraviolet (UV) radiation, which acts in the tumor microenvironment inducing dendritic cells' apoptosis and reducing their lymphatic migration. Thus, it impairs the CD8+ T-lymphocyte cytotoxic response mediated by CDs. UV radiation also stimulates the pro-inflammatory mediators released by infiltrating keratinocytes and leukocytes that favor the SCCs initial development.[27,31]

From another perspective, Bottomley *et al.* proposed the concept of "immunoediting", a process where the tumor cells' elimination by immune defense mechanisms would lead to the neoplastic cells selection without specific immunogenic antigens. These cells, when not recognized by the immune system, would then have the ability to proliferate in the tumor microenvironment.[31]

However, 'immunoediting' is not a mechanism of "escape" per se, which can result in three types of outcomes: elimination, where the immune system can totally eliminate the tumor cells; equilibrium, where the immune mechanisms control the tumor progression but fail to eradicate the cancer cells completely; and escape, where tumor cell lines proliferate, combining characteristics of immune evasion and resistance to apoptosis.[31]

Immunological tolerance has also been recognized as one of the main "escape" tumor cells mechanisms. Under physiological conditions, inactivated and immature dendritic cells stimulate the regulatory T cells (Treg) differentiation, which acts by inhibiting the effector T cells cytotoxic responses, limiting excessive immune reactivity.[31,40]

Nevertheless, Treg cells act by preventing the secretion and proliferation of dendritic cells in the tumor microenvironment. It reduces the presentation quality of neoplastic neoantigens and results in an imbalance towards the inhibition of effector T activation.[22,31,40] Regulatory T cells are identified in tumor infiltrates of BCCs and SCCs.[2] This fact can be explained by the ability of tumor cells to recruit immunosuppressive cells, such as Treg cells and myeloid-derived suppressor cells (MDSCs), favoring neoplastic evolution.[8]

It is worth highlighting the influence of individual variants on composition of the tumor microenvironment - cytokines, interleukins, interferons and infiltrating immune cells (T effector lymphocytes, Treg and B) - determining the pattern of immune response and control of tumor progression.[22]

Immune checkpoints and immunomodulation

Self-tolerance represents an essential element of the immune system. It promotes immune response regulation, pre-

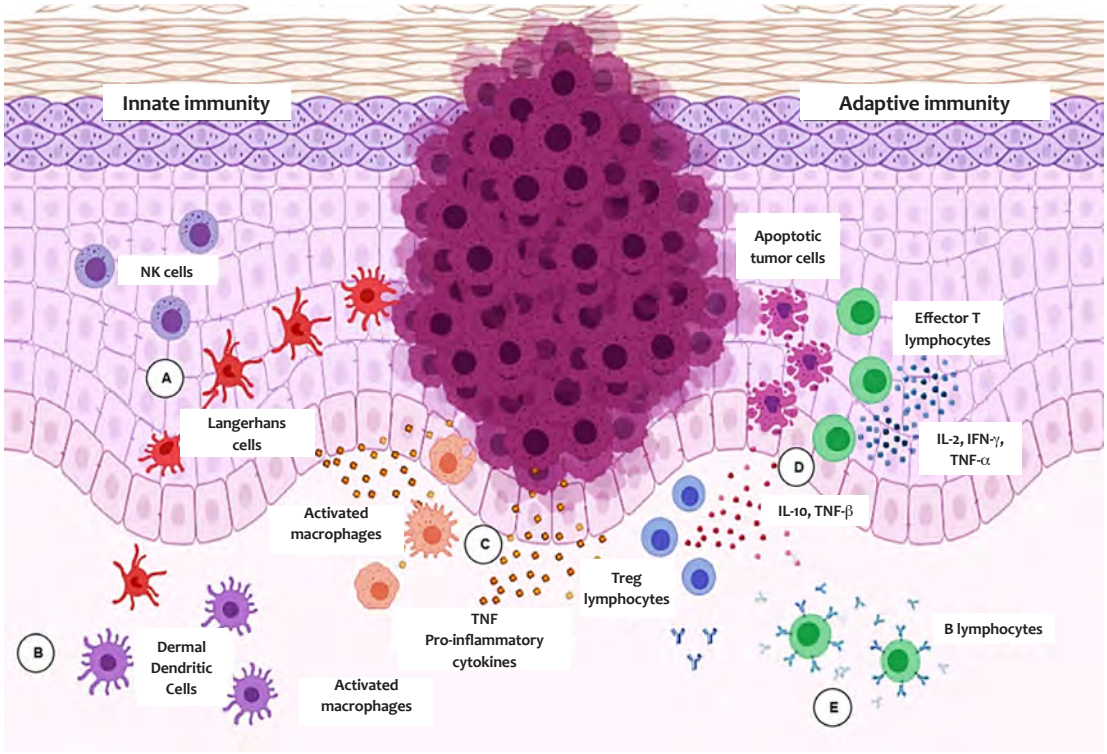

FIGURE 2:
A – NK cells and Langerhans cells recognizing tumor antigens and initiating the innate immune response.
B – Dermal dendritic cells recognizing tumor antigens.
C – Macrophages phagocytizing tumor cells and secreting pro-inflammatory cytokines.
D – Effector T cells triggering the tumor cells apoptosis through a cytotoxic response, in addition to secreting pro-inflammatory cytokines. Treg cells secreting cytokines that inhibit the activity of effector T cells.
E – Activated B cells producing antitumor immunoglobulins.

venting excessive inflammatory and cytotoxic processes that would cause the degradation of healthy tissues adjacent to the lesions. Under physiological conditions, immune modulation results from the activity of cellular molecules and receptors called immune checkpoints.[8,9]

Nevertheless, cancer cells have acquired the ability to overexpress molecules and receptors of immune checkpoints, evading the antitumor mechanism and, consequently, progressing uninhibitedly.[8] Programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), and epidermal growth factor receptor (EGFR) represent the main immune checkpoints expressed in SCC tumor cells, signaling their relevance as potential therapeutic targets.[8,9,14]

CTLA-4 is expressed on the surface of cytotoxic T-lymphocytes and acts to prevent these cells' activation, triggered by the binding with CD80 and CD86 dendritic cells proteins. However, T cells also have the surface protein CD28, which promotes the stimulation of cytotoxic T activity through CD80 and CD86 ligands. Therefore, the effector T-lymphocyte's response will depend on the balance of the bindings between CD80 and CD86 with the CTLA-4 ("inhibitory") and CD28 ("stimulator") receptors.[8]

PD-1 is a cell surface receptor found on T and B cells, NK cells, dendritic cells, and monocytes. In T cells, PD-1 is only expressed after their activation, promoting effector T cells apoptosis. Also, it inhibits Treg cells apoptosis by binding to PD-L1 and PD-L2 proteins (programmed cell death ligands 1 and 2) present on the surface of tumor cells.[8,14,31,32] Thus, cancer clones can increase their PD-L1 surface presentation, avoiding immunological surveillance.[19,32] Amoils et al. corroborated this understanding, emphasizing the association of increased PD-L1 expression with metastatic and recurrent SCCs. From another perspective, Pezeshki *et al*. highlighted the PD-1 and PD-L1 role in the "T cell exhaustion" phenomenon, resulting from the potency reduction in the T cell clones from chronic exposure to a particular antigen.[16]

The EGFR gene is another important tumor checkpoint component, encoding a transmembrane glycoprotein receptor responsible for activating multiple downstream signaling pathways – including MAPK/ERK and PI3K/AKT/mTOR – that control processes of maturation, proliferation, apoptosis inhibition, and cells angiogenesis.[29] EGFR deregulation has been observed in head, neck, ovary, breast, bladder, colon, and lung carcinomas, and it is related to tumor proliferation. In cutaneous SCC cases, despite the low incidence of EGFR mutations – ranging from 2.5% to 5% – this gene overexpression has been associated with metastases and a worse prognosis.[21,29]

In this respect, the study of the immune response role in the tumor microenvironment in recent years has stimulated the development of target therapies aimed at overexpressed ligands in tumor tissue.[8] The mechanisms of inhibition of CTLA-4 and PD-1 receptors on immune cells and PD-L1 on neoplastic cells were described for the first time in 2018. It enabled the

interruption of the mechanism of the tumor evasion, allowing the effector T cells action to control the cancers' progression (Figure 3).[8,9,18,22,32]

In this perspective, CTLA-4 blocking would allow the effector T-lymphocytes activation, while blocking PD-1 or PD-L1 would inhibit the effector T-lymphocytes apoptosis, as well as the phenomenon of "T cell exhaustion". Thus, both therapeutic pathways would promote increased cellular immunity activity mediated by T cells.[8] On the other hand, blocking the EGFR would inhibit one of the mechanisms of tumor cells "evasion", allowing the immune system to act on them.[21,29]

Still, it is noteworthy that the immune activity stimulation by immunotherapy drugs can trigger nonspecific immune responses, in the form of autoimmune diseases such as vitiligo. Furthermore, these medications also demonstrate the potential to cause adverse events such as pruritus, lichenoid rash, papulopustular eruptions, among other skin manifestations, as well as diarrhea and hypothyroidism.[19,24,39]

Understanding the immune surveillance of cancers and the mechanisms of tumor "evasion" allowed the development of drugs that block the receptors involved in these pathways, with greater emphasis on the CTLA-4, PD-1, and EGFR receptors.[8]

Due to the high mutational load of SCCs, they become very susceptible to blocking immune checkpoints.[8]

The main indications for immunotherapy are locally advanced, unresectable, incurable, metastatic SCCs and cases of good tolerability to medications with potential increased survival.[15] The combination of anti-CTLA-4 and anti-PD-1 medications has been reported in specific cases of melanoma, renal cell carcinoma, and recurrent and metastatic SCCs of head and neck, demonstrating better therapeutic responses.[8,25] However, such combinations have higher toxicity, with the risk of triggering colitis and hypophysis.[24]

The advent of checkpoint inhibitor therapy has raised promising expectations for the treatment of locally advanced, recurrent, and metastatic SCCs, with improved patient overall survival as well as progression-free survival.[8,25] Ipilimumab, CTLA-4 inhibitor, nivolumab, pembrolizumab, cemiplimab, PD-1 inhibitors, cetuximab, and anti-EGFR are the immunological checkpoint inhibitors currently approved for skin neoplasms (Table 2).[8,18,35]

IMMUNOTHERAPY DRUGS AND TREATMENT OF SQUAMOUS CELL CARCINOMA:

Ipilimumab

Ipilimumab can cause adverse events such as autoimmune dermatitis, colitis, and diarrhea, in addition to skin reactions such as pruritus, morbilliform eruption, nodular pruritus, lichenoid rash, and photosensitivity. In general, these adverse events present after three to six weeks from the start of the medication, being dose-dependent and reversible with the end of the treatment.[39]

Nivolumab

Nivolumab is a PD-1 receptor inhibitor that prevents the T-lymphocyte's deactivation and preserves the cellular

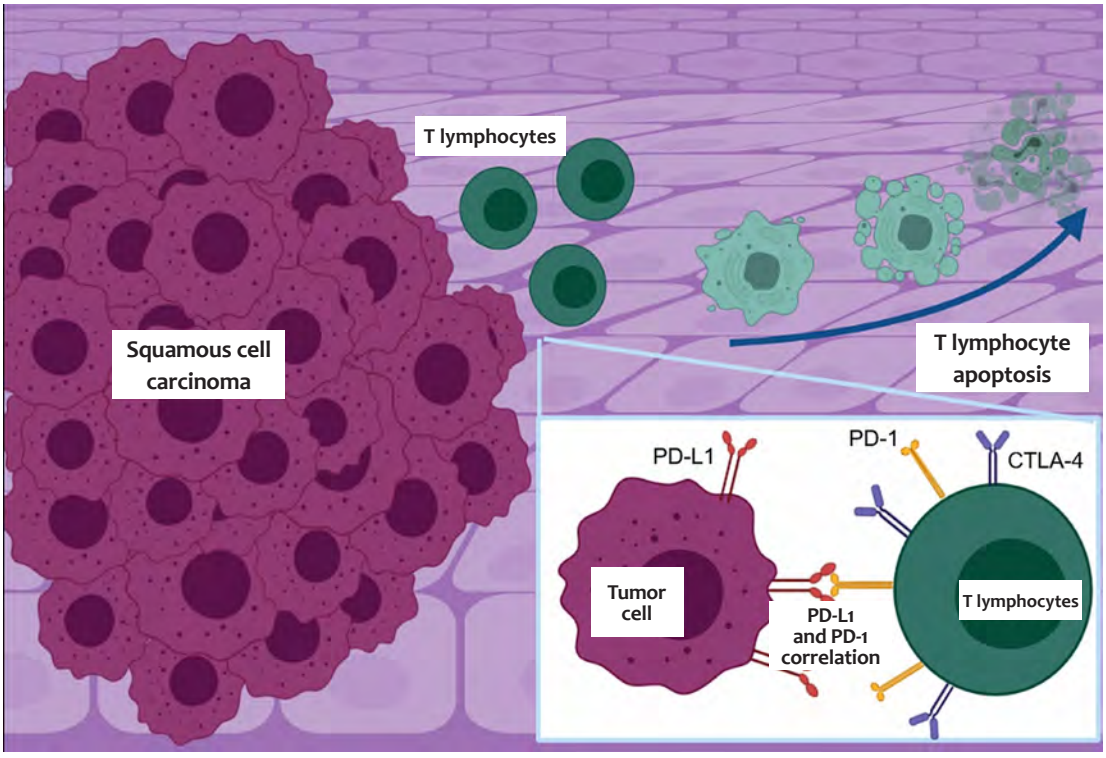

FIGURE 3: T-lymphocytes recruited to the tumor site. PD-L1 ligands of tumor cells activating PD-1 receptors on T-lymphocytes, triggering apoptosis of these cells

Table 2: Immunotherapy drugs used in the squamous cell carcinomas treatment

Immunotherapy drugs	Class	Clinical Applications	Adverse Events
Cemiplimab	PD-1 inhibitor	Metastatic and/or locally advanced cutaneous SCC	Diarrhea, fatigue, nausea, constipation, and rash.
Cetuximab	Anti-EGFR	Colorectal cancer, head and neck SCC, and unresectable cutaneous SCC.	Papulopustular eruption, desquamative rash, eczema, xerosis, paronychia, and alopecia.
Ipilimumab	Anti-CTLA-4	Metastatic melanoma, non-melanoma skin cancer, renal cell carcinoma, and colorectal cancer	Mild diarrhea, mild rash or itching, hypopituitarism, hypothyroidism, reduced appetite, dizziness, headache, fatigue.
Nivolumab	PD-1 inhibitor	Non-small cell lung cancer, renal cell carcinoma, recurrent or metastatic cutaneous SCC of the head and neck, and advanced melanoma	Diarrhea, nausea, rash, itching, fatigue, headache, mental status changes, abdominal pain, hypotension.
Pembrolizumab	PD-1 inhibitor	Non-small cell lung cancer, melanoma, and advanced cutaneous SCC	Diarrhea, hypothyroidism, rash, and rare immunological adverse events, especially grade 3 to 5 pneumonitis.

immunity function. The FDA approved the drug in 2017 to treat recurrent or metastatic head and neck SCCs, and advanced melanoma.[21,26] However, nivolumab's role in non-melanoma skin cancers has not yet been fully elucidated.[7]

Chen et al. reported a case of complete remission of an invasive and poorly differentiated SCC in the auricle. The treatment was based on immunotherapy using a combination of nivolumab and cetuximab – antibody against the epidermal growth factor receptor (EGFR). The case reported by Chen et al. avoided extensive surgery with a potential risk of facial nerve palsy through these immunotherapy drugs and showed promising results.[7]

Regarding adverse events, mild fatigue represented the most common condition. However, the literature has also reported dermatological disorders such as vitiligo, skin rash, itching, endocrine hypofunction, and hip fracture.[26,39]

Cemiplimab

Cemiplimab is a human IgG4 monoclonal antibody with a high affinity for the PD-1 receptor. It promotes the blocking of PD-L1 (expressed in tumor cells) and stimulates the effector T cells' action. It was the first systemic therapy approved to treat metastatic or locally advanced SCCs not suitable for curative surgery or radiotherapy.[17,20,23,26,37]

Several studies have demonstrated the effectiveness of cemiplimab use to treat SCCs, reducing the diameters of target lesions.[17,23,37] Ahmed et al. demonstrated a cemiplimab response rate of 50% in advanced SCC cases – in a phase 1 study – and a response rate of 47% in metastatic disease cases – in a phase 2 study.[23]

Regarding the adverse events, the most common are diarrhea, fatigue, nausea, constipation, and rash,[23,33] which are solved by adjusting the therapeutic doses and/or discontinuing the treatment.[23] Despite the adverse events, cemiplimab has a clinically significant lasting effect, with acceptable safety and tolerability profile.[20]

Cetuximab

Cetuximab is a chimeric immunoglobulin (IgG1mAb) that binds to domain 3 of the extracellular domain of the epidermal growth factor receptor (EGFR), leading to innate and adaptive immune responses in tumors dependent on this oncogenic pathway.[13,21] The response to cetuximab correlates to the tumor's EGFR expression. It can restore the anti-tumor immune response, lead to cell cytotoxicity of NK cells, in addition to maturation and crosstalk between NK and dendritic cells.[13,21]

Cetuximab was initially approved to treat colorectal cancer. Currently, it has been approved for advanced head and neck and/or platinum-refractory SCCs, and it can be adopted as adjuvant therapy to surgery and radiotherapy.[4] Cetuximab has been described as the most effective anti-EGFR in SCC treatment, with promising results when combined with other therapeutic alternatives.[4,13]

A 2014 study on the treatment of unresectable SCCs compared the use of cetuximab in monotherapy with combinations of the drug with carboplatin or radiotherapy. The results showed control rates of 50% for monotherapy, 87.5% for cetuximab + carboplatin, and 100 % for cetuximab + radiotherapy.[4] Another phase 2 clinical trial study on the use of cetuximab in monotherapy to treat unresectable SCCs observed disease stabilization in 58% of cases.[21] However, the medication still presents unpromising cure rates: 3% of complete remission and 8% partial response in advanced SCC cases.[21]

CONCLUSIONS

The treatment of cutaneous neoplasms is at an advanced stage, benefiting patients affected with tumors that are challenging to access surgically and reconstruct anatomically. The use of many of these therapies is still under investigation, clinical trial, or approval. Still, the literature already presents evidence to support the consideration of the great importance and benefit of these new therapeutic strategies.

It's essential to understanding the physiopathogenesis of SCCs to promote the development of new therapeutic approaches that may soon benefit a more significant number of patients. ●

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Effectiveness of cryolipolysis for subcutaneous fat reduction: a systematic review and meta-analysis

Eficácia da criolipólise para redução de gordura subcutânea: uma revisão sistemática e metanálise

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ABSTRACT

Introduction: *Cryolipolysis produces selective, controlled cooling, and it's based on the concept that lipid-rich tissue is more susceptible to cold injury, reducing subcutaneous fat.*

Objective: *To review the literature to assess the effectiveness of cryolipolysis in reducing subcutaneous fat.*

Methods: *Systematic review with meta-analysis of studies published in the EBSCOhost, LILACS, and PUBMED databases.*

Results: *Only one study did not present significant reduction in subcutaneous fat compared to the control group. There was a difference among the parameters in the studies.*

Conclusion: *Cryolipolysis is an effective tool for localized fat reduction.*

Keywords: *Apoptosis. Freezing. Subcutaneous Fat*

RESUMO

Introdução: *a criolipólise produz um resfriamento seletivo e controlado e baseia-se no conceito de que tecidos ricos em lipídios são mais suscetíveis a lesões por frio, reduzindo gordura subcutânea.*

Objetivo: *revisar a literatura para avaliar a eficácia da criolipólise na redução de gordura subcutânea.*

Métodos: *revisão sistemática com metanálise de estudos publicados nas bases de dados EBSCOhost, LILACS e PUBMED.*

Resultados: *apenas um estudo não apresentou redução significativa na gordura subcutânea quando comparado o grupo de intervenção ao grupo controle. Houve diferença entre os estudos em relação aos parâmetros.*

Conclusão: *a criolipólise é uma ferramenta eficaz para redução de gordura localizada.*

Palavras-chave: *Apoptose. Congelamento. Gordura Subcutânea*

Review

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INTRODUCTION

The fact that more than 56.3% of Brazilian adults are overweight or obese,[1] in addition to the desire to quickly lose fat without undergoing surgery,[2] drive the growing demand for fat reduction methods. In this scenario, cryolipolysis emerges as one of the most recently developed modalities for the noninvasive reduction of localized fat.[3]

The US Food and Drug Administration (FDA) authorized the first cryolipolysis device (CoolSculpting system, Zeltiq Aesthetics, Pleasanton, CA, USA) to reduce flank fat (K080521) in 2010; abdominal fat (K120023) in 2012; and inner thigh fat (K133212), in April 2014.[4] According to Suh et al.,[5] the use of cryolipolysis was also approved for inner thigh, submental fat, arms, back, and lower buttocks.

This technique produces selective and controlled cooling. It is based on the concept that lipid-rich tissues are more susceptible to cold injuries than the water-rich tissues around them.[6] Adipocytes undergo apoptosis more quickly because they are sensitive to cooling than the dermis, epidermis, muscles, vessels, and nerves. These dead cells cause an inflammatory process and are metabolically eliminated as part of normal digestion.[7] According to Avram and Harry,[8] the changes are not noticeable immediately after the treatment. Therefore, adipocytes and cell membranes are not affected. However, three days after the intervention, there is evidence that an inflammatory process occurs only in adipocytes. Between 14 and 30 days, lipid phagocytosis is apparent, resulting in decreased tissue volume in 60 days.

According to the literature, this procedure is safe, with report of patient satisfaction, especially when compared to other methods for localized fat reduction.[9] However, with all its benefits, there is still a lack of substantial literature demonstrating this tool's effectiveness. Therefore, this study has the general objective of systematically review the available literature to assess the effectiveness of cryolipolysis in reducing subcutaneous fat. Its specific objectives are to determine the temperature values and the application time commonly used to reduce subcutaneous fat and search the literature if the temperature and cryolipolysis application time specified in the cryolipolysis equipment influences the subcutaneous fat reduction.

MATERIALS AND METHODS

This study is a systematic review conducted according to the PRISMA methodology (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).[10] The guiding question of the present study was elaborated using the PICOS strategy: (P) individuals with subcutaneous fat, (I) cryolipolysis, (C) control group or placebo group, that is, who did not receive the cooling intervention, (O) subcutaneous fat reduction, and (S) randomized clinical trials.

We performed a systematic review search using the EBSCOhost, LILACS, and PUBMED databases. The search was conducted using the following terms: (tw:(cryolipolysis)) OR (tw:(lipocryolysis)) OR (tw:(fat freezing)) OR (tw:(coolsculpting)) OR (tw:(adipocytolysis)) OR (mh:(cryotherapy)) AND (mh:(adiposity)) OR (mh:(subcutaneous fat)) OR (tw:(fat reduction)) OR (tw:(fat)) OR (tw:(localized fat)) OR (mh:(body contouring)) OR (tw:(nonsurgical reduction of fat)) OR (tw:(noninvasive fat removal)) OR (tw:(noninvasive body contouring)). In addition to the electronic search, we performed a manual search in the bibliographic references of the previously selected studies.

Randomized clinical trials published between 2010 and 2019 in English, Portuguese, and Spanish, which had full text, were included. We selected the articles conducted in humans, both sexes, aged between 18 and 59 years old, analyzing cryolipolysis to reduce localized fat in the thigh, flank, abdomen, arm, or submental regions.

Review articles, animal research, studies that used another therapy combined with cryolipolysis aiming at localized fat reduction other than local massage were excluded. We also excluded studies with an intervention objective other than reducing localized fat and those that performed the treatment with cooling application three or more times in the same area.

Two researchers independently and blindly reviewed the titles and abstracts of potential articles and extracted the data. The selected titles and abstracts were submitted for a complete review. A third researcher was consulted when there were differences in the inclusion and exclusion of articles. The methodological quality of the studies was assessed using the PEDro scale, developed by the Physiotherapy Evidence Database to be used in experimental studies. According to Morton,[11] the PEDro scale is a valid measure to assess the methodological quality of clinical trials. The scale has a total score of up to 10 points, including internal validity assessment criteria and presentation of the statistical analysis employed. For each criterion defined in the scale, one point (1) is attributed to indicators of the quality of the evidence, and zero (0) in the case of absence of these indicators. Two researchers applied the PEDro scale independently and blinded.

Statistical analysis was performed using the Review Manager (RevMan) program developed with the Cochrane collaboration. The characteristics of the samples between the studies were different, resulting in greater heterogeneity. In the case of significant statistical heterogeneity (I^2>50%), a random-effect model n was used for the meta-analysis.

RESULTS

Searches in databases and other additional 30 studies identified through manual search resulted in 1,147 articles. After eliminating duplicates, 972 articles remained, of which 862 were excluded by title and 51 by abstract. Among the 59 articles assessed for eligibility, 55 were excluded because 22 were cohort studies, systematic or literature review, case report, or pilot study; 17 had participants' ages incompatible with the inclusion criteria (over 59 years old); five were quasi-experimental studies; three

studies used multiple treatments combined with cryolipolysis; two applied cryolipolysis to the breast and back region; one did not have cryolipolysis as primary endpoint; and five were not found for download or were not available. Thus, this systematic review included four articles (Figure 1). We found the highest percentage of articles (79.08%) in the PubMed database, followed by the EBSCOhost (11.68%) and LILACS (6.62%).

The four studies included in this review[5,12,13,14] comprised a total of 117 participants, varying between 11 and 60 in each study. The sample was composed predominantly of women (81.20%), and the age ranged between 25 and 49 years. All studies assessed the cryolipolysis effect to reduce localized fat. The measurement instruments used were ultrasound,[5] photography,[5,13] visual analogue scale,[14] satisfaction questionnaire,[13] body mass index (BMI),[12] anthropometry,[5,14] pachymetry,[12,13] perimetry,[5,14] and weight.[12, 13] The treated regions were abdomen[5,12,14] and flank.[13]

All the studies analyzed showed a significant reduction in subcutaneous fat and/or a decrease in the localized fat circumference (Table 1), except for the study by Falster, et al.[14] However, there was a difference regarding the parameters for applying cryolipolysis among studies.

When analyzing the cooling temperature adopted by the studies included in the present review, we observed that it varied by a few degrees and the way of adjusting the temperature in the equipment. Two studies adjusted the temperature in degrees Celsius, and two others in CIF, with a variation of 1 degree Celsius and 0.4 CIF, respectively.

The average methodological quality assessed by the PEDro scale was 6.75, with no article scoring lower than five or higher than nine. The criteria with the highest deficit among the articles were related to the blinding of subjects, therapists, and assessors (Table 2).

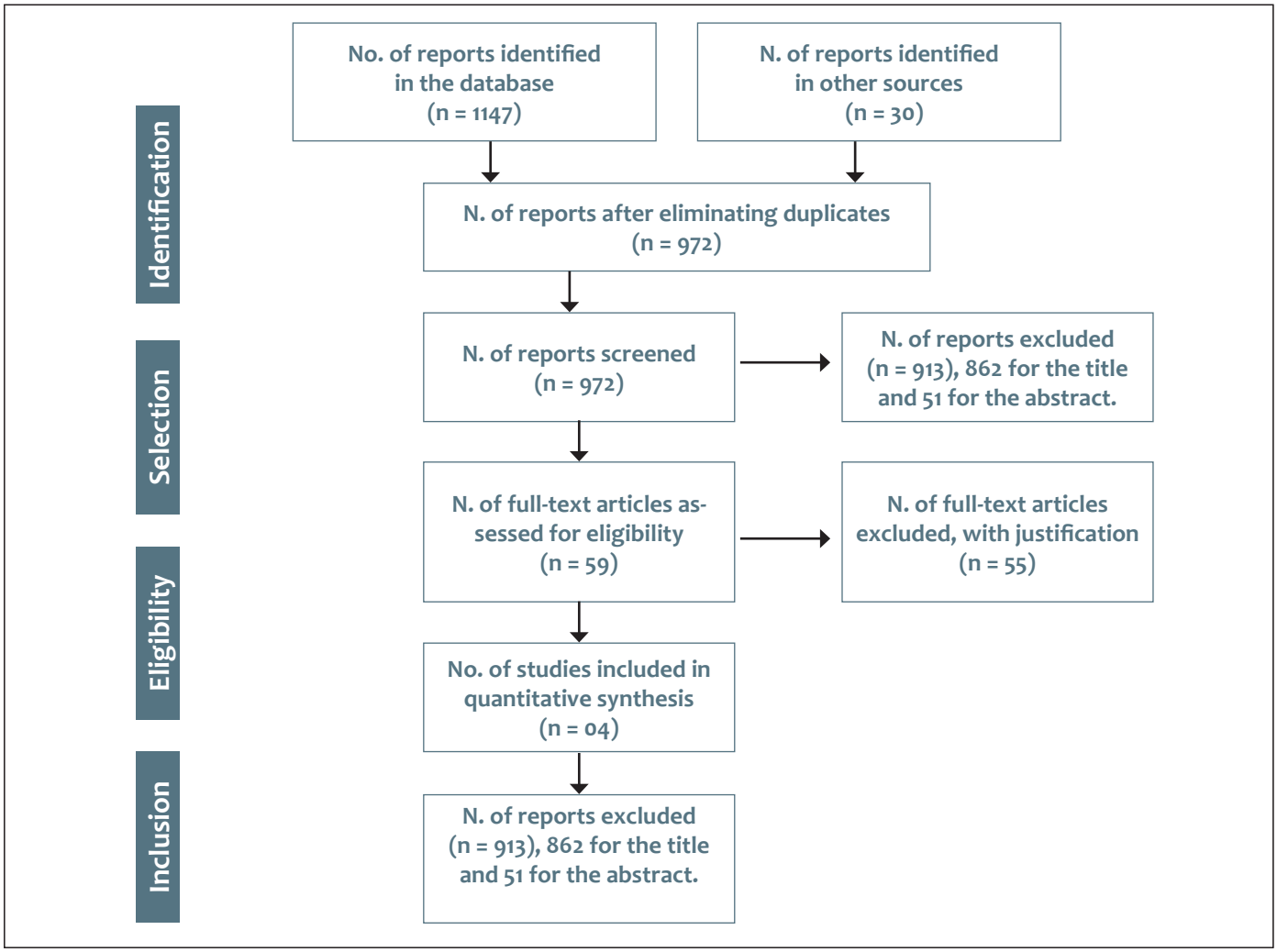

Figure 1: Flow diagram of included studies

Table 1: Characterization of the studies

Author (s)/year	Study design	Sample	Intervention group and control group	Assessment form	Follow up time	Results
Garibyan et al., 2014	RCT	n = 11 (6W and 5M)	60 minutes, CIF 41.6. IG: randomized flank and CG: contralateral flank.	Pachymetry, weight, photography, three-dimensional system, and satisfaction survey.	2 months	Significant reduction in volume and pachymetry. Improved patient satisfaction.
Eldesoky et al., 2015	RCT	n = 60 (44W and 16M)	30 minutes, ICF 42. IG: A (US + diet), B (cryo + diet) and CG: C (diet only).	Pachymetry, weight, height, BMI.	2 months	Weight, perimeter, and pachymetry reduction in both intervention groups compared to the control group.
Suh et al., 2018	RCT	n = 12 (11W and 1M)	70 minutes, -11 °C. IG: left side of the abdomen and CG: right side.	Anthropometry, photography, perimeter, pachymetry, high resolution ultrasound.	2 months	Significant reduction when comparing sides with ultrasound. There was a reduction in perimeter and skinfold. Nine of the 12 patients reduced their weight.
Falster et al., 2019	RCT	n = 34 (34W)	50 minutes, -10 °C. IG: randomization for the cryolipolysis group (n=17) and CG: control group with 17 individuals.	Anthropometry, high-resolution ultrasound, pachymetry, perimeter, and VNS.	3 months	No significant difference between groups in the subcutaneous fat layer.

Subtitle: RCT = Randomized Clinical Trial, W = Women, M = Men, TS = Therapeutic Ultrasound, BMI = Body Mass Index, CIF = Cooling Intensity Factor, IG = Intervention Group, CG = Control Group, VNS = Visual Numeric Scale.

Also, we conducted a meta-analysis comparing three of the four studies in this review.[12,13,14] These studies used an equivalent assessment method (pachymetry) to measure the abdomen and flanks skinfold. In total, 96 participants were included in the meta-analysis, 48 in the experimental group, and 48 in the control group. We observed a statistically significant 2.27 mm reduction in body fat (95% CI -5.40 to -0.04; $Tau^2 = 3.16$; $Chi^2 = 4.52$; $I^2 = 56\%$) in the intervention group compared to control (Figure 2).

Temperature and time values found in the articles were not standardized. Temperatures varying between -5 °C and -15 °C and time ranging from 30 to 60 minutes were common-

Table 2: Pedro Scale

Studies	Random allocation	Concealed allocation	Groups similarity at baseline	Blinding of subjects	Blinding of therapists
Eldesoky *et al.*, 2015	Y	Y	Y	N	N
Garibyan *et al.*, 2014	Y	Y	Y	N	N
Suh *et al.*, 2018	Y	N	Y	N	N
Falster *et al.*, 2019	Y	Y	Y	N	Y

Studies	Blinding of assessors	Adequate follow-up	Intention to treat analysis	Between-group comparisons	Mean and standard deviation	Level of evidence
Eldesoky *et al.*, 2015	N	Y	N	Y	Y	6
Garibyan *et al.*, 2014	Y	Y	N	Y	Y	7
Suh *et al.*, 2018	N	Y	Y	Y	N	5
Falster *et al.*, 2019	Y	Y	Y	Y	Y	9

ly observed. The review by Borges and Scorza[15] reported this variation, also describing that the temperature adjusted in the equipment is not the same as that observed in adipose tissue, mainly at deep levels. However, this effect is not harmful to the intervention. The authors also claim that, despite varying, the most used time in clinical practice is 60 minutes.

When searching the literature, it was not possible to find many articles relating the influence of time and temperature on reducing subcutaneous fat. However, in the study by Maia,[16] 53 individuals received an application of cryolipolysis in the lower abdominal region. Different from the temperature treatment applied in the Maia[16] study, two groups (a total of four groups) received the treatment for 70 minutes. In this study, the protocol that showed the most significant results was the combination of a 70-minute time and variable temperatures (-5 °C and -8 °C). It corroborates the statement by Grivicich et al.,[17] who stated that when the temperature decreases, there is a higher energy reserve expenditure (lipids) because of the increase in the metabolic rate. This theory indicates that the lower the temperature, the better localized fat reduction of due to the adipose tissue transformation from liquid (body temperature) to solid (post-cooling) (Limonta et al.).[18]

DISCUSSION

According to the study by Adjadj et al.[19], cryolipolysis has become the gold standard for reducing subcutaneous fat in areas such as the abdomen, knees, flanks, inner thighs, back, and arms, being a good alternative for reducing subcutaneous tissue in patients with moderate fat. It corroborates the result found in the meta-analysis, where we observed the significance of the studies to apply cryolipolysis to reduce the subcutaneous skinfold. However, this decrease had an average of -2.72 (95% CI -5.40 mm to -0.04 mm), casting doubts regarding this method's applicability to the clinical environment since this subcutaneous fat reduction is not essentially visible to the patient in the clinic.

Although there is no conformity on application time and temperature in most studies, cryolipolysis effectively reduces localized fat. The temperature varied between Celsius (-10 ° C and -11 ° C) and CIF (41.6 and 42); the application time varied between 30 and 70 minutes.

This systematic review included three studies that indicated significant results regarding subcutaneous fat reduction. The study by Garibyan et al.[13] observed that, after two months of treatment, the mean reduced volume was 39.5 cm^3 compared to the control side ($p<0.01$). The decrease in fat thickness was 14.9% on the treated side and 0.7% on the control side ($p<0.01$).

Criolipólise				Controle				Mean Difference IV, Randsom, CI 95%	Year
Estudo ou subgrupo	Mean	SD	Total	Mean	SD	Total	Weight		
Garibyan 2014	38.6	4.6	11	44.6	5.1	11	25.1%	-6.00 (-10.06, -1.94)	2014
Eldesoky 2015	25.14	2.79	20	27.69	2.73	20	47.7%	-2.55 (-4.26, -0.84)	2015
Falster 2019	35.5	5.1	17	6.1	6.1	17	27.2%	0.00 (-3.78, 3.78)	2019
Total (IC 95%)			**48**			**48**	**100.0%**	**-2.72 (-5.40. -0.04)**	
Heterogeneity: $Tau^2 = 3.16$; $Chi^2 = 4.52$; df = 2 (p = 0,10), $I^2 = 56\%$									
Test for overall effect: Z = 1.99 (p = 0,05)									

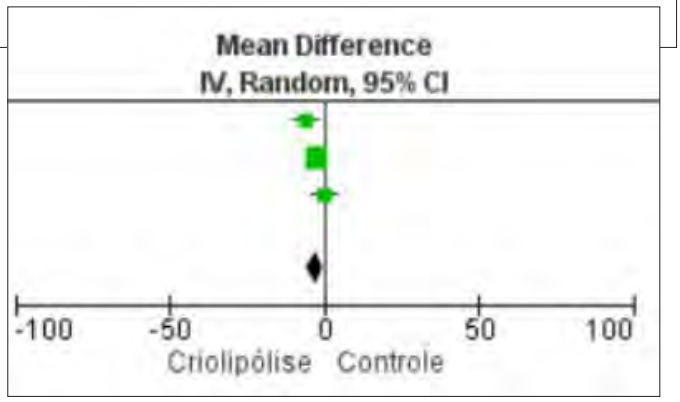

Figure 2: Meta-analysis of studies on the abdominal skinfold

Eldesoky et al.[12] also pointed out significant results in the group receiving cryolipolysis and diet (group B). There was a body mass index reduction of 5.83% (p<0.01), a waist circumference of 6.47% (p<0.0001), and a suprailiac skinfold of 17.41% (p<0.01). Finally, the study by Suh et al.[5] showed significant results when observing, through ultrasound, a decrease of 6.04 mm (standard deviation of 4.57 mm) in the treated abdomen (p 0.03). However, one study[14] did not show significant results when comparing the control group with the experimental group in all evaluation methods. The fact that the average age and weight of the participants were lower than that found in the studies included in this research may explain this difference.

The studies by Garibyan et al.[13] and Suh et al.[5] used a system developed by Zeltiq Aesthetic Inc (Pleasanton, CA), which developed a unique temperature mechanism, named Cooling Intensity Factor (CIF), which represents the rate of heat flow into or out of the tissue opposite the cooling device.[12] Both studies obtained significant results concerning subcutaneous fat reduction. The other studies included measured the temperature in degrees Celsius. The equipment currently available on the market has a temperature range of -5 °C to -15 °C.[15]

In the study by Eldesoky et al.[12], low temperatures (CIF 42) demonstrated a significant result in the cryolipolysis technique regarding the fat thickness reduction, with a higher apoptotic lesion in the adipocytes. However, the study by Falster et al.,[14] which used a temperature of -10 °C, did not obtain significant improvement results in any of the instruments assessed.

Regarding the application time, the study by Garibyan et al.[13] used 60 minutes, with a reduction in flank volume and caliper measurements (p<0.01). In the study by Eldesoky et al.[12], the cryolipolysis group used the therapy for 30 minutes and also obtained satisfactory results, such as significant decrease in weight, skinfolds, and circumference (p<0.01). The study by Suh et al.[5] used 35 minutes, repeated twice, totaling 70 minutes of cryolipolysis application, obtaining a significant result of subcutaneous fat reduction (p=0.03). Finally, the study by Falster et al.[14] applied cryolipolysis for 55 minutes, according to the protocol by Derrick et al.,[20] not obtaining significant results (p>0.05), which can be explained by the difference presented in the age and weight of the participants regarding the other studies.

The literature shows that the protocols used for the cryolipolysis application vary from 30 to 60 minutes,[13,15,21,22] and they present good statistical and clinical results. Only one article did not fit this pattern: the study by Suh et al.,[5] which used cryolipolysis for 70 minutes, and was taken from the research by Kilmer et al.[23] Also, the study by Falster et al.,[14] even using the application time within the literature standards, did not obtain a significant result, making it challenging to analyze the direct relationship between the application time and better outcomes.

The adverse events of cryolipolysis found in the researches were: erythema after the session;[13,19] skin hyperpigmentation;[19] blisters in the treated area;[12] edema;[13] and pain.[13] Among the adverse events, it was also observed that 100% of the partic-

ipants had reduced sensitivity for 10 minutes after application, 73% after three weeks, and 18% in the second month after treatment.[13] Several studies report these events after the cryolipolysis use. However, numerous researchers state that they occur in a short period and do not have significant repercussions.[24,25]

This research's findings evidence the need for further studies in the area – studies with good methodological quality and standardized assessment instruments that allow conducting new meta-analyses, ensuring the safe application of cryolipolysis as a method to reduce subcutaneous fat. However, the study presented as limitations the failure to research all scientific databases and the inclusion of only articles published between 2010 and 2019, in English, Portuguese, Spanish, which had full text available.

CONCLUSION

The assessment method of areas submitted to cryolipolysis did not present conformity: the articles used parameters repeated in different authors or cited in a single study. However, as the meta-analysis demonstrated, cryolipolysis is an effective tool in reducing subcutaneous fat. Nevertheless, other studies with better methodological quality, investigating temperature and application time for subcutaneous fat reduction and presenting a standardization of assessment methods, should be proposed, given the scarcity in the literature. ●

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Use of laser technologies and intense pulsed light in the treatment of exogenous ochronosis: a literature review

Uso de tecnologias a laser e luz intensa pulsada no tratamento da ocronose exógena: uma revisão da literatura

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ABSTRACT

Exogenous ochronosis is a cutaneous hyperpigmentation condition caused by the accumulation of substances derived from phenol on the skin or mucous membranes without affecting other tissues. It occurs mainly due to the use of bleaching agents, most frequently hydroquinone. The lesions are difficult to treat, being resistant to several approaches. Sometimes it's necessary to use laser technologies or intense pulsed light to achieve some degree of improvement. The present work consists of a literature review of publications on these technologies in exogenous ochronosis from January 1990 to July 2020.

Keywords: Hyperpigmentation; Intense pulsed light therapy; Lasers; Ochronosis

RESUMO

A ocronose exógena é um quadro de hiperpigmentação cutânea por acúmulo de substâncias derivadas de fenol em pele ou mucosas, sem acometimento de outros tecidos. Ocorre, principalmente, por uso de clareadores, sendo mais frequente na hidroquinona como despigmentante. As lesões apresentam difícil tratamento, sendo resistentes a diversas abordagens. Por vezes, é necessário utilizar tecnologias com laser ou luz intensa pulsada para atingir algum grau de melhora. O presente trabalho realizou pesquisa bibliográfica na forma de revisão de literatura entre janeiro de 1990 e julho de 2020, organizando publicações acerca do uso destas tecnologias na ocronose exógena.

Palavras-chave: *Hiperpigmentação; Lasers; Ocronose; Terapia de luz pulsada intensa*

Review

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INTRODUCTION

Exogenous ochronosis (EO) is described as skin and mucous membranes hyperpigmentation caused by phenol-derived substances deposits, most commonly after the use of whitening creams containing hydroquinone, topical resorcinol, or intramuscular or oral antimalarials.[1,2,3,4] Contrary to endogenous ochronosis, which arises from homogentisic acid deposition in soft areas and internal tissues, exogenous ochronosis does not affect these sites. EO is considered uncommon:[5] it presents a moderate incidence in South Africa,[6] with isolated reports in Asia, Africa, and Latin America in patients with Hispanic ancestry and high skin phototypes.[7,8,9]

Rudolph Virchow named EO in 1865.[10,11] Findlay[6] related the disease to the use of bleaching cream with hydroquinone in 1975, and Beddard and Plumtre[12] associated it to with use of phenol to treat leg ulcers in 1912.[12]

A recent review of cases in the American literature showed a total of 39 reports of EO in the United States, from January 1983 to June 2020. Of these cases, 18 described the disease onset from the use of whitening creams, and, among these, 14 had hydroquinone in the composition. The concentrations ranged from 2% to 7.5%, with application time from two months to 30 years until the onset of the lesions.[2,3,8]

Clinically, EO presents as asymptomatic bluish-black or yellow-brown macules, or areas of hyperpigmentation in sun-exposed regions, such as the face, neck, back, extensor zones of the upper limbs, distal portions of the forearms, legs, and dorsum of hands or feet.[13] At the histological level, the clinical picture is similar to that of endogenous ochronosis, but with no pigment accumulation in joints, bones, urine, other secretions, or tissues.[14,15]

For some authors, the condition occurs due to resistance of melanocytes to the effect of whitening agents, with consequent pigment leakage in the papillary dermis and accumulation of this pigment in fibroblasts, resulting in phenols presence in elastotic fibers and their hyperchromia.[6] Other authors argue that hydroquinone is oxidized to quinone forming hydroxylated indoles similar to melanin precursors.[16] A third group believes that high hydroquinone concentrations stimulate melanocytes to produce more melanin.[17] However, the most widely accepted theory is that hyperpigmentation results from homogentisic acid oxidase enzyme inhibition by hydroquinone, causing local homogentisic acid accumulation. The homogentisic acid then polymerizes, forming an ocher pigment in the papillary dermis, as occurs in other tissues in cases of endogenous ochronosis due to a primary structural defect of this enzyme.[18]

Exogenous ochronosis lesions observed in dermoscopy were initially described in 2008[19,20] as sites of blue-gray or brown to black, amorphous globules, with follicular obliteration areas. It contrasts with melasma cases where dermoscopy demonstrates a pattern of reticular pigmentation, pseudonet accentuation, and brownish granules and globules, sparing the follicles.[21]

At the histological level, the lesions show collagen fibers with a yellow-brownish color in a "banana shape", degradation of these fibers, and formation of colloid milium amid an inflammatory infiltrate with plasma cells, histiocytes, and multinucleated giant cells in the development of the lesions.[16,22]

In 1979, Dogliotti and Leibowitz classified the clinical stages of exogenous ochronosis into stage I (lesions with erythema and some pigmentation); stage II (injuries presenting hyperpigmentation, hyperpigmented colloid milium, atrophy); and stage III (presence of papulonodular eruptive elements in a lesion with stage II features plus inflammatory characteristics in more recent wounds that are less pronounced in older injuries).[23] In 1986, Phillips *et al.* classified ochronosis as mild, moderate, and severe in a series of 395 cases in patients assessed by the Dermatology Service of a hospital in Johannesburg, South Africa, during one year. Only lesions with altered skin hyperpigmentation and hypertrophy were considered as mild; presence of hyperchromic papules was the standard for moderate degree; and lesions with hyperchromic caviar-like papules, coalescent in plaques, were deemed as severe.[8] In a third classification, in 1989, Hardwick *et al.* considered five grades of presentation: grade 1 comprised lesions with hyperchromic macules; grade 2, with macules and micropapules; grade 3 included injuries with darkened deposits and larger papules; grade 4, with colloid milium of 1 mm or more; and grade 5 encompassed lesions with keloid nodules and hyperchromic cysts.[24]

According to the European Society of Laser Dermatology (ESLD), the exogenous ochronosis treatment is challenging, with unpredictable results, often below expectations. The use of photoprotection becomes a relevant element in the initial approach by slowing the progression of the lesions and preventing the emergence of new hyperpigmented areas.[15] Some cases achieved a partial response with topical retinoic and glycolic acid in low concentrations and oral use of tetracycline in papular presentations or with sarcoidosis-like lesions.[25] In a recent review on the use of these technologies, the ESLD recommends such therapies associated with multiple laser technologies sessions, combining fractional ablative modalities such as CO_2 or Erbium 2940nm with Q-Switched 1064nm for better and faster results.[26,15]

The present study reviews publications containing a therapeutic approach to exogenous ochronosis conditions using laser technologies or intense pulsed light, demonstrating the described protocols and results obtained from 1990 to July 2020.

METHODS

Four databases were searched from June 15 to August 5, 2020: Embase, MEDLINE/Pubmed, LILACS, and Cochrane Library. The selected languages were English, Spanish, and Portuguese. In the first stage, the keywords used were chronosis, exogenous ochronosis, ocronose, and ocronosis. They generated a total of 1,377 results in the Embase platform, 978 in the MEDLINE/Pubmed, 32 in the LILACS, and 16 results in the Cochrane Library platform.

After this stage, the terms *treatment, therapy, tratamento, tratamiento, efficacy, upade laser and intense pulsed light* were included in the search. The results with crossings between these keywords obtained 79 results in the Embase platform, 19 in the MEDLINE/Pubmed, two in the LILACS, and one result in the Cochrane Library platform. Considering the objectives of the review, we selected studies that cited the use of laser technologies and intense pulsed light to treat exogenous ochronosis conditions published from January 1990 to July 2020.

Thus, the selection criteria were scientific articles on exogenous ochronosis regardless of its cause, approached with the use of laser or intense pulsed light at some point in the therapy. Studies on other pathologies, other ochronosis forms, or other therapies that did not address the use of lasers or intense pulsed light were excluded. The entire method of research and selection of articles containing the terms described was repeated by a secondary researcher, following the same methodology, generating the same data and articles.

RESULTS

Among several therapeutic modalities, lasers are considered excellent options to treat hyperpigmented lesions, promoting selective photothermolysis of pigments.[27] The most used lasers for this purpose are Q-Switched Ruby (QSRL), Q-Switched Alexandrite 755nm, Q-Switched Nd:YAG 1064nm, Q-Switched Nd:YAG 532nm, picosecond lasers,[28,29] and intense pulsed light with specific filters.[30] Technologies such as non-ablative Erbium-Glass 1550nm laser, ablative Erbium:YAG 2940nm,[31] CO_2 laser 10600nm,[32] and Thulium laser 1927nm[33] use water as a chromophore and can be alternatives both in pigments vaporization and in facilitating depigmenting agents penetration. In 2015, a review on therapeutic modalities in exogenous ochronosis cases was published. The main technologies used for this purpose were Q-Switched Ruby (694nm), Q-Switched Alexandrite (755nm), Q-Switched Nd:YAG (1064nm), CO_2 lasers, and intense pulsed light.[1] Only recently the picosecond laser was also reported as an option for treating hyperpigmented lesions (Table 1).[34,35,36]

In 1990, Diven *et al.* reported a case of exogenous ochronosis in the face of a 53-year-old African-American woman treated with dermabrasion and CO_2 laser. It resulted in the first description of the use of laser technologies to approach ochronosis. After using 2% hydroquinone cream for two to three months, the patient had progressive darkening of the area. Approach attempts with tretinoin 0.025% topical gel, cryotherapy, and peeling with ATA 50% did not achieve improvement. Therefore, we opted for dermabrasion of the whole face, followed by CO_2 3-6W application in defocused irradiation mode in the periocular regions, nose, and forehead, obtaining satisfactory results.[32]

Ten years later, Kramer *et al.* reported an exogenous ochronosis case treated with laser technology in bilateral zygomatic arch in a 50-year-old woman of Hispanic origin. At the time, the patient mentioned the use of 2% hydroquinone cream in the area for 30 years to treat melasma. Exogenous ochronosis was diagnosed histologically with yellow to brown pigment deposits and collagen fibers degeneration in the dermis, in addition to sparse lymphocytic infiltrate. The authors used a Q-Switched Ruby laser 694nm (7J/cm^2), 5mm spot size. The patient reported improvement in the condition after the session.[37]

Elizabeth Arnold Spenceri, in a publication on Pigmentation Disorders in 2003, summarized as the main exogenous ochronosis treatment the discontinuation of the triggering factor and application of Q-Switched laser in refractory cases.[38] In the following year, Bellew and Alster treated two exogenous ochronosis cases with Q-Switched Alexandrite laser 755nm. The first was a 47-year-old African-American woman with a history of hyperchromic lesions on the face for eight years, which worsened after using whitening creams in the area for several months, without specifying the period of time. The second was a 46-year-old man of indigenous origin presenting hyperchromic macules on the face for seven years, which worsened after using a bleaching cream containing hydroquinone for a year. In the first patient, the lesions were initially addressed with Q-Switched Alexandrite 755nm at 7 J/cm^2 fluency, 3 mm spots, every 15 days, with an increase in fluency up to 8 J/cm^2 (mean of 7.8 J/cm^2). The whitening was achieved after six sessions. In the second patient, the initial fluency was 6 J/cm^2 and the final fluency was 7 J/cm^2 (mean of 6.9 J/cm^2), totaling four sessions. There was a four-month interval for the resolution of post-inflammatory hyperpigmentation, considering the high sun exposure reported by the patient. The authors reported significant improvement of the lesions in both cases, with significant lightening.[39]

In 2006, Huerta Brogeras and Sanchés-Vieira presented the case of a 70-year-old woman with a history of melasma on the face and the use of 2% hydroquinone bleaching cream for six months, who had hyperpigmentation in the bilateral malar region and eyelids. Anatomopathological examination of the hyperpigmented area showed deposition of yellow-brown globules in the dermis, confirming the diagnosis of exogenous ochronosis. The authors used a Q-Switched Nd:YAG 1064nm laser for the treatment, with sessions still in progress at the date of publication of the report.[40]

Two years later, Charlín *et al.* published four cases of exogenous ochronosis triggered by topical use of hydroquinone for melasma. In one of the cases, the patient was a 56-year-old woman, with skin phototype V and melasma for 25 years, treated with 6% hydroquinone without specifying the duration of use. In this case, other topical medications were not reported, and the patient presented darkening of almost the entire face, except for the upper region of the lips and forehead. Therapeutic testing was performed with a Q-Switched Nd:YAG laser 1046nm, with no improvement. The authors do not describe the parameters used or the application protocol.[19]

Table 1: Studies involving the use of laser technologies or intense pulsed light in exogenous ochronosis

Year	Author	Case	Causal factors	Treatment	Protocol	Results
1990	Diven *et al.*	Woman, 53 years old, African American	Topical hydroquinone 2% during 2-3 months	Dermabrasion across the face and CO_2 laser (3-6W) in periocular, nasal, and forehead regions	One session each	Satisfactory whitening of areas
2000	Kramer *et al.*	Woman, 50 years old, Hispanic origin	Topical hydroquinone 2% during 30 years	Q-Switched Ruby Laser 694 nm (7 J/cm^2) 5mm spot-size	One application	Whitening of the hyperpigmented area
2004	Bellew and Alster	Woman, 47 years old, African American	Face whitening creams during several months (unspecified usage time)	Q-Switched Alexandrite laser 755nm initial fluency 7.0 J/cm2 and final fluency 8.0 J/cm^2 (mean of 7.8 J/cm^2)	6 sessions	Significant lightening of hyperchromias
		Man, 46 years old, Indigenous origin	One year using whitening cream containing hydroquinone	Q-Switched Alexandrite laser 755nm initial fluency 6.0 J/cm^2 and final fluency 7.0 J/cm^2 (mean of 6.9 J/cm^2)	4 sessions	
2006	Huerta Brogeras and Sánchez Vieira	Woman, 70 years old	Topical hydroquinone 2% during 6 months	Q-Switched Nd-YAG laser 1064 nm	Still in progress until the date of publication	Treatment not completed until the publication date
2008	Charlin *et al.*	Woman, 56 years old, skin phototype V	Topical hydroquinone 6% (unspecified usage time)	Q-Switched Nd-YAG laser 1046 nm (parameters used not described)	Not reported	No improvement in condition
2010	Gil *et al.*	Woman, 56 years old, skin phototype V	Whitening cream with 2% to 3% hydroquinone and 2% oxybenzone for several (unspecified usage time)	Intense Pulsed Light 645 nm, 6 milliseconds, 20-22 J/cm^2	6 sessions	Moderate whitening of lesions
				Depigmenting cream with 4% kojic acid and 0.2% salicylic acid	2 months of use	
2010	França *et al.*	Woman, 40 years old	Topical hydroquinone for 8 Years (non-detailed concentration)	Q-Switched Nd:YAG Laser 1064nm 4mm spot at 2.9-3.05J/cm2 fluency	4 sessions	No satisfactory response with Q-Switched
				Ultrapulsed CO_2 laser 5W	6 sessions	Nd:YAG laser 1064nm, partial response with ultrapulsed CO_2 laser, and resolution of lesions with IPL, microdermabrasion and peelings
				Intense Pulsed Light (IPL) 36J - 10 ms with microdermabrasion and peeling with 5% hydroquinone, 5% retinoic acid, and 14% salicylic acid	1 session	
				Intense Pulsed Light (IPL) 36J - 10 ms and peeling with 20% trichloroacetic acid (ATA)	3 sessions	
2013	Kanechorn-Na-Ayuthaya *et al.*	Woman, 67 years old, skin phototype V	Whitening creams during long periods without to specify (unspecified usage time)	Q-Switched Nd:YAG laser 1064nm at 1.9-2.2 J/cm2 fluency and fractional CO_2 laser	3 sessions + 1 session	Significant improvement with important whitening
		Woman, 58 years old, skin phototype III		Q-Switched Nd:YAG laser 1064nm at initial 1.9 J/cm^2 fluency and fractional CO_2 laser	3 sessions + 1 session + 1 session	
		Woman, 66 years old, skin phototype IV		Pulse-Dye Laser, Q-switched Nd:YAG laser 1064 nm, and fractional CO_2 laser	2 sessions + 1 session	

Year	*Author*	Case	Causal factors	Treatment	Protocol	Results
2013	Tan	Six women, from 37 to 69 years old	Whitening creams	Q-Switched Nd:YAG laser 1064nm at 1.2 J/cm² fluency in hyperpigmented areas of exogenous ochronosis and melasma Q-Switched Nd:YAG laser 1064nm at 4-6 J/cm² fluency in exogenous ochronosis areas	8 sessions + 16 sessions	Two showed relevant improvement, four showed mild improvement.
2014	Liu *et al.*	Woman, 50 years old, skin phototype IV	Whitening creams for long periods often with hydroquinone (unspecified usage time)	Q-Switched Nd-YAG laser 1064nm at 6-9 J/cm² fluency	6 sessions	No improvement
2014	Lee and Weiss	Woman, 48 years old	Whitening cream (unspecified usage time)	Intense Pulsed Light in 570 nm waves at 12J/cm² fluency and 15 milliseconds pulse	Total of sessions not reported	Whitening of the hyperpigmented area
2015	Ko *et al.*	Woman, 50 years old	Whitening cream with 4% hydroquinone	Q-Switched Nd-YAG laser 1064nm at 5.3 J/cm² fluency in left zygomatic region Q-Switched Alexandrite laser 755 nm at 8.5 J/cm² fluency in right zygomatic region	2 sessions	Therapeutic failure with worsening of the hyperchromic areas
2016	Carvalho *et al.*	Woman, 46 years old, skin phototype V	Topical hydroquinone 4% during 5 years	Fractional CO_2 laser with 120mm tip, 120mJ, and 150 points stitches per cm²	12 sessions	Significant improvement
2018	Méndez Baca *et al.*	Woman, 55 years old, skin phototype IV	Whitening cream containing hydroquinone for 5 years (the concentration was not specified)	Non-Ablative Fractional picosecond laser 1064nm and 532nm at initial fluency of 1.30 and 0.18 J/cm² with an increase of 0.20/0.02 J/cm² at each application up to a maximum fluency of 2.9/0.30 J/cm²	9 sessions	Improvement in skin color and appearance
2019	Lee *at al.*	Woman, 66 years old	Not described	CO_2 and Q-Switched Nd-YAG Lasers in the same session with no description of the parameters used	3 sessions	Lost to follow-up due to no response to therapy

Gil *et al.*, in 2010, reported a case of exogenous ochronosis in a 63-year-old woman, with skin phototype V, developed after using a whitening cream with 2% to 3% hydroquinone and 2% oxybenzone for several years, without specifying the duration of use. The diagnosis was confirmed histologically by the presence of yellow-brown material deposits in the papillary and medial dermis. She was treated with intense pulsed light 645nm, six milliseconds, 20-22J/cm², associated with depigmenting cream with 4% kojic acid and 0.2% salicylic acid. Moderate lightening of the lesions was achieved after two months of topical use and six sessions of intense pulsed light.[41]

Also in 2010, França *et al.* described an exogenous ochronosis case in a 40-year-old woman with hyperchromic macules and papules in the malar region and a history of topical hydroquinone use for eight years (the study did not describe the concentration). A histopathological examination revealed yellow-brown filaments in the papillary dermis, and investigation of deposits in other tissues was negative, ruling out an endogenous picture. In this report, the approach started with four sessions of Q-Switched Nd:YAG 1064nm laser, 4 mm spot, and 2.9-3.05 J/cm² fluency, without satisfactory response. Then, the authors opted for six sessions of ultrapulsed CO_2 laser, with one-month interval between each session, at 5W fluency, reaching some response. Finally, intense pulsed light (IPL) 36 J-10 ms was associated with the therapy, applied to the malar area, followed by microdermabrasion and chemical peeling with 5% hydroquinone, 5% retinoic acid, and 14% salicylic acid. The lesions resolved only after three more sessions, with intervals of 30 days of intense pulsed light (IPL) 36 J-10 ms and trichloroacetic acid (ATA) 20% peeling.[13]

Kanechorn-Na-Ayuthaya *et al.*, in 2013, assessed the use of the combination of Q-Switched Nd:YAG and fractional CO2 laser to treat exogenous ochronosis. They applied these modalities in three cases. The first was a 67-year-old woman, skin phototype V, with a history of face melasma for 28 years and use of whitening cream for long periods (the time has not been determined), presenting darkening of the malar and zygomatic areas. She received three sessions of Q-Switched Nd:YAG 1064nm at 1.9-2.2 J/cm^2 fluency and one session of fractional CO_2 laser, totaling four months of applications. The second patient was a 58-year-old woman, skin phototype III, with a history of recalcitrant melasma for 28 years and long-term use of hydroquinone bleaching cream, presenting hyperchromia in the temporal, malar, eyelid, and perilabial regions. For the treatment, she also received three applications of Q-Switched Nd:YAG 1064nm laser every 30 days, with an initial fluency of 1.9 J/cm^2 progressively increasing in multiple passes until the appearance of petechiae or purpura. After the third application, a CO_2 laser was performed only once at the end of four months of treatment. Three months later, pulse-dye laser was applied for telangiectasias in the areas. The third case described was a 66-year-old woman, skin phototype IV, with a history of melasma for 20 years. She used whitening creams and complaint of bilateral darkening of the malar region. In this case, a Q-Switched Nd:YAG laser 1064nm was used in two sessions with a 30-day interval, resulting in purpura after each application. Fractioned CO_2 laser was performed after the second Q-Switched session. All the cases showed significant skin improvement, with lightening of hyperchromic lesions and skin rejuvenation with enhancement of telangiectasias.[26]

In the same year, Tan described six cases of exogenous ochronosis successfully treated after sessions of Q-Switched Nd:YAG 1064nm. Six women aged between 37 and 69 years, with a history of melasma and the use of whitening creams, two of them containing hydroquinone, presented hyperchromia in the application areas. The diagnosis was confirmed with histopathological examination, and the conditions were classified according to the ochronosis staging method described by Dogliotti and Leibowitz: stage I, lesions with erythema and some pigmentation; stage II, lesions with hyperpigmentation, hyperpigmented colloid milium, and atrophy; and stage III, papulonodular eruptive elements in a lesion with stage II characteristics.[23] Four of the patients had stage I EO; one, stage II; and one, stage III. The cases were treated with a Q-Switched Nd:YAG 1064nm laser at 1.2 J/cm^2 fluency, 8 mm spot size, in four passes in the hyperpigmented areas, which included lesions of exogenous ochronosis and melasma. Subsequently, only areas considered as having exogenous ochronosis received new applications at 4-6 J/cm^2 fluency, 4 mm spot size, with two or three applications in stacks in each macula until the appearance of erythema or petechiae. Stage II and III patients showed significant improvement in areas of exogenous ochronosis after eight and 16 sessions, respectively. Nevertheless, stage I patients had no resolution of the lesions, but slight improvement in color after treatment.[42]

In 2014, Liu *et al.* reported an exogenous ochronosis case in a 50-year-old woman, skin phototype IV, with a history of hyperchromic macules in malar areas. She was treated with whitening creams for long periods, often with hydroquinone, in different concentrations, which had been darkening for one year of the description, even with adequate photoprotection. The dermoscopy showed areas with sparse blue-gray dots and globules, and homogeneous follicular ostia obliteration. Histological examination revealed dilated and basophilic collagen fibers, fragmented and with ocher pigmentation. Exogenous ochronosis was classified as Dogliotti stage II, and the patient received six sessions of Q-Switched Nd:YAG 1064nm laser with 6-9 J/cm^2 fluency, with no improvement.[43]

Also in 2014, Lee and Weiss presented an exogenous ochronosis case in a 48-year-old woman, after years of using a bleaching cream for facial dyschromia. Intense pulsed light in waves of 570nm was used for the treatment, at 12 J/cm^2 fluency, 15 milliseconds pulse, with sessions every six weeks, without description of the total number of sessions. The authors observed whitening of the maculae since the first application.[44] The following year, Ko and Wang reported exogenous ochronosis in a 50-year-old woman after using a whitening cream containing 4% hydroquinone. Therapeutic response test was performed using Q-Switched Nd:YAG laser 1064nm at 5.3 J/cm^2 fluency, 3 mm spot size, in the left zygomatic region, and Q-Switched Alexandrite laser 755nm at 8.5 J/cm^2 fluency, 3 mm spot size, in the right zygomatic region. After two applications with a 5-week interval, both areas showed darkening, indicating therapeutic failure.[45]

In 2016, Carvalho *et al.* described ochronosis lesions like hyperchromic papules and macules on the forehead, nasal dorsum, and malar regions of a 46-year-old woman, skin phototype V, using topical 4% hydroquinone for five years to treat melasma on the face. After ruling out endogenous ochronosis due to the absence of pigmentary deposits in other tissues, joint pain, and urinary alterations, the application of fractional CO_2 laser was started on the entire face, using a 120 mm tip, 120 mJ energy, and 150 points per cm^2 density, in monthly sessions for one year, totaling 12 applications and reaching significant improvement of the condition.[46]

Méndez Baca *et al.*, in 2018, depicted the case of a 55-year-old woman, skin phototype IV, with exogenous ochronosis lesions in the bilateral malar region, reporting the appearance of blue-gray macules in the area after applying bleaching cream containing hydroquinone for five years to treat hyperpigmented lesions. The condition had been previously approached with intense pulsed light associated with depigmenting agents with 4% hydroquinone, kojic acid, phytic acid, ferulic acid, citric acid, as well as topical pimecrolimus and sunscreens, without improvement. It was then decided to use a fractionated nonablative picosecond laser 1064nm and 532nm, at an initial 1.30-0.18 J/cm^2 fluency, with an increase of 0.20/0.02 J/cm^2 each session, up to a maximum 2.9/0.30 J/cm^2 fluency. The sessions

occurred every two months, with applications until obtaining uniform facial erythema. After nine sessions, there was an improvement in skin color and texture.[47]

In 2019, Lee *et al.* reported an exogenous ochronosis case in a 66-year-old woman with hyperpigmented perilabial and scleral lesions for one year. Skin lesions were treated with CO_2 laser and Q-Switched Nd:YAG in the same session, without description of the parameters used. After three applications, the patient was lost to follow-up due to lack of response.[48]

CONCLUSION

Despite the extensive use of hydroquinone bleaching agents in Dermatology, reports of exogenous ochronosis are infrequent. The difficulty in treating hyperchromic lesions reinforces the need for multiple therapeutic approaches to reach satisfactory results. In this context, the use of lasers or light therapies can be a promising alternative. However, there are several types of technologies used without a specific protocol.

The vast majority of studies on the topic refer to isolated cases of the use of lasers or different light technologies, without respecting standardization both in the clinical evaluation of the response and in the selected modalities. The need for population studies considering a larger number of cases, assessment standardization, exogenous ochronosis lesions and treatment classification, becomes, therefore, crucial for further clarification. ●

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Alopecia Areata after COVID-19: causal or casual relationship?

Alopecia Areata pós-Covid-19: relação causal ou casual?

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ABSTRACT

A Covid-19, doença causadora de síndrome gripal e insuficiência respiratória aguda, vem demonstrando provocar danos a diversos outros órgãos e sistemas. Várias manifestações dermatológicas já foram descritas. Relatamos um quadro de alopecia areata (AA) desencadeada possivelmente pela Covid-19 em paciente que, apesar de ter seu RT-PCR para SARS-CoV-2 negativo, apresentou IgM reagente e sintomatologia clássica relacionada à doença. Acreditamos que a Covid-19 possa ter desencadeado resposta imunológica autoimune, com a consequente produção de interferons, que levou ao quadro de AA.

Palavras-chave: Alopecia em áreas; Autoimunidade; Coronavirus

RESUMO

COVID-19, a disease that causes flu-like syndrome and acute respiratory failure, has been shown to cause damage to several other organs and systems. Several dermatological manifestations have been regular. We report a case of Alopecia Areata possibly triggered by COVID-19 in a patient who, despite his negative SARS-COV 2 RT- PCR, presented IgM reactor, in addition to classic symptoms related to the disease. We believe that a COVID-19 can trigger the autoimmune immune response with the consequent production of interferons that led to Alopecia areata.

Keywords: *Alopecia areata; Autoimmunity; Coronavirus*

Case report

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INTRODUCTION

Since its appearance, COVID-19, a disease that causes acute respiratory failure (SARS-CoV-2),[1] has been shown to damage several organs such as the nervous, cardiovascular, renal, and gastrointestinal systems. It also favors the onset of secondary infections.[2]

The literature already described several manifestations affecting the skin, such as skin rash, acro-ischemia, erythematous maculopapular rashes, livedo, cyanosis, purpura, petechiae, blisters, gangrene, urticaria, varicella-like exanthem, pernio-like lesions (COVID toes), and red half-moon nail sign.[3-8] We describe a picture of alopecia areata, probably triggered by COVID-19.

CASE REPORT

A 31-year-old patient, physician, presented sudden onset of anosmia with a three-day evolution. The patient showed a drop in blood-oxygen saturation to 95% at rest and dyspnea on exertion in the following days. The nasopharyngeal swab was collected to perform RT-PCR for SARS-CoV-2 on Day 6 of symptoms, with undetected viral load. However, over the next three days, he developed myalgia, a fever of 38oC, night chills, and mild dyspnea. In the following week, the patient presented only anosmia, which lasted approximately 15 days. On the 16th day of symptoms, he collected serology for COVID, which was positive for IgM (2.5) and IgG (1.4).

Twenty-nine days after the onset of symptoms, the patient noticed a sudden loss of beard hair, forming circular areas of alopecia. These areas increased in size and converged into two large bilateral hairless regions on the chin. The patient used topical betamethasone with no improvement. The alopecia region is stable for a month but with no hair regrowth.

Alopecia areata (AA) is a chronic condition of hair follicles and nails. Its etiology is unknown, probably multifactorial. However, it has an evident association with other autoimmune diseases and may also be linked to genetic factors, cellular immunity, or even psychological trauma. The condition determines hair loss in a rounded or oval pattern with no evident inflammatory process in the skin due to follicular damage in the anagen phase, without destructing or atrophying the follicles, which is why it can be reversible.[9]

Studies show that patients with AA have a mean increase in interferon-gamma (IFN-γ) serum levels.10 The AA physiopathogenesis involves the body's self-reactivity. The possibility of a significant rise in interferons (INF) production after inflammatory processes, stimulating the action of cells of the immune system, explains its relationship with viral infections.[11]

The increase in IFN-γ levels is associated with the severity of COVID-19.[12] We can infer that a rise in IFN-γ rates occurred due to the disease inflammatory process, which may be related to the AA's triggering factor (Figure 1 and 2).

Since the AA appeared after the COVID-19 symptomatic period, this relationship may be causal or just casual. Nevertheless, as this is a new disease, from which we obtain further information and scientific knowledge each day, we believe that the autoimmune immune response triggered by the disease led to the onset of AA. ●

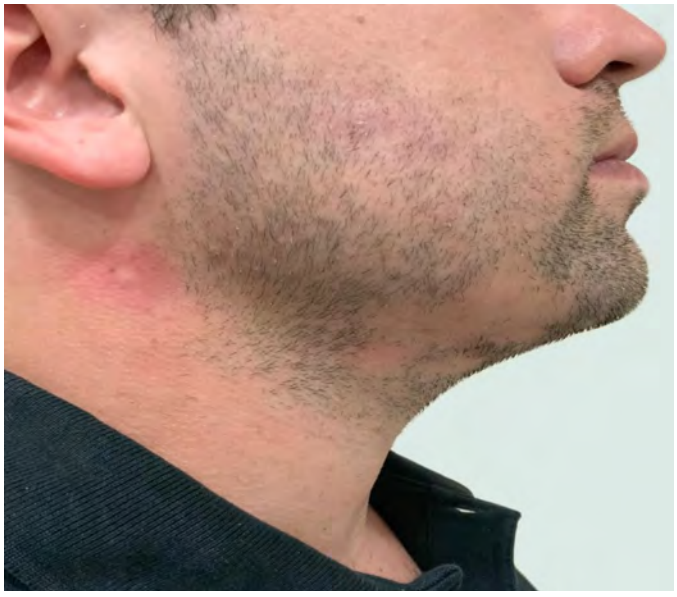

Figure 1: Alopecic area in right side beard

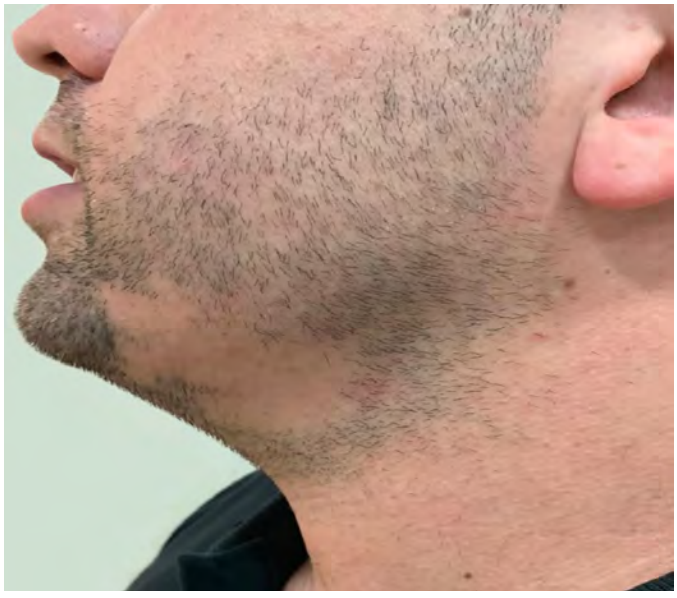

Figure 2: Alopecic area in left side beard

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Basal cell carcinoma of the vulva: a case report of cutaneous neoplasia in a special area

Carcinoma basocelular na vulva: um relato de caso de neoplasia cutânea em área especial

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ABSTRACT

Basal cell carcinoma (BCC) is the most common skin cancer[1]. Among the risk factors for its development are exposure to ionizing and non-ionizing radiation, some chemicals, and previous scars.[2] However, the most important factor is exposure to ultraviolet radiation, which explains the higher incidence of this neoplasm in photo-exposed areas.[1] BCC in unexposed areas is uncommon. The purpose of this report is to describe a case of recurrent BCC in the vulva, to demonstrate the importance of dermatological examination in unusual areas, and to report the application of Mohs micrographic surgery.

Keywords: Basal cell carcinoma;Vulvar diseases;Vulvar neoplasms

RESUMO

O carcinoma basocelular (CBC) é o câncer de pele mais comum.[1] Entre os fatores de risco para seu desenvolvimento estão a exposição a radiações ionizantes e não ionizantes, alguns produtos químicos e cicatrizes prévias.[2] Porém, o fator mais importante é a exposição à radiação ultravioleta, o que explica a maior incidência dessa neoplasia em áreas fotoexpostas. O CBC em áreas não expostas é incomum. O objetivo deste relato é descrever um caso de CBC recorrente na vulva, demonstrar a importância do exame dermatológico em áreas incomuns e relatar a aplicação da cirurgia micrográfica de Mohs.

Palavras-chave: *Carcinoma basocelular; Doenças da vulva; Neoplasias vulvares*

Case report

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INTRODUCTION

Basal cell carcinoma (BCC) is the most common skin cancer, representing approximately 70% of cases.[1] Among the risk factors for developing this type of tumor is exposure to ionizing and non-ionizing radiation, some chemical substances, such as tar and arsenic derivatives, and previous scars.[2] However, the most important factor in BCC pathogenesis is exposure to ultraviolet radiation. This explains this neoplasm's higher incidence in sun-exposed areas, affecting mainly fair-skinned and light-eyed people.[1]

BCC in non-photo exposed areas such as underarms, groin, buttocks, perianal, genital, and pubic regions is uncommon. BCCs that arise in the perianal area or on the vulva, specifically on the non-mucous surface of the labia majora, represent less than 2% of this type of epithelial tumor.[3]

This study aims to describe a case of recurrent BCC in the vulva, demonstrating the importance of surveillance of dermatological examination in unusual areas and reporting the application of Mohs micrographic surgery to spare and preserve special anatomical sites.

CASE REPORT

The 70-year-old white female patient, noticed. a mildly painful and slightly itchy lump inside her vulva, on the left (Figure 1). During a gynecological consultation in 2015, the patient's physician observed the lesion and referred her to the dermatologist.

The dermatologist performed the analysis and raised the hypothesis of basal cell carcinoma. The lesion's biopsy confirmed the hypothesis, showing a superficial basal cell carcinoma (Figure 2). However, as this is a rare involvement site for this type of skin cancer, the patient was referred to another Dermatology service in the state of São Paulo to get a second opinion from a dermatologist specialized in Cutaneous Oncology on the appropriate treatment for the lesion. In this service, the patient started treatment with imiquimod five times a week for six weeks and, after this cycle, the lesion disappeared.

However, a year later, the lesion reappeared in the same site, and a new biopsy was performed. The pathological examination confirmed that it was a recurrence of the previous basal cell carcinoma. The dermatologists who accompanied the patient, after discussing the case, suggested that the lesion was removed using the Mohs micrographic technique due to its greater precision and safety.

In 2016, the patient underwent surgical excision of the lesion, performed with free lateral and deep margins (Figure 3). Since then, the patient has undergone annual visits to the dermatologist. There has been no recurrence of the lesion to date.

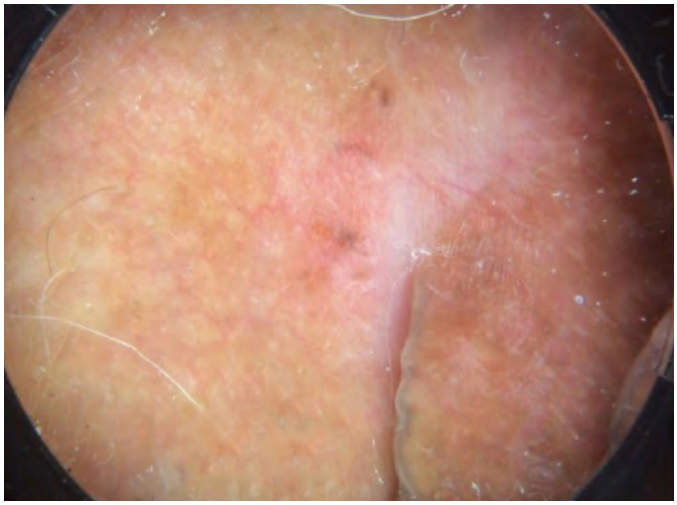

Figure 2: Dermoscopy of the primary skin lesion

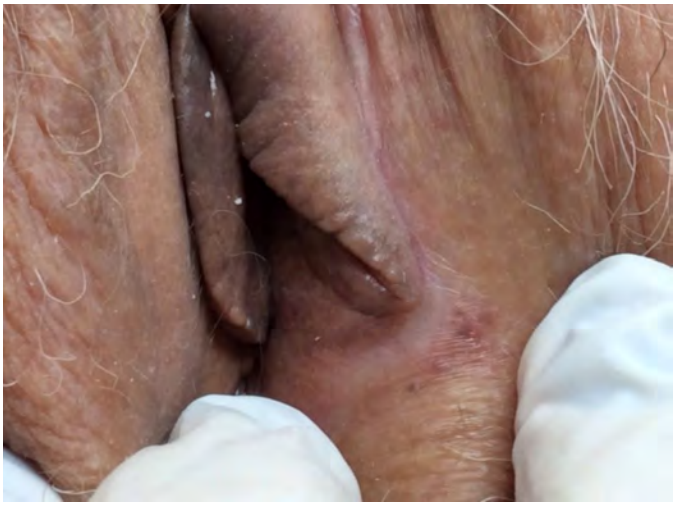

Figure 1: Primary skin lesion

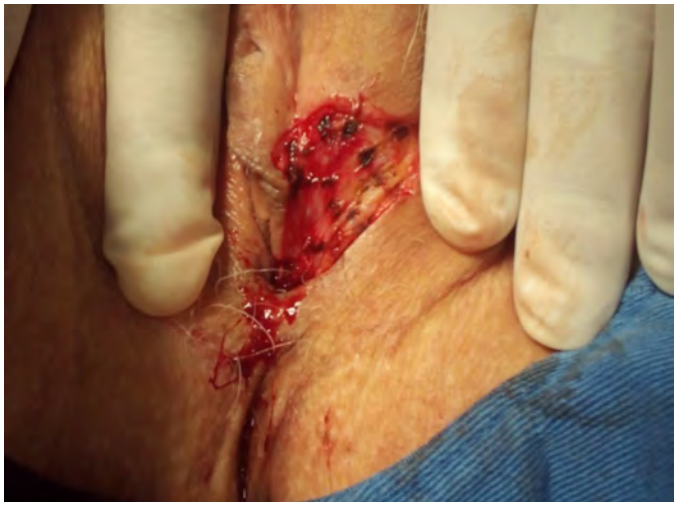

Figure 3: Surgical wound after tumor debulking and margin resection

DISCUSSION

BCC arises from follicular stem cells. Thus, its development in hairless areas is uncommon.[4] The site of greatest involvement is the cephalic region (90%), mainly in the orbitopalpebral and nasal area, followed by the trunk and limbs.[2] The most important factor in the pathogenesis of BCC is exposure to ultraviolet light. However, up to a third of cases occur in covered areas, such as armpits, groin, buttocks, perianal, genital, and pubic region.[3,5,6]

To date, the literature has described less than 300 cases of vulvar BCC. Tumors in this location represent approximately 2% of all BCCs and less than 3% of vulvar carcinomas.[4] The exact cause of BCC development in non-sun exposed areas is still uncertain, but the relationship with increasing age has been reported in two large case series, in which the mean age of vulvar BCC development was between 70 and 73 years.[7,8]

Vulvar BCC shares the same risk factors as the sun-exposed BCCs. What sets them apart is that exposure to ultraviolet (UV) radiation does not play an important factor in the pathogenesis of vulvar BCC. Nevertheless, some authors suggest that exposure to UV radiation causes systemic immunosuppression, and it could be related to the BCC appearance in areas not exposed to the sun.[9] Previous radiation is also one of the factors that predispose to vulvar BCC. Usually, the onset of lesions occurs years after exposure to irradiation.[10,11] Another risk factor is genetic defects that can predispose to the development of BCC, such as the PTCH mutation, which leads to basal cell nevus syndrome and substantially increases the susceptibility to this neoplasm.[12]

The clinical manifestations of vulvar BCCs are nonspecific and don't have classic BCC features. Lesions can appear as papules, nodules, or lesions that can be exophytic, pediculated, infiltrative, pigmented, and ulcerated in more advanced cases, or even in the combined form of these items.[13] The signs and symptoms are not characteristic. The most reported ones are irritation, pain, and local itching. The nonspecificity of the symptoms often causes the lesions to be treated as inflammatory and infectious dermatoses, leading to late diagnosis and, consequently, to an increase in the size of the neoplasm and local invasion.[8]

The vulvar BCCs are more aggressive when compared to the sun-exposed BCCs, and they are associated with deep local infiltration and occasional perineural extension. This type of neoplasm has a greater recurrence, as well as higher levels of local and distant metastases. It varies according to the histological pattern, and morphea-like, metatypic, adenocystic, and infiltrative tumors tend to be more recurrent and aggressive. [14, 15, 16]

Surgical excision is the best form of treatment for vulvar BCC. Surgical margins should be wide, as a retrospective study showed that up to 25% of excisional biopsy margins were compromised. It is mainly due to the difficult demarcation, as this site is naturally erythematous, and the edges of the lesion are easily confused with healthy skin.[8] The involvement of the margins results in a higher recurrence rate, which may reach 10% to 20% of cases.[14]

In large, histologically aggressive BCCs and in those with recurrence and poorly delimited borders, such as the tumor in this case report, Mohs micrographic surgery is the treatment of choice. It provides histological control of 100% of the margins, preserving normal skin, in addition to reducing changes in anatomical structures, making the reconstruction safer and with better aesthetic and functional results. In cases where the surgical approach is contraindicated or where there is edge involvement, radiotherapy is a therapeutic option, but it can lead to complications in the irradiated site.[3,17,18]

Early diagnosis is crucial to ensure less invasive surgery. However, vulvar BCC often has a delayed diagnosis because it occurs in a location that is less monitored during the physical examination.[8] We concluded that there must be awareness that BCCs can appear in non-photo exposed areas and, many times, they can mimic other dermatoses. Thus, dermatologists, general practitioners, and gynecologists should perform a complete skin examination, especially in patients with a history of skin cancer, and biopsy is advisable in any suspicious skin lesion in these regions. ●

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Closure of a large nasal dorsum defect using a bilateral crescent advancement flap from the malar region to the nose

Fechamento de um grande defeito do dorso nasal por retalho de avanço crescente bilateral da região malar ao nariz

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ABSTRACT

The closure of large defects on the nasal dorsum is a challenge for dermatologic surgeons. The alternatives to repair the defect are a skin graft and some forms of skin flaps. One particular defect closure technique is the crescentic advancement flap, which uses crescent incisions at the nasolabial fold to accommodate the excess tissue. This flap is best used if the defect is in the lateral nose, alar, and nasolabial fold. We report a large defect of the nasal dorsum in a 65-year-old woman that was successfully reconstructed using bilateral cheek-to-nose crescentic advancement flap. The patient showed excellent cosmetic and outcome.

Keywords: Dermatology; Nasal Bone; Surgical Flaps

RESUMO

O fechamento de grandes defeitos no dorso nasal é um desafio para o dermatocirurgião. As alternativas para reparar o defeito são enxertos e algumas formas de retalho de pele retalhos de pele, como o retalho de avanço crescente, que utiliza incisões em crescente no sulco nasolabial para acomodar o excesso de tecido. Esse retalho apresenta melhores resultados em defeito nas regiões lateral do nariz, alar e dobra nasolabial. Relatamos um grande defeito do dorso nasal em uma mulher de 65 anos, reconstruído com sucesso com o retalho de avanço crescente bilateral da bochecha ao nariz. A paciente apresentou excelente resultado cosmético.

Palavras-chave: *Dermatologia; Osso nasal; Retalhos Cirúrgicos*

Case report

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INTRODUCTION

The crescentic perialar flap was firstly introduced in 1955 to repair defects of the upper lip. The principle of this flap is to remove redundant tissue in a crescentic form to allow lateral movement that is then followed by the advancement flap to cover the defect. It is a variation of a unilateral advancement flap.[1] The benefit of this flap is facilitating defect closure with minimal tissue distortion and, when properly executed, facial symmetry, superior cosmetic results, and a minimal scar can be achieved.[2] The use of a crescentic flap is useful for defects on the lip, nasal ala, nasolabial fold, nasal dorsum, sidewall, nasofacial fold, and along the lateral forehead.[2,3] Although the skin contour of the nasal sidewall and cheek are similar, the nasofacial fold that unites these two cosmetic subunits needs to be maintained to achieve optimal aesthetic consideration.

We report a case of a large BCC defect on the dorsal nasal that extended to the sidewall.

CASE REPORT

A 65-year-old woman presented with a 2.5 cm defect on the nasal dorsum, which extended to the lateral sidewalls resulting from BCC removal. Histopathological examination confirmed that all margins had been free of tumor. The design of the flap was done before local anesthesia with bilevel anesthesia based on the technique by Prof. Lawrence Field.[4] After complete local anesthesia was achieved, an incision was conducted in a juxtaposed triangle-like incision according to the previously drawn marks (Figure 1). Marking was critical to avoid distorting the anatomical landmarks resulting from anesthesia infiltration. Removal of the skin superior to the defect was required to avoid dog-ear formation.

The incision was done bilaterally from the inferomedial sides of the triangle base with a length three times the distance between the medial edge to the midline and extended inferiorly along the alar crease and sulcus to the nasolabial fold (Figure 2).[5] The length of the incision was three times the length from the medial edge to the midline.[6] Subcutaneous blunt dissection at the superficial muscular aponeurotic level was done on the lateral cheek to facilitate approximation and reduce stress on the medial edge. We performed a trial advancement flap to estimate the amount of tissue needed to be incised to make the crescentic incision (Figure 3).[2] A crescentic excision was then carefully done to ensure symmetry of the nasolabial fold. Excessive excision may cause elevation of alar, whereas too little excision may cause depression. Both flaps were elevated above the nose and medially advanced from cheeks to the nose, forming a bilateral cheek-to-nose crescentic advancement flap.[3] The primary defect was suture with the largest diameter suture.[6] The defect was sutured on both sides along the midline, alar crease, and nasolabial fold (Figure 4). Each flap was sutured to the periosteum at the nasofascial sulcus which functioned to maintain the contour of the alar crease sulcus and nasal sidewall.[7] Hemostasis was maintained throughout the procedure to aid intraoperative visualization and avoid post-operative bleeding. Wound edges were closed with a 5.0 monofilament suture.

The patient showed excellent cosmetic and functional recovery after three months (Figure 5).

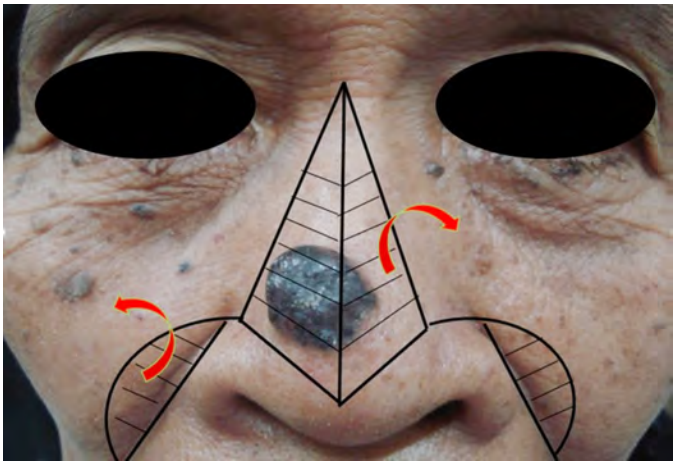

FIGURE 1: Incision marking

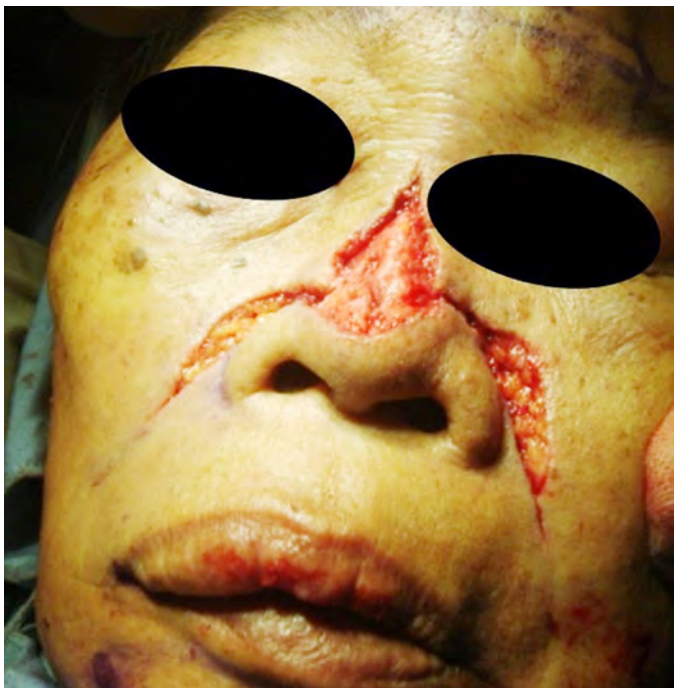

FIGURE 2: Diamond-shaped incision and incision along the nasolabial fold. A crescentic incision was made on both sides of the perialar region

DISCUSSION

Closure of defects on the nasal dorsum or sidewall with a size of more than 2 cm often has only limited options; some

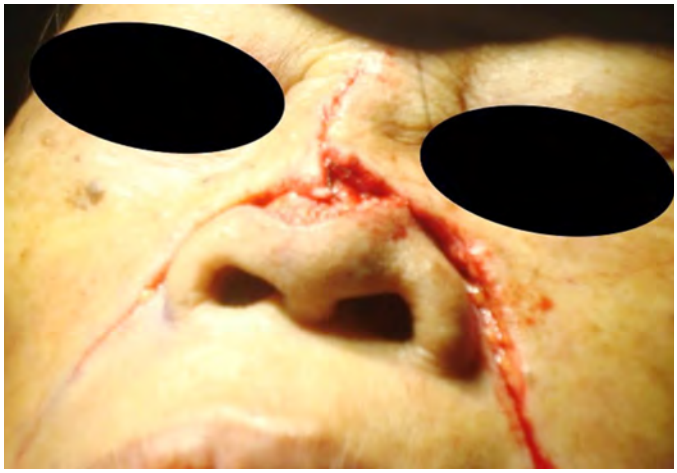

Figure 3: Trial advancement flap to ensure accurate and aesthetically pleasing defect closure

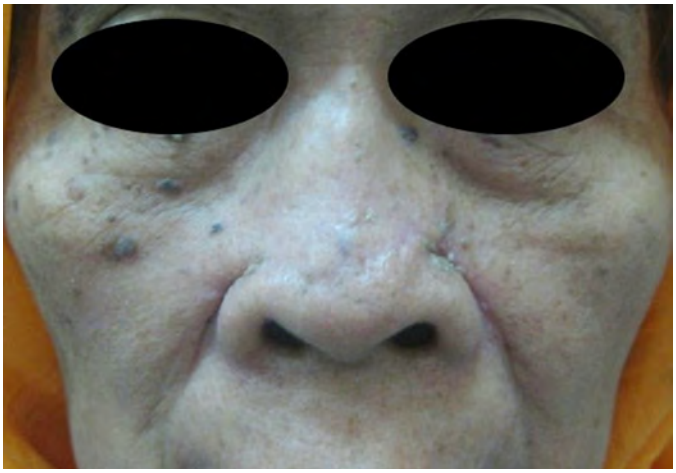

Figure 5: Result after 3 months, excellent functional and cosmetic result

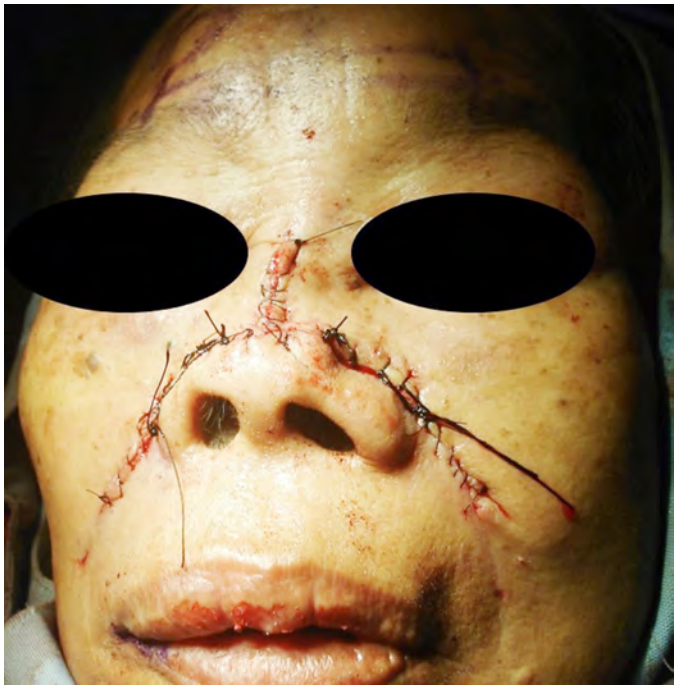

Figure 4: Post-operative result

possible approaches include dorsal nasal rotation flap, birhombic flap, Rintala flap, Peng flap, a two-staged paramedian forehead flap, and full-thickness skin graft (FTSG). However, the cosmetic result of grafts will not be optimal if they are not placed within the same cosmetic subunits. A paramedian forehead flap required at least 2 stages and, given the different thicknesses of skin on the forehead and nasal dorsum or sidewall, has a potential risk of tissue mismatch.[7]

A bilateral crescentic advancement flap should be considered for large defects of the nose. The success of this flap depends on the laxity of the surrounding skin because tension on the wound edge may cause ischemia and necrosis. The crescentic flap is a modification of Burrow's advancement flap,[6] where a crescent-shaped excision, instead of a triangle, is used to correct any tissue redundancy that occurred. The sutures were then tacked on the alar crease or nasolabial line.[5] The ideal defect locations for this technique are the nasofacial sulcus and lateral alar crease. Putting sutures in these natural anatomic lines allows optimal concealment of the scar. Defects that cross the nasolabial fold can cause aesthetic deformity of the natural nasolabial boundary; patients with prominent nasolabial fold can even develop bridging after the closure of the defect. Furthermore, defects located inferior to the nasolabial fold can potentially cause lip retraction and asymmetry of the nasolabial fold. Thus, both sides of the flap were sutured to periosteum at the nasofascial sulcus to maintain the contour of the alar crease sulcus and nasofacial sulcus.[7] In addition, the medial suture was made directly on the nasal midline to camouflage the suture.

The bilateral crescentic advancement flap is a good option to repair larger defect of nasal dorsum with a large height-to-width ratio or defects with curved borders.[1] Thus, this technique is suitable for defects above the nasal supratip with a relative midline location, nasal dorsum, and nasal sidewall. This single-stage bilateral cheek-to-nose crescentic advancement flap was advantageous in avoiding the morbidity often associated with multistage repairs and preserve facial symmetry.[8] The use of bilateral cheek-to-nose crescentic advancement flap has been reported in a case of a large symmetric defect on the nasal dor-

sum.[5] This technique was also successfully used in an asymmetric lesion above the nasal supratip by placing incision lines on the junction between the nasal supratip and alar crease cosmetic subunits.[9]

In this case, we successfully conducted reconstructed a large defect on the nasal dorsum with satisfying cosmetic, functional results, and without any significant complications. Factors that played a central role in the successful reconstruction of this case were dog-ear excision at the superior of the defect, properly executed crescentic incision on both nasolabial folds, key suture to the periosteum in the nasofascial sulcus, and placing the sutures on the nasal midline. ●

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Pigmented columns as a dermoscopy feature in a seborrheic keratosis associated with a squamous cell carcinoma

Colunas pigmentadas como um achado dermatoscópico de queratose seborreica associada a carcinoma espinocelular

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.2021130049

ABSTRACT

Introduction: Seborrheic keratosis (SK) has the typical pigmented dermoscopy features such as fissures and ridges, fat fingers, and cerebriform patterns. Here we describe a case where pigmented columns (PC) were visualized on SK's dermoscopy associated with a squamous cell carcinoma (SCC). Case presentation: We report a case of a lesion whose dermoscopy showed PC. Histopathological report showed well-differentiated SCC and associated SK. Discussion: The PC was visualized in an area of dendritic melanocytes in the epidermis, correlating with the pigmented SK component of the lesion. To our knowledge, this is the first time PC is described in SK´s dermoscopy.

Keywords: Carcinoma squamous cell; Dermoscopy; Skin neoplasms.

RESUMO

Introdução: As queratoses seborreicas (QS) têm achados dermatoscópicos pigmentados clássicos, como: fissuras e sulcos, "fat-fingers" e padrão cerebriforme. Relatamos um caso onde colunas pigmentadas (CP) foram visualizadas na dermatoscopia de uma QS associada a um carcinoma epidermoide (CEC). Relato do caso: Relatamos o caso de uma lesão onde a dermatoscopia demonstrou CP. O anatomopatológico foi compatível com CEC associado a QS. Discussão: As CP foram visualizadas em área de melanócitos dendríticos na epiderme, correlacionando-se ao componente de QS da lesão. Ao que se sabe, esta é a primeira vez que CP são descritas como achado dermatoscópico de QS.

Palavras-chave: *Carcinoma de células escamosas; Dermoscopia; Neoplasias cutâneas*

Case Report

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INTRODUCTION

Seborrheic keratosis (SK) has the typical pigmented dermoscopy features such as fissures and ridges, fat fingers, and cerebriform patterns. Here we describe a case where pigmented columns (PC), not characterized as any of the pigmented structures mentioned before, were visualized at dermoscopy. The histopathological report revealed a squamous cell carcinoma (SCC) with SK associated.

CASE PRESENTATION

A 66-year-old man presented to the clinic reporting recent growth and bleeding of a lesion he has had for a few years. The patient had no previous history of skin cancer. Physical examination revealed a 1cm-brownish plaque with hemorrhagic crust on the preauricular area. Dermoscopy showed milium cyst-like structures in the posterior portion of the lesion, a hemorrhagic crust inferiorly and, superiorly, a blue-white veil followed by PC at the top of the lesion. (Figure 1).

We performed the excisional biopsy. The histopathological report showed well-differentiated SCC with clear surgical margins and associated SK (Figure 2). The patient has been followed for three years with no signs of lesion recurrence to date.

DISCUSSION

Regarding SCC dermoscopy structures, one can find polymorphous vessels. If ulceration and blood crusts are present, these appear as reddish to brownish or black blotches on the surface of the tumor. Pigmented invasive SCC is rare, and, on dermoscopy, it is characterized by a diffuse, homogeneous blue pigmentation with irregularly distributed blue-gray granular structures.[1]

In this case, the PC at the lesion's periphery intrigued us. Fissures and ridges, fat fingers, and cerebriform patterns are the well-known pigmented dermoscopy structures in SK. In histopathology, they correlate to wedge-shaped clefts of the sur-

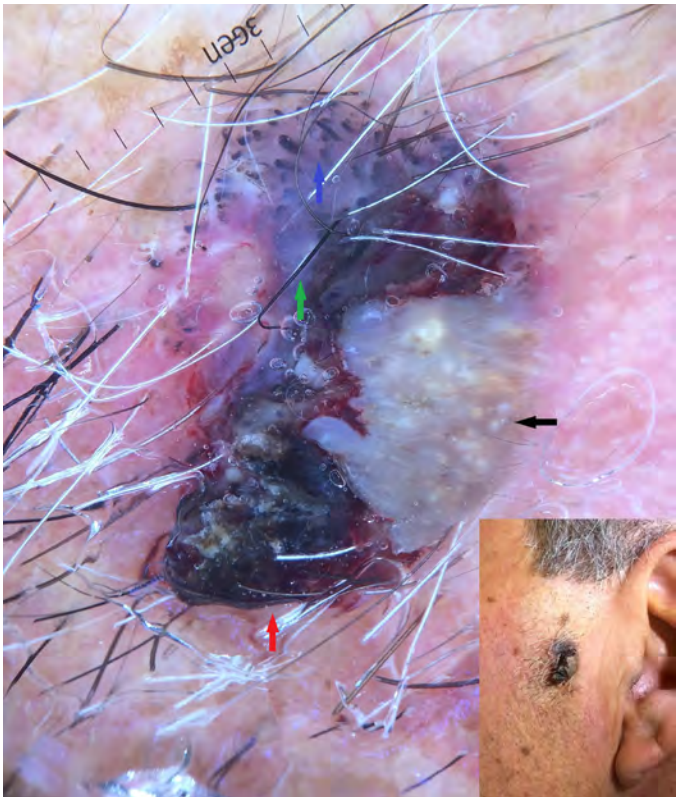

Figure 1: Polarized light dermoscopy image. Dermoscopy shows: milium cyst-like structures (black arrow); hemorrhagic crust (red arrow); blue-gray veil (green arrow); and pigmented columns (blue arrow). Insert: clinical image.

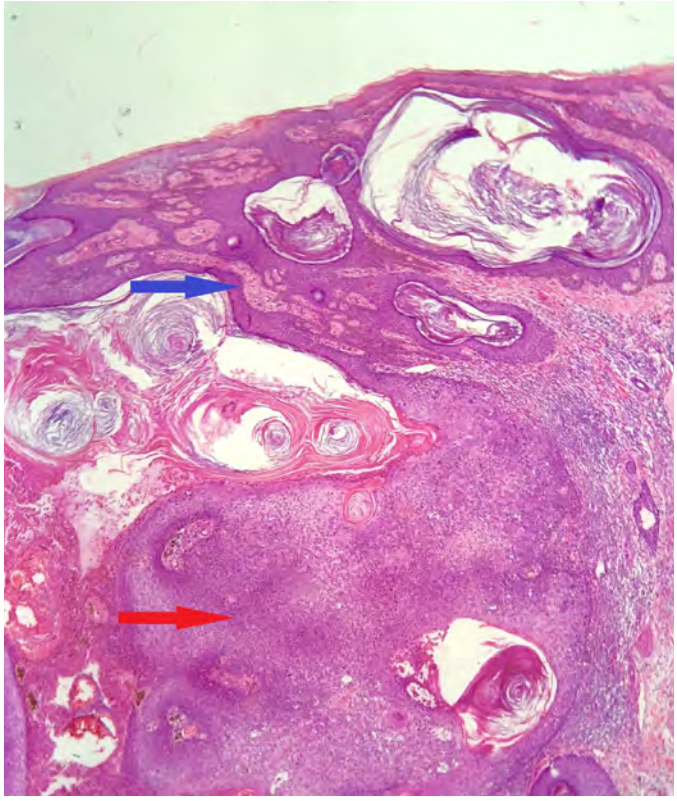

Figure 2: Histopathology shows, at the top of the image, proliferation of basaloid cells with pigmented keratinocytes in the basal layer and horn pseudocysts formation, corresponding to the SK component of the lesion (blue arrow). At the bottom of the image, proliferation of atypical keratinocytes with the presence of mitotic figures, corresponding to the SCC component of the lesion (red arrow). Haematoxylin Eosin (HE) magnification 4x.

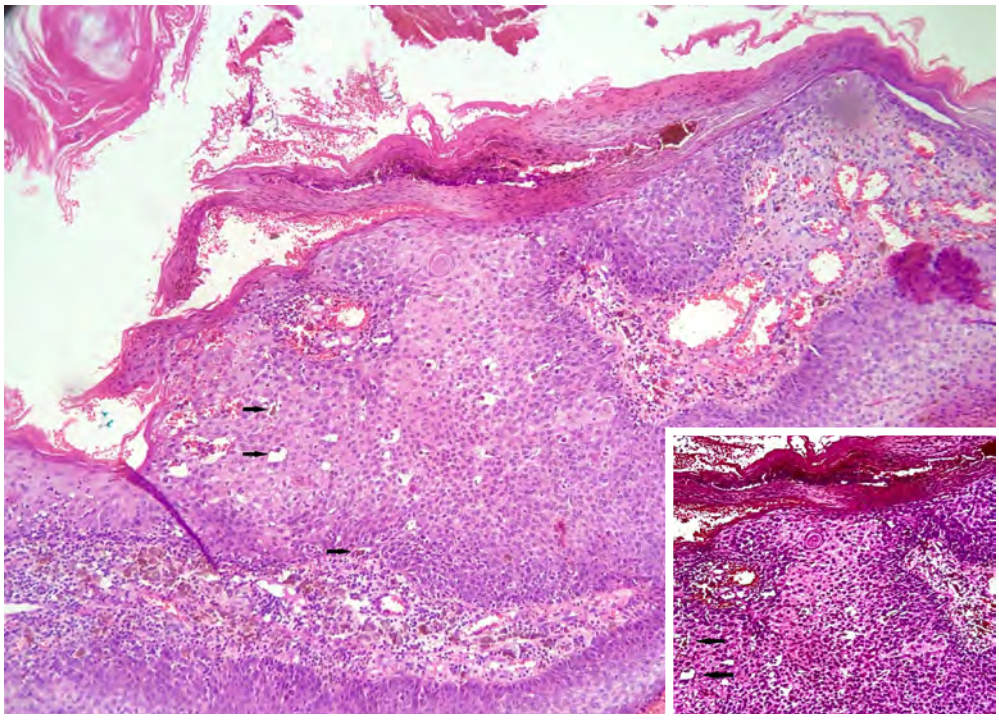

Figure 3: Histopathology shows dendritic melanocytes (arrows) amidst epidermal keratinocyte proliferation and melanophages in the dermal papilla.
HE magnification 10x and 40x.

face of the epidermis often filled with keratin. In our case, we visualized these PC in an area of dendritic melanocytes seen amidst basaloid keratinocytes in the acanthotic epidermis, correlating with the pigmented SK component of the lesion (Figure 3).

Besides this exciting finding in the SK dermoscopy, our case consisted of an SK with malignant transformation into an invasive SCC. It's a rare event, considering that the transformation into an in situ SCC is much more common than into an invasive SCC. According to Vun et al., in a retrospective study of 813 histological specimens reported as seborrheic keratosis, 43 were associated with non-melanoma skin cancer. Among these, 36 were associated with squamous cell carcinoma in situ, and only two were associated with invasive squamous cell carcinomas.[2]

To our knowledge, this is the first time these dermoscopy structures (PC) are described in an SK. Further studies are necessary to determine its prevalence and to analyze its exact histopathology correlation. ●

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Frontal fibrosing alopecia development in two patients after botulinum toxin applications: relationship or coincidence?

Desenvolvimento de alopecia fibrosante frontal em duas pacientes usuárias de toxina botulínica: relação ou coincidência?

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ABSTRACT

Frontal fibrous alopecia is a primary lymphocytic scarring alopecia that is difficult to control, with a perifollicular lichenoid infiltrate marking its histology. Since its description in 1994 by Kossard, there has been an increase in cases reported worldwide. This article reports two cases that underwent incisional biopsies with longitudinal and transverse sections in areas presenting higher disease activity and reviews some aspects of this dermatosis. It also addresses the suspicion of a possible relationship with the application of botulinum toxin – a question already raised by other authors but with no established confirmation.

Keywords: Alopecia; Botulinum toxins; Botulinum toxins type A

RESUMO

A alopecia frontal fibrosante é uma alopecia cicatricial linfocítica primária de difícil controle, com infiltrado liquenoide perifolicular marcando sua histologia. Desde a sua descrição em 1994 por Kossard houve um aumento de casos descritos pelo mundo. Este artigo relata dois casos em que foram realizadas biópsias incisionais com cortes longitudinais e transversais nas áreas que apresentaram maior atividade da doença e revisa alguns aspectos dessa dermatose, além de abordar a suspeita de uma possível relação com a aplicação de toxina botulínica - questão já aventada por outros autores, porém sem estabelecimento de confirmação.

Palavras-chave: *Alopecia; Toxinas botulínicas; Toxinas botulínicas tipo A*

Case report

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INTRODUCTION

Frontal fibrosing alopecia (FFA) has a still unknown etiology and has evolved increasingly worldwide. Kossard first described it in 1994,[1] in Australia, and it is more common in postmenopausal women, although cases in childbearing age women and men have also been reported.[2]

FFA is characterized by the loss of terminal hair and/or vellus follicles in the frontotemporal region, associated with perifollicular erythema and follicular hyperkeratosis. It may also present nonspecific symptoms such as itching and trichodynia. It presents fibrosing, scarring, progressive, and, most of the time, irreversible characteristics.[3] It is currently classified in the spectrum of lichen planopilaris (LPP) – an entity that has been subdivided today into FFA, classic lichen planopilaris, and Graham-Little-Piccardi-Lasseur Syndrome (GLPLS).

It is common to observe terminal follicles and tufted hair loss in the front temporal region during the dermatological examination, associated with erythema and flaking in the alopecia plaque.[1,2] The affected area may be slightly atrophic, with follicular ostia loss. It is also common to observe perifollicular erythema at the frontal hairline.[2,3]

Dermoscopy is a non-invasive method that assists in disease diagnosis and follow-up, and it provides a better site identification for a biopsy. The dermoscopy contributes to findings such as perifollicular erythema, follicular hyperkeratosis, follicular ostia reduction, and absence of vellus follicles, which are significant findings for better diagnostic clarification.[3]

Although it is an invasive procedure, scalp biopsy contributes significantly to the diagnosis through histopathological examination. For the biopsy, the material must be collected from a hair carrier area with clinical signs of active disease, which endorses the importance of using dermoscopy to identify the best site.[4]

Histopathological findings of FFA are similar or almost identical to those seen in the lichen planopilaris. Both diseases exhibit lymphocytic inflammatory infiltrate involving the isthmus and infundibulum hair follicles. The follicular epithelium shows exocytosis of lymphocytes, apoptotic and/or dyskeratotic cells, concentric fibroplasia around the inflamed follicles, and subsequent destruction of some follicles.[5]

A possible correlation between botulinum toxin application and the presence of FFA has been recently investigated.[6,7]

Two cases report

1. A 54-year-old-woman received botulinum toxin application (Botox® - Allergan, Irvine, CA, USA) on the upper third of the face and filling with hyaluronic acid in the nasolabial folds for more than five years before the dermatological examination, presenting no local complaints. The patient reported frontal hair loss and thinning hair presence in the frontal region. The dermatological examination evidenced high capillary implantation when raising the patient's bangs and decreased vellus in the frontal hairline. Dermoscopy examination showed lonely hair, perifollicular scales, and black spots without eyebrows changes (Figure 1). An incisional biopsy was performed. In the optical microscopy, the cross-sections presented cicatricial tracts at the follicular isthmus levels, and a moderate perifollicular lymphomononuclear inflammatory infiltrate at the level of the infundibulum and follicular isthmus. The follicular epithelium showed lymphocyte exocytosis and vacuolar alteration. The treatment consisted of topical therapy with clobetasol propionate and 5% minoxidil solution on the scalp and eyebrows. After eight months of clinical follow-up, the patient remained without signs of FFA activity.

2. A 79-year-old woman, hypertensive, received botulinum toxin (Botox® - Allergan, Irvine, CA, USA) applications on the upper third of the face one year before the dermatological examination; filling with hyaluronic acid five years before examination on the nasolabial folds; and a complete facial lifting 15 years before examination. She presented a surgical scar on the front hairline implantation. The patient sought dermatological care for a new botulinum toxin application in the upper third of the face. She did not report any hair or scalp complaints, and she used a haircut with bangs that completely covered her frontal region to hide her frontal hairline loss. The dermatological examination showed high capillary implantation noticed when raising her bangs; alteration of the skin color in the frontal hairline capillary implantation; contraction of the frontal muscle more evident with enlargement of the hairline capillary implantation; vellus hair reduction on the frontal hairline; and eyebrows thinning (Figure 2A). Dermoscopy showed lonely hair; scales; perifollicular erythema; capillary rarefaction in the frontal, midline, and vertex areas; and rarefaction in the eyebrows (Figure 2B). An incisional biopsy was performed. The microscopy examination revealed a peri-

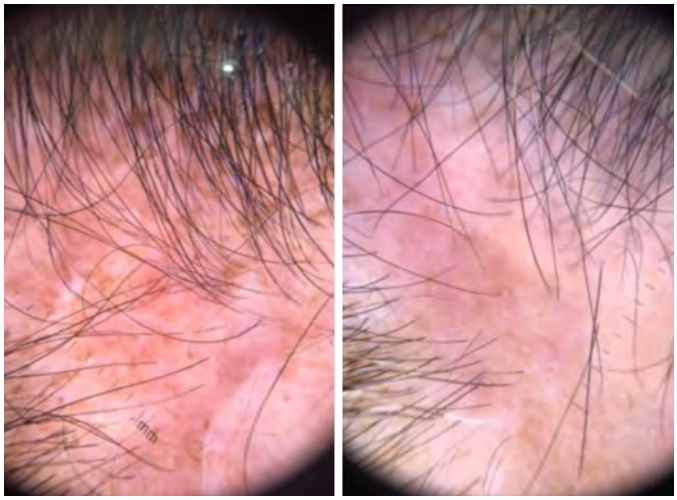

Figure 1: Dermoscopy showing lonely hair and perifollicular scales

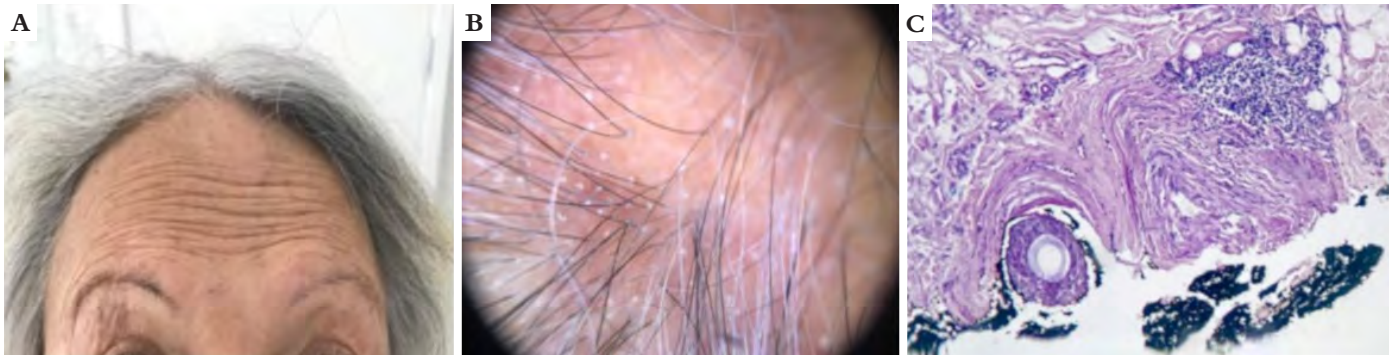

Figure 2: A - High capillary implantation with change in skin color and rarefied eyebrows; **B -** Dermoscopy with lonely hair, scales, and perifollicular erythema; **C -** Optical microscopy of the lesion with moderate lymphomononuclear inflammatory infiltrate around the cicatricial tract in longitudinal section

pheral lymphomononuclear inflammatory infiltrate at the level of the infundibulum, perifollicular fibrosis, and a moderate lymphomononuclear inflammatory infiltrate around the scar tract (Figure 2C). The patient underwent oral therapy with finasteride, topical therapy with clobetasol propionate and 5% minoxidil solution on the scalp and eyebrows. After seven months of clinical follow-up, she remained free of FFA activity signs.

DISCUSSION

In the two cases reported, the patients were women aged between 54 and 79 years. Also, the patients received botulinum toxin (Botox® - Allergan, Irvine, CA, USA) applications and hyaluronic acid. The second patient also had a complete facial lifting 15 years before the dermatological examination, presenting a surgical scar on the frontal hairline. We found a report in the literature about a 55-year-old patient presenting sclero-atrophy on the frontal hairline of the scalp insertion ten days after local injection of botulinum toxin type A for aesthetic purposes. However, the authors did not discard an inappropriate toxin application or an overdose of the drug.[6] Another article reports five cases of patients who were submitted to botulinum toxin periodically. These cases reported regression of the frontal hairline, which led the authors to question a correlation known as "botulin-induced frontal alopecia (BIFA)". However, it was impossible to confirm this likely disease's aspects because the patients did not accept to undergo biopsy.[7]

A recent case-control study showed that the relationship between FFA and environmental factors is still controversial. According to this study, FFA was associated with the use of facial moisturizers, non-dermatological facial soaps, and hair straightening with formalin. Literature has suggested the use of capillary anti-residue solutions and tobacco as protective factors. There was no association with the use of sunscreens. The application of botulinum toxin or hyaluronic acid was not mentioned in this study.[8] The cases reported in the present study showed an association of FFA with the application of botulinum toxin. Further studies are needed to ascertain this possible relationship, a fact that corroborates with the Piraccini[6] and Persechino[7] studies.

Regarding the patient who also underwent a facelift, the possible correlation between the procedure and FFA was described in a case series where three patients developed FFA after a facelift. A possible explanation for this correlation is the induction of the Koebner phenomenon in which a trauma or non-specific inflammatory process in healthy skin occurs in susceptible individuals.[9]

CONCLUSION

We report two cases of alopecia in the present study, in women aged between 54 and 79 years, with clinical, dermoscopic, and histological findings compatible with FFA. They were treated and presented no progression of the lesions in clinical follow-up. Both had a previous history of a single application of botulinum toxin (Botox® - Allergan, Irvine, CA, USA). The present study addresses a possible relationship between FFA and botulinum toxin's application and presents studies that suspected this relationship. ●

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Malignant fibrous histiocytoma in ankle: case report

Histiocitoma fibroso maligno no tornozelo: relato de caso

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ABSTRACT

Malignant fibrous histiocytoma (MFH) or undifferentiated pleomorphic sarcoma (UPS) is a sarcoma capable of invading adjacent structures. It is a mesenchymal neoplasia that predominates in men between the sixth and seventh decades of life. It is located mainly in the lower limbs and may affect the head and neck, trunk, and retroperitoneum, presenting a tendency to recurrence and local metastasis. This report aims to present a case of MFH in the ankle of a 49-year-old woman with an adjacent bone invasion, which evolved with transtibial amputation. Clinical, radiological, histopathological, and therapeutic aspects were addressed, highlighting the importance of early diagnosis.

Keywords: Amputation; Malignant fibrous histiocytoma; Sarcoma

RESUMO

Histiocitoma fibroso maligno (MFH) ou sarcoma pleomórfico indiferenciado (UPS) é um sarcoma moderadamente agressivo, capaz de invadir estruturas adjacentes. Trata-se de neoplasia mesenquimal que predomina em homens entre a sexta e sétima décadas de vida. Localiza-se, principalmente, nos membros inferiores, podendo acometer cabeça e pescoço, tronco e retroperitônio, com tendência à recorrência e à metástase local. O presente relato tem como objetivo apresentar um caso de MFH no tornozelo de uma mulher de 49 anos, com invasão óssea adjacente, que evoluiu com amputação transtibial. São abordados aspectos clínicos, radiológicos, histopatológicos e terapêuticos, salientando-se a importância do diagnóstico precoce.

Palavras-chave: *Amputação; Histiocitoma fibroso maligno; Sarcoma.*

Case Report

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INTRODUCTION

Malignant fibrous histiocytoma (MFH), first described by O'Brian and Staut in 1964,[1] is characterized by a high-grade mesenchymal neoplasm, composed of fibroblasts, myofibroblasts, and histiocytes.[2] It predominates between the sixth and seventh decades of life and in men (2/3 of the cases).[3,4]

It mainly affects the lower limbs, and the distal femur, proximal fibula, and proximal femur[2] are the most frequent topographies. Nevertheless, it can also occur in the lung, kidney, bladder, heart, aorta, stomach, small intestine, orbit, central nervous system, spinal cord, sinuses, nasal and oral cavities.[5]

MFH is associated with hematopoietic diseases (non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, and malignant histiocytosis). It can also result from radiation, fracture, osteonecrosis, Paget's disease of bone, non-ossifying fibroma, and fibrous dysplasia – cases where it is more aggressive.[5]

It has a moderately aggressive behavior that can invade adjacent soft tissues, skeletal system, and retroperitoneum. The main prognostic factor is the clinical stage of the tumor, defined by the degree of differentiation, size, and presence of distant metastases. Histological subtype, anatomical location, tumor depth, and treatment performed also influence the prognosis.[6]

CASE REPORT

A 49-year-old black housewife sought medical help due to a friable tumor measuring 7.0 cm x 5.5 cm, with progressive growth in the last nine months. The tumor presented a bleeding surface, fibrous and adhered consistency, with a defined contour, located in the right lateral malleolus (Figures 1 to 3). The patient reported episodes of bleeding associated with local pain. She sought medical care and was treated for a bacterial infection with antibiotic therapy, without improvement.

The patient had a history of portal vein thrombosis (PVT), heart failure, and arterial hypertension. Lymphadenopathies, visceromegaly, or lymphedema were not identified. The diagnoses suggested amelanotic melanoma, sarcoma, and Merkel cell carcinoma (MCC).

Histopathological examination revealed an ulcerated mesenchymal neoplasm, composed of spindle-shaped and epithelioid cells, with nuclear pleomorphism and accentuated mitotic activity (Figures 4 and 5), characterizing high-grade MFH. Immunohistochemistry showed positivity for CD68 (Figure 6) and negativity for p63, AE1/E3, CK5/6, MELAN A, CD34, AML, and S100, SOX-10.

General biochemical exams results were within normal values; however, magnetic resonance imaging evidenced invasion of the distal fibula (Figure 7).

The set of histopathological, immunophenotypic, and imaging findings confirmed the diagnosis of malignant fibrous histiocytoma (deep)/undifferentiated pleomorphic sarcoma, stage IIIA.

Due to bone involvement and tumor unresectability with deep structures preservation, transtibial amputation was chosen. The patient has been under follow-up with Oncology for 11 months, without recurrence. The presence of heart disease contraindicated the adjuvant chemotherapy.

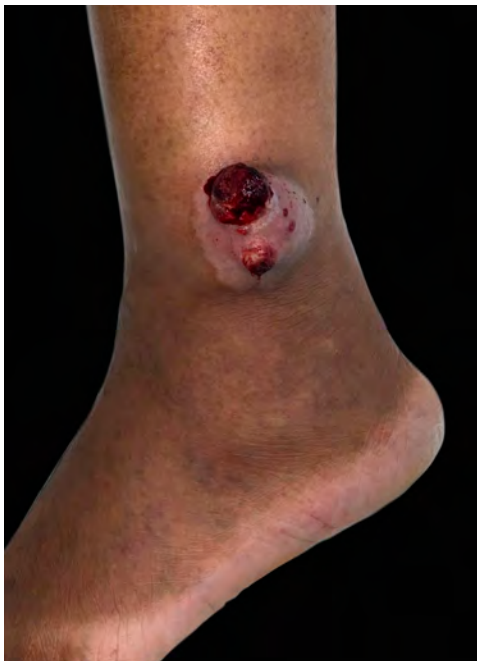

Figure 1: Malignant fibrous histiocytoma. Tumor above the lateral malleolus of the right leg

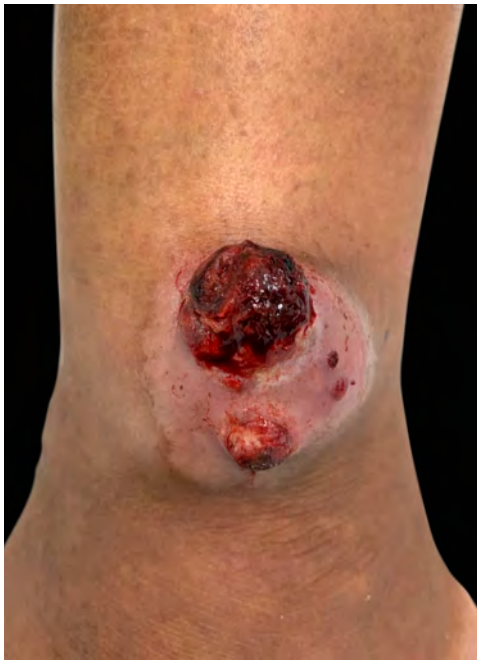

Figure 2: Malignant fibrous histiocytoma. Tumor with a fibrous surface, adhered, with defined boundaries and friable areas

DISCUSSION

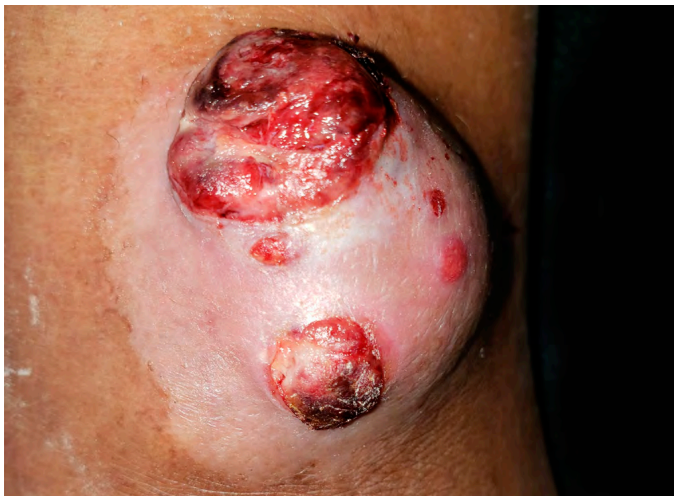

Figure 3: Immunohistochemical staining. Smooth surface detail, with friable papules and nodules

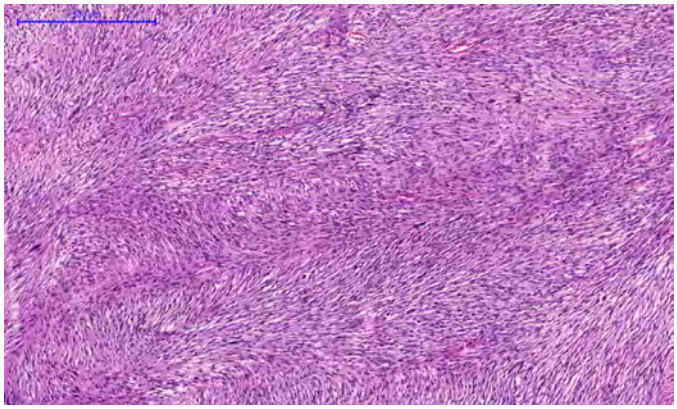

Figure 4: Malignant fibrous histiocytoma. Proliferation of spindle cells forming short bundles in different directions (Hematoxylin & eosin,25x)

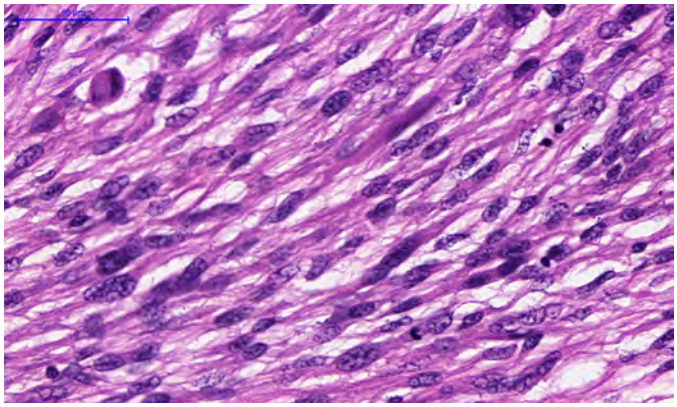

Figure 5: Spindle cell bundes detail with. Spindle cell bundles with intense cellular pleomorphism and mitotic activity (Hematoxylin & eiosin,100x)

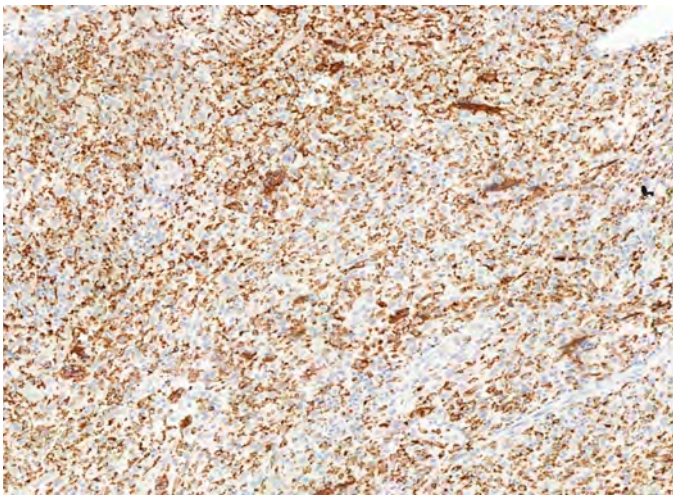

Figure 6: Immunohistochemical staining. Extensive CD68 positivity (histiocytes)

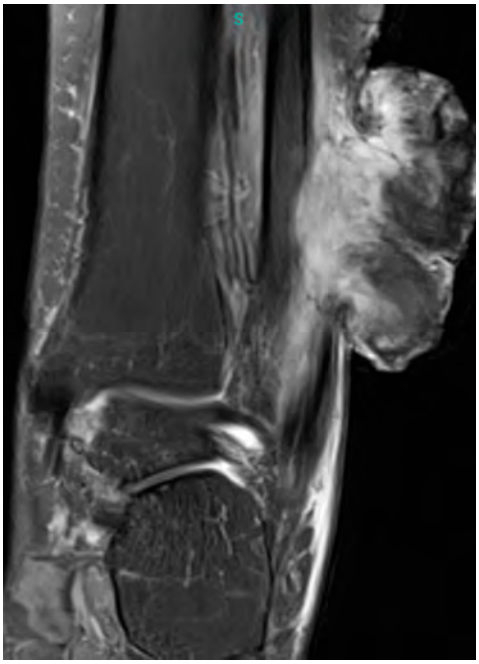

Figure 7: Malignant fibrous histiocytoma. Magnetic nuclear resonance image showing a vegetating mass with hypersignal invading the distal portion of the fibula

Soft tissue sarcomas are rare neoplasms, accounting for approximately 1% of solid cancers in adults, representing a heterogeneous group of disorders arising from mesenchymal tissue.[7]

In 2003, Coindre described a new grading for sarcomas, based on immunohistochemical criteria:[8]

- Well-differentiated sarcomas: rhabdomyosarcomas, epithelioid sarcoma, clear cell sarcoma, desmoplastic small round cell tumor, and gastrointestinal stromal tumors.

- Sarcomas with specific histologic typing: Ewing's sarco-

ma, leiomyosarcoma, malignant peripheral nerve sheath tumor, dermatofibrosarcoma protuberans, giant cell fibroblastoma, extraskeletal myxoid chondrosarcoma, liposarcomas, and alveolar soft part sarcoma.

- Undifferentiated sarcomas, or sarcomas of doubtful type (not showing specific markers): fibrosarcoma, myxofibrosarcoma, and malignant fibrous histiocytoma. In these cases, immunohistochemistry can help exclude other non-mesenchymal tumors.

Undifferentiated pleomorphic sarcoma (UPS) can be divided into superficial and deep subtypes, also called atypical fibroxanthoma (AFX) and malignant fibrous histiocytoma (MFH), respectively. The distinction between the entities is essential to predict the locoregional aggressiveness of the tumor and its prognosis.[9,10]

In this report, MFH occurred in the ankle of an adult woman. However, these tumors predominate in men older than 50 years.[4] Typically, it presents as a painless, fast-growing tumor, with reports of lesions exclusively subcutaneous.[11]

UPS diagnosis requires the histopathological differentiation of tumors such as melanoma, squamous cell carcinoma, angiosarcoma, leiomyosarcoma, and other undifferentiated neoplasms.[12,13]

MFH is recognized as a heterogeneous group of tumors that share a common phenotype, requiring immunohistochemistry, electron microscopy, or molecular studies for better characterization.[14]

Histopathology revealed pleomorphic spindle cells arranged in bundles with a storiform pattern, and multinucleated histiocytes infiltrated in the deep dermis and subcutaneous cellular tissue.[15,16]

MFH has immunoreactivity for vimentin and CD68 (histiocytic marker).[17,18] S100, desmin, S-100, and HMB-45 are antibodies found in liposarcoma or malignant peripheral nerve tumors, nerve sheath tumor, rhabdomyosarcoma, and malignant melanoma, respectively. Moreover, CD34 shows reactivity in angiosarcomass.[15,16]

Magnetic resonance imaging is the imaging modality of choice to assess soft tissue sarcomas, particularly to determine the local extent of the lesion. On examination, the MFH shows a heterogeneous pattern that is hyperdense on T2-weighted images and isodense to muscles on T1-weighted images.[19]

Wide excision (margin ≥2cm) is the recommended approach. Nevertheless, there is a limitation due to the proximity to noble structures depending on the topography,[14] indicating micrographic surgery.[6,20]

Local recurrence high rates are reported in patients undergoing surgical excision (19% to 66%).[20-22] In this case, we completely removed the lesion and, due to comorbidities, decided not to perform adjuvant chemotherapy.

A study analyzing 167 individuals found that 66% of patients treated with marginal resection had local recurrence compared with 27% of patients who underwent wide resection (margin ≥3cm).[23]

Radiotherapy can be beneficial as an adjuvant treatment, using a radiation field covering the tumor site and 5 cm around it, with doses ranging between 50 and 65 Gray. However, the overall impact on recurrence and survival is not fully defined.[24]

Chemotherapy is typically used for generalized diseases but with poor prognoses.[25,26] Currently, studies assessing immunobiologicals in patients with advanced diseases are in the clinical phase. This is the case for ipilimumab (anti-CTLA-4), comprising 33 children and young adults, and sunitinib (oral multi-kinase inhibitor) including 48 young adults, which analyzes unresectable or metastatic sarcoma.[27]

CONCLUSION

MFH presents clinically indistinguishable from other entities, being mainly characterized by aggressive growth behavior. This case report aimed to highlight its main characteristics and the importance of diagnostic suspicion and early treatment to avoid unfavorable outcomes. ●

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Giant hand lipoma: a surgical challenge

Lipoma gigante na mão: um desafio cirúrgico

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ABSTRACT

Lipomas are frequent soft tissue tumors and can be found anywhere in the body; however, their location in hand is rare. They are called giants when they exceed 5 cm. In these cases, the differential diagnosis must be made with liposarcoma. These benign tumors must be characterized preoperatively with an imaging study, and their treatment is surgical. We present the case of a patient with a giant hand lipoma successfully treated with a modified Bruner incision approach.

Keywords: Lipoma; Liposarcoma; Neoplasms, adipose tissue; Hand

RESUMO

O lipoma é um tumor frequente dos tecidos moles e pode localizar-se em qualquer parte do corpo; no entanto, sua apresentação na mão é rara. São chamados gigantes quando excedem 5 cm; nestes casos, o diagnóstico diferencial deve ser feito com lipossarcoma. Os lipomas devem ser caracterizados no pré-operatório com um exame de imagem, e seu tratamento é cirúrgico. Apresentamos o caso de uma paciente com um lipoma gigante da mão dominante, tratada com sucesso com uma abordagem cirúrgica modificada de Bruner.

Palavras-chave: *Lipoma; Lipossarcoma; Neoplasias lipomatosas; Mãos*

Case report

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INTRODUCTION

Lipomas are the most common soft tissue tumors in the population. They are benign and composed of adipose tissue. These tumors can present anywhere on the body, often affecting the upper limbs but rarely the hand.[1]

Slow growing, fibroelastic consistency, mobility, and absence of pain characterize lipomas. They can be located subcutaneously, intermuscularly, or intramuscularly.[1]

Tumors measuring more than 5 cm in diameter are considered giant lipomas. This form of presentation is rare, mainly when located in hand. In this case, these tumors can act as a mass and limit function or generate symptoms such as paresthesia, requiring a surgical approach. Likewise, it is critical to rule out malignant degeneration, usually rare, represented mainly by liposarcoma.[1]

We report a case of giant lipoma case on the dorsum of the dominant hand. The patient had function limitations when performing daily tasks, without other symptoms. We describe the successful surgical approach performed by the modified Bruner incision technique.

CASE REPORT

A 62-year-old woman, without comorbidities, consulted the dermatological surgery service for presenting a swelling on the dorsum of the right hand (dominant hand) extending to the index finger, with progressive growth over the last year. The patient did not present pain, paresthesia, or change in sensitivity but had limited mobility for her daily activities. Physical examination revealed a tumor with a soft consistency, smooth surface, not adhered to the deep planes. The tumor measured 7x4 cm and was located on the dorsum of the hand over the second and third metacarpals up to the second interdigital space and the proximal phalanx of the index finger (Figure 1). We performed an ultrasound that suggested lipoma.

Regarding the surgical approach, we first demarcated the tumor, then drawing a zigzag incision on the dorsum of the hand and index finger, according to Bruner's surgical principles (Figure 2). Anesthesia was regional for the radial nerve block and subsequently

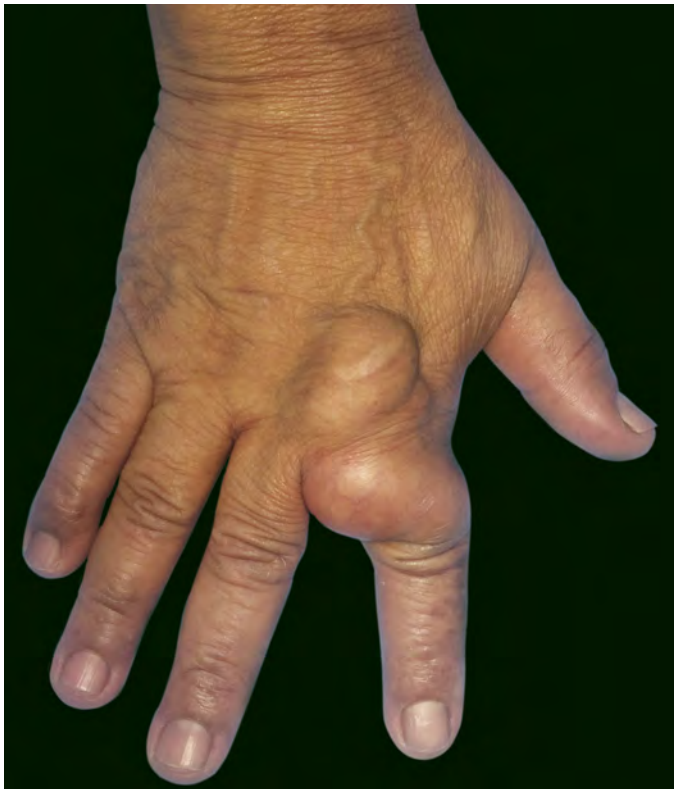

Figura 1: Swelling on the dorsum of the right hand extending to the proximal phalanx of the index finger

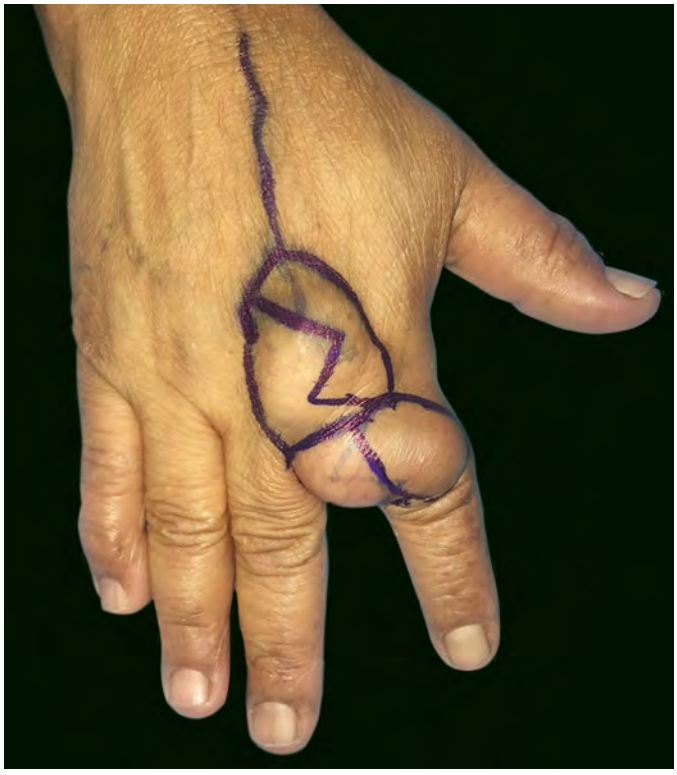

Figura 2: Marking of the modified Bruner incision approach

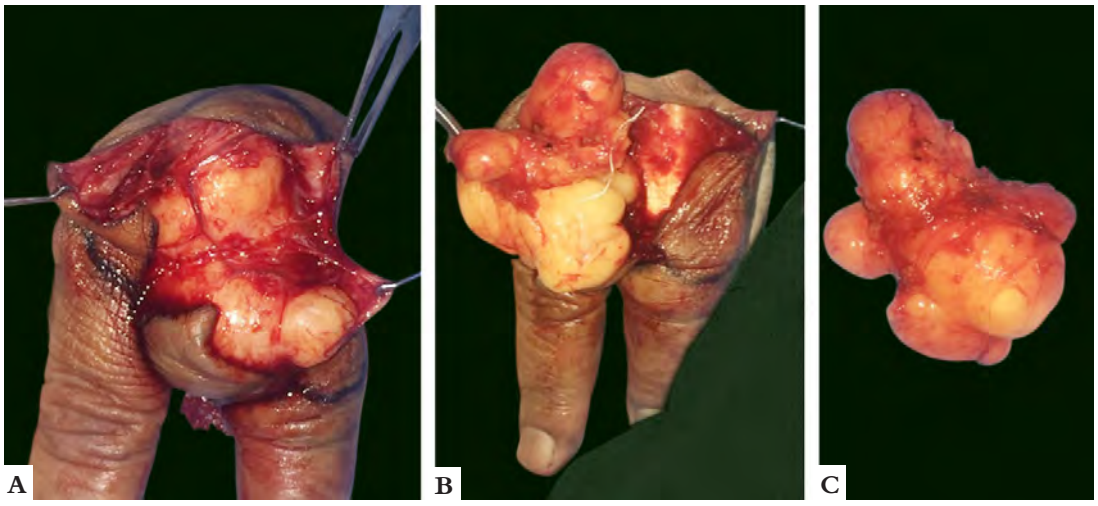

Figura 3: A, B e C - Intraoperative images of giant hand lipoma

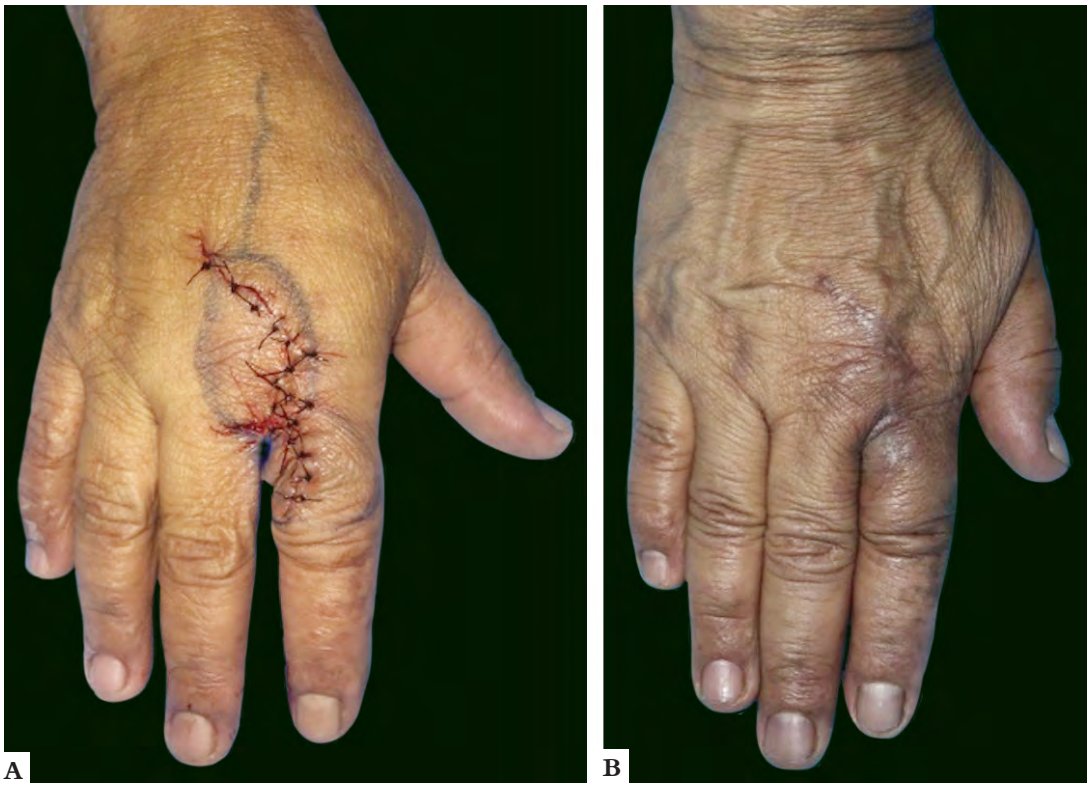

Figura 4: A - Images from the immediate postoperative period and **B -** after four months

tumescent to obtain hydrodissection and protect the tendinous structures around the tumor. We carefully dissected the lesion from the tendon sheaths and neurovascular structures, performing a complete excision (Figures 3a, 3b, and 3c and Figures 4a and 4b). The procedure had no complications and the mobility and sensitivity of the patient's hand were preserved. The histopathological study confirmed the diagnosis of lipoma.

DISCUSSION

Lipomas are benign tumors formed by mature adipocytes, responsible for approximately 16% of soft tissue mesenchymal tumors. They are the most com-

mon tumors in adults with a prevalence of 1% and can be found in any part of the body at the subcutaneous, intermuscular, or intramuscular level, and, less frequently, in internal organs.[2,3,4]

Its location in the hands is infrequent, around 5%. In this case, the thenar and hypothenar regions are the most prevalent, and the phalanges are the rarest, with a 1% prevalence. The most common benign soft tissue tumors in hand are pyogenic granuloma, ganglion cyst, giant cell tumor of the tendon sheath, hemangiomas, and others.[2,3,4,5]

Clinically, lipomas are firm, flexible, and relatively mobile subcutaneous nodules, slow-growing and asymptomatic. However, when they are extensive or in hand, they can compress a nerve and cause changes in sensitivity (paresthesias and dysesthesias). They can also produce functional changes, as in our patient's case, who had limited index finger flexion.[3,4] Lipomas appear mainly in the fifth and sixth decades of life, as evidenced in this patient.[2]

The etiology of these tumors is unknown. Nevertheless, multiple causal factors have been proposed, such as genetic, traumatic, and metabolic factors.[2,4] Concerning genetic factors, lipomas are commonly associated with translocations and rearrangements of the 12q13-q15 and 6p13q chromosome regions.[4,6] Regarding traumatic factors, lipomas were previously believed to be a herniation of preexisting adipose tissue through the fascia. Later, the theory emerged that growth factors, cytokines, and other inflammatory mediators released after trauma could induce the differentiation of preadipocytes into mature adipocytes, forming the tumor.[6]

Rapid growth, pain, large size (tumors larger than 5 cm are considered giant), or the presence of local invasion to other structures on magnetic resonance imaging may be signs of malignancy. Therefore, it is critical to conduct an imaging study, both for planning the surgical approach and to rule out malignancy, with liposarcoma as its main differential diagnosis.[2,7]

Imaging studies are diagnostic in 71% of cases, and computed tomography and magnetic resonance imaging are the gold standards.[2] Other low-cost modalities can be used, such as radiography and ultrasound. Our patient underwent an ultrasound examination, which demonstrated a circumscribed and homogeneous hyperechoic area. Ultrasound is diagnostic in most cases, but magnetic resonance sensitivity is 94%, in addition to defining the anatomical extent of the lesion and its relationship with critical structures.[4,7]

Regarding surgery, the first step was to mark the tumor. The approach followed the principles of Bruner incision, especially for the flexion and extension areas of the fingers, which could extend to the hand to avoid further functional limitation with hypertrophic scars and contractures. Bruner described a zigzag volar-digital incision, where the flap angles are 90 degrees or more and are at the level of the joint folds, ensuring that the incision does not cross them.[8,9] In our patient's case, we modified the Bruner method: the zigzag incision was made at the dorsal level of the hand and index finger, due to the tumor location, without crossing the second metacarpophalangeal joint, with 90 degrees angles or less in the flaps. It allowed a good exposure of the lipoma and surrounding structures and maintained the vascularity and sensitivity of the flaps.

This modified Bruner incision approach enabled performing a complete excision of the giant lipoma, preserving hand sensitivity and motricity and managing to prevent compartment syndrome. After more than one year of follow-up, the patient also did not present contractures, hypertrophic scars, or complex regional pain syndrome, which are possible post-surgical complications.[2,4]

CONCLUSION

Giant hand lipomas are rare, benign tumors with an excellent prognosis after successful surgical excision and low recurrence. However, preoperative imaging assessment is essential for planning the surgical approach. Bruner incision technique is an interesting strategy to be considered in the hand region for its satisfactory functional and cosmetic outcomes. ●

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Molluscum contagiosum as a tattoo complication: a case report and literature review

Molusco contagioso como complicação de tatuagem: um relato de caso e revisão da literatura

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ABSTRACT

Tattooing is an ancient practice and very popular nowadays. The pigments used have changed over time but still present varied and poorly regulated compositions. There are many described cases of adverse effects after tattooing, mainly infectious and hypersensitivity reactions. We report the case of a 64-year-old woman, healthy, with papules on her eyebrows one month after performing micropigmentation. The excisional biopsy diagnosed molluscum contagiosum, and the lesions were curetted. There are few reports in the literature of the spread of molluscum contagiosum caused by tattooing.

Keywords: Molluscum contagiosum. Tattooing. Poxviridae infections.

RESUMO

A tatuagem é uma prática antiga e muito popular atualmente. Os pigmentos utilizados mudaram com o tempo, mas continuam apresentando composições variadas e pouco regulamentadas. Há inúmeros casos descritos de efeitos adversos pós-tatuagem, em sua maioria infecciosos, e reações de hipersensibilidade. Relatamos o caso de uma mulher de 64 anos, hígida, com pápulas nas sobrancelhas um mês após realizar micropigmentação. A biópsia excisional fez o diagnóstico de molusco contagioso, e o tratamento foi realizado com curetagem das lesões. Na literatura, existem poucos relatos de disseminação de molusco contagioso causada por tatuagem.

Palavras-chave: *Molusco contagioso. Tatuagem. Infecções por poxviridae*

Case report

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INTRODUCTION

Tattooing is an ancient practice that is becoming increasingly popular. It is estimated that 10% to 30% of the population currently have tattoos.[1-4] There are different types and purposes of tattooing, such as artistic, religious, social, and cosmetic expression.[1,4,5] The procedure consists of introducing pigments into the dermis through needles, manually or electrically, to produce a permanent design. Cosmetic tattooing, also known as micropigmentation or permanent makeup, is gaining more popularity. They can be used to camouflage skin conditions, act as adjuvants in reconstructive surgery, or replace makeup. The micropigmentation deposits the pigment more superficially in the dermis. It has a temporary effect because it reaches more superficial layers than conventional tattoos. Despite being an invasive procedure, it is an accessible procedure to the population.[6-10]

The inks and pigments used in tattoos are impure chemical mixtures that contain heavy metal oxide, salts, and organic molecules. Modern color inks often include azo pigments and polycyclic compounds. Health surveillance agencies do not always regulate these mixtures, and there is no control over the application of these products.[1,2,4,6,11,12] In Brazil, Despite the numerous ink brands available, the Brazilian Health Regulatory Agency (ANVISA) approves only three.[13] Histology shows pigments free in the dermis or phagocytized by macrophages. They can also be found in lymph nodes, illustrating the close contact that the pigment and its metabolites can have with our immune system.[1,2,1]

The tattoo poses a relevant risk of infection, considering the skin barrier. There is a possibility of contamination by the ink, not properly sterilized instruments, inappropriate skin antisepsis, in addition to the possibility of secondary infection during the healing process.[1,2] Skin infections range from pyoderma to endocarditis and sepsis, syphilis, leprosy, mycobacteriosis, fungal contamination, and the spread of viral diseases such as HPV, molluscum contagiosum, herpesvirus, hepatitis B and C, and even HIV.[1,2,3,12]

Hypersensitivity reactions also occur, as the pigment acts as a foreign body in the dermis, triggering lichenoid, granulomatous, and even pseudolymphoma lesions. Immunological reactions can be immediate or delayed and manifest locally or systemically. The most common skin manifestation related to tattooing is allergic contact dermatitis.[3] The red ink is the most frequently involved, probably due to mercury formerly used as a pigment.[2,3] There are also reports of the onset of Koebner phenomenon triggering psoriasis, vitiligo, and lichen planus lesions.[2,3,14,15]

The potential local and systemic carcinogenic effects of the tattoos and inks used remain uncertain.[11] Dermatofibroma, keratoacanthoma, pseudoepitheliomatous hyperplasia, basal and squamous cell carcinomas, melanoma, and other skin tumors have already been found on previously tattooed skin.[11] It is advised not to tattoo on a melanocytic nevus due to the difficulty of monitoring it. It also becomes a challenge to identify new lesions on tattooed skin, which could delay the diagnosis of a malignant tumor.[2,3]

CASE REPORT

A 64-year-old woman, white, presented intense itching with papule formation strictly on the tattoo site one month after performing eyebrows micropigmentation in an aesthetic clinic (Figure 1). She had no previous comorbidities. The dermatological examination showed numerous 1 mm to 4 mm papules, pearly and normochromic, on the tattoo area on the right eyebrow (Figure 2). After the excisional punch biopsy, the anatomopathological examination revealed a hyperplastic region in the epidermis characterized by cell proliferation from the Malpighian body, forming piriform invaginations into the dermis (Figure 3). We also found progressive accumulation of amorphous and eosinophilic material, compatible with molluscum contagiosum (Figure 4). Serologies for hepatitis B and C and HIV were negative. We performed the treatment with curettage of the lesions, with good results and no recurrence (Figures 5 and 6).

DISCUSSION

Molluscum contagiosum is a dermatovirus caused by a poxvirus. Usually, its transmission requires contact with infected hosts or contaminated fomites. It has a universal distribution, affecting more often children at school age. In healthy adults, it can manifest in the anogenital region, mainly through sexual transmission. Thus, it is also considered a sexually transmitted disease (STD). It is more commonly found in immunocompromised adult individuals, and it may present a disseminated picture or even inflammatory phenomena such as uveitis.[16-19]

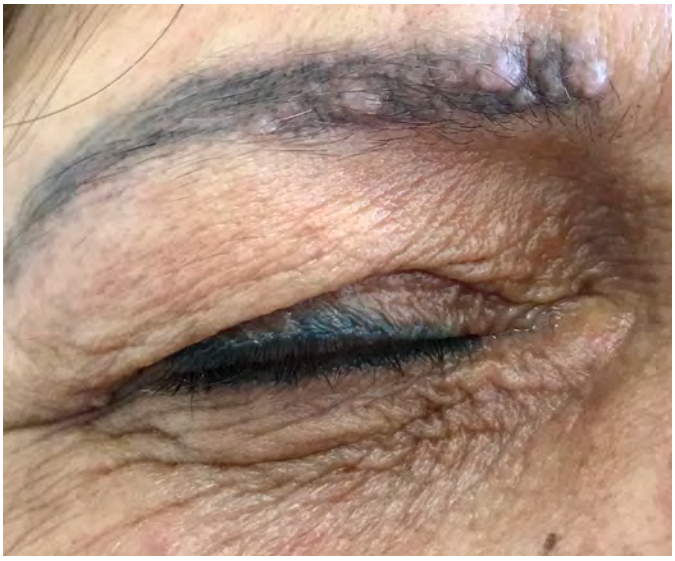

Figure 1: Pearly papules on tattoo

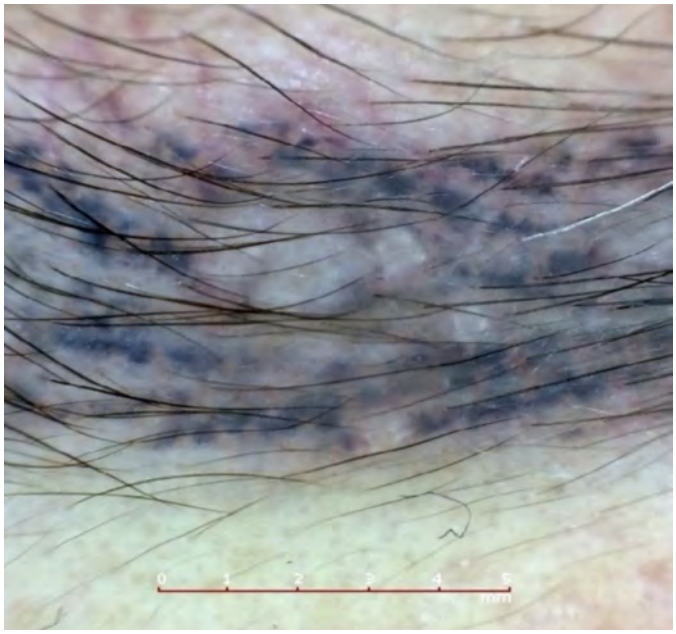

Figure 2: Dermoscopy revealed amorphous, polyglobular, white structures surrounded by fine telangiectasias

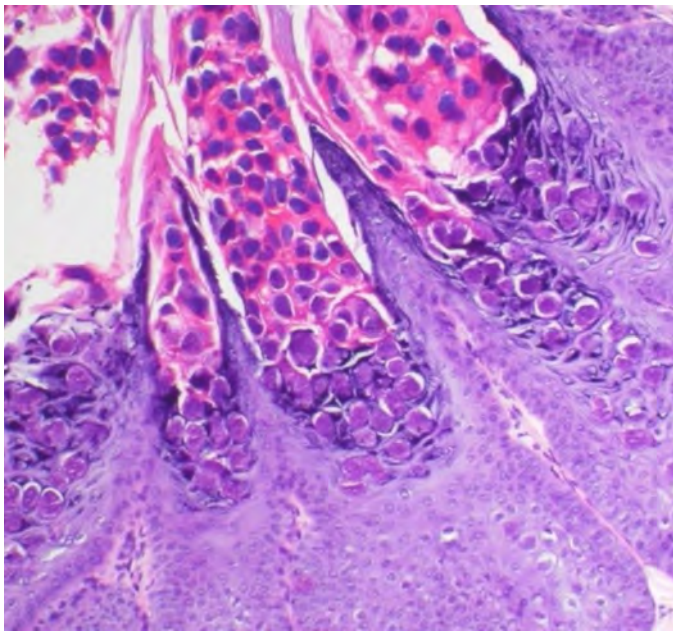

Figure 4: Accumulation of amorphous and eosinophilic material in cells that occupy the entire cell at the level of the granular and corneal layers

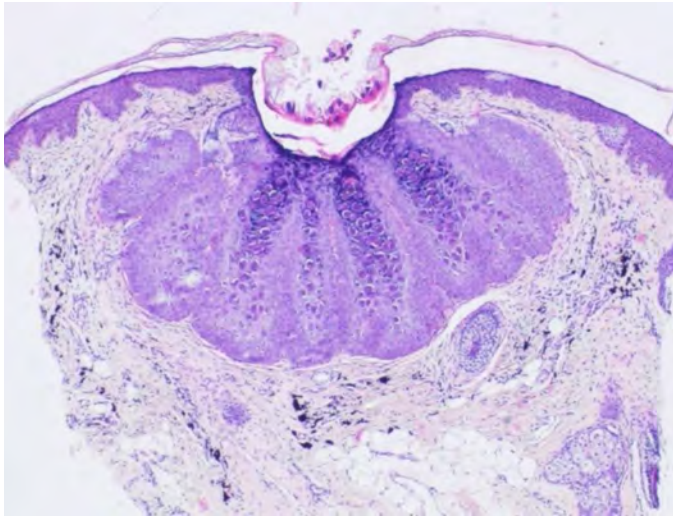

Figura e: Hyperplastic lesion in the epidermis characterized by cell proliferation from the Malpighian body, forming piriform invaginations into the dermis

As other infections spread through tattoos, the two most plausible possibilities for transmitting molluscum contagiosum are the contamination of the ink or instruments used.[18,21]

A firm and umbilicated pearly papule, normochromic, measuring a few millimeters characterizes the clinical lesion, which is more common in skin folds, trunk, thighs, buttocks, and face.[17] Dermoscopy presents a rounded, shiny lesion, with hairpin (looped) vessels in the periphery and a small circular central area, lighter in color, resembling a target (white target pattern).[20] Differential diagnoses are adnexal tumors, viral warts, juvenile xanthogranuloma, basal cell carcinoma, Spitz nevus, and granuloma annulare, among others.[17] In immunocompromised patients, systemic and subcutaneous mycoses may have a similar presentation.[19] This dermatosis spontaneously regresses in immunocompetent patients, but some therapeutic options are available to accelerate its eradication, such as curettage, cryotherapy, keratolytics, imiquimod, and other chemovesicants.[17]

After searching the PubMed database using the words "Molluscum contagiosum" and "tattoo" or "Molluscum contagiosum" and "tattooing", we found only ten published cases,[18-27] the oldest from 1982 and the most recent from 2013. All patients were immunocompetent, aged from 20 to 59 years, and there were nine men and one woman. Most individuals had the lesions strictly over the tattooed area, except for one, who also had lesions on the adjacent skin. Five patients presented the condition within one month after tattooing, and four within five months (one case did not describe the presentation time). Some subjects refused treatment modalities, and all others had their lesions curetted successfully and without recurrence. One case had spontaneous disappearance of the lesion in six months.

Skin disorders after micropigmentation and permanent make-up on the face have also been reported. For example, cutaneous and systemic sarcoidosis[28] and mycobacteriosis[29] after tattooing for eyebrows design. We found no report of molluscum contagiosum as a complication of micropigmentation or cosmetic tattooing.

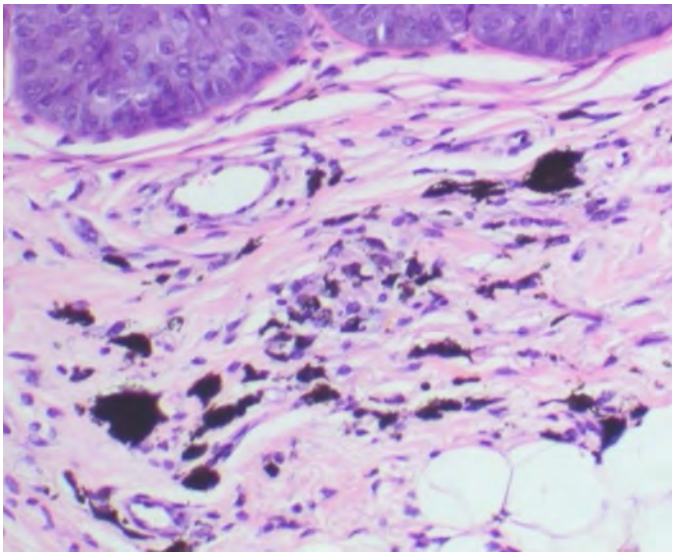

Figure 5: Highlight for the pigment in the dermis

Figure 6: Result after curettage of all lesions

It is important to emphasize that our search in PubMed was limited to articles in English or with at least the title translated. In addition, any similar cases that have not been reported and published in the scientific community must be considered.

CONCLUSION

Since tattooing is increasingly popular, its complications will be more recurrent. Therefore, dermatologists must be prepared to suspect, investigate, diagnose, and treat these skin conditions. The medical knowledge on the technique and its possible complications is also critical to guide and inform the patient who wishes to perform it.

Procedures such as micropigmentation and permanent makeup are widespread and easily accessible to the population, and they are considered safe and straightforward techniques. However, they are also tattoo methods, being likewise subject to all the risks presented here.

It is essential to regulate and control the quality of the pigments and the technique through public agencies and health surveillance, as this is an invasive procedure with serious complications. ●

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Divided nevus in the genital region: report of six cases

Nevo dividido na região genital: relato de seis casos

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ABSTRACT

The divided nevi occur in contiguous areas of the skin that are mostly benign lesions. We report six cases of nevus divided on the penis and its dermoscopic patterns. Clinical follow-up was the best therapeutic option for this group of patients, considering the location of these lesions.

Keywords: Dermoscopy; Nevus; Intradermal nevus; Pigmented nevus; Penis

RESUMO

Os nevos divididos ocorrem em áreas contíguas da pele e, em sua grande maioria, são lesões benignas. Relatamos seis casos de nevo dividido no pênis e seus respectivos padrões dermatoscópicos. Levando em consideração a localização dessas lesões, o acompanhamento clínico foi a melhor opção terapêutica para este grupo de pacientes.

Palavras-chave: *Dermoscopia; Nevo; Nevo intradérmico; Nevo pigmentado; Pênis*

Case Report

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INTRODUCTION

Divided nevus, also known as "kissing nevus", result from opposite migrations of contiguous areas that that undergo embryonic cleavage, which can occur in the penis, labia minora or majora, and upper and lower eyelids – the latter is the most common location.[1,2,3] Despite presenting different dermoscopic patterns, they are usually nevi with a benign evolution, and clinical follow-up is one of the possibilities for follow-up.[4,5]

METHODS

We report six cases of divided nevus or "kissing nevus" located on the penis glans and foreskin in male patients, aged between 5 and 26 years, asymptomatic, and without prior treatment. We used clinical examination and dermoscopy with a DL3 3GEN dermatoscope with polarized light and ultrasonography gel as the interface liquid for diagnosis. Images were obtained with a Nikon Coolpix P6000 camera.

RESULTS

We observed the following dermoscopic patterns: homogeneous reticular (Figures 1 and 2), homogeneous globular (Figures 3 and 4), mixed (reticular-globular, with peripheral pigment network and central globules), and some cases presented granularity (Figures 5 and 6). Guided by the clinical examination and dermoscopy, we chose not to biopsy any patient and perform the follow-up every three months in the first semester, every six months in the second semester, and every year after that.

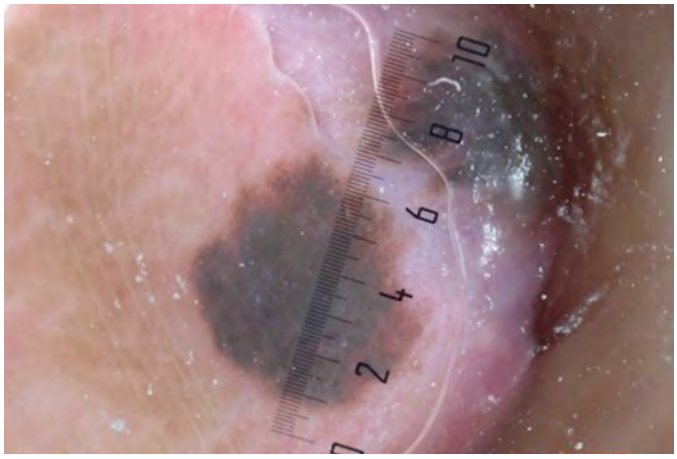

Figure 2: Melanocytic lesion on the glans, with homogeneous reticular dermoscopic pattern

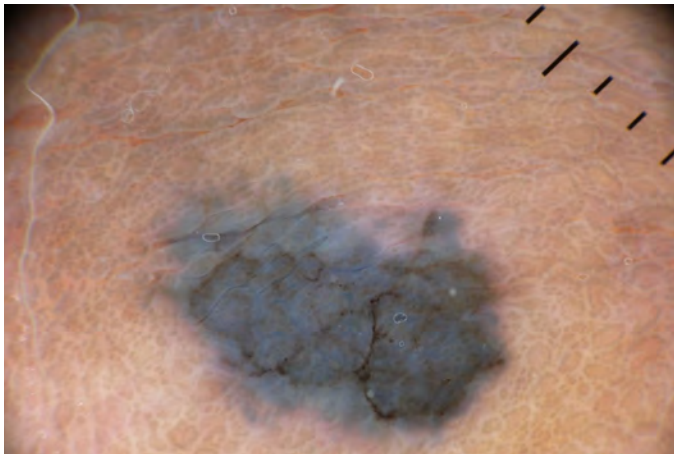

Figure 3: Melanocytic lesion in the foreskin, with homogeneous globular dermoscopic pattern

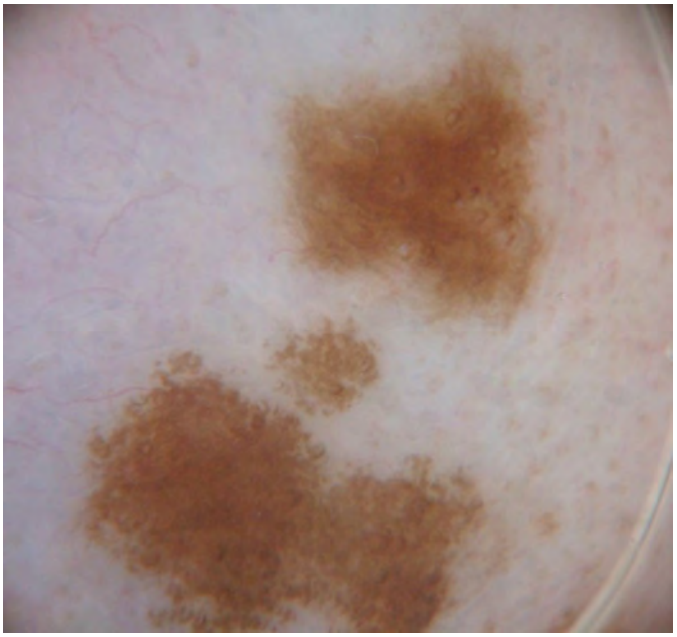

Figure 1: Melanocytic lesion on the glans, with homogeneous reticular dermoscopic pattern

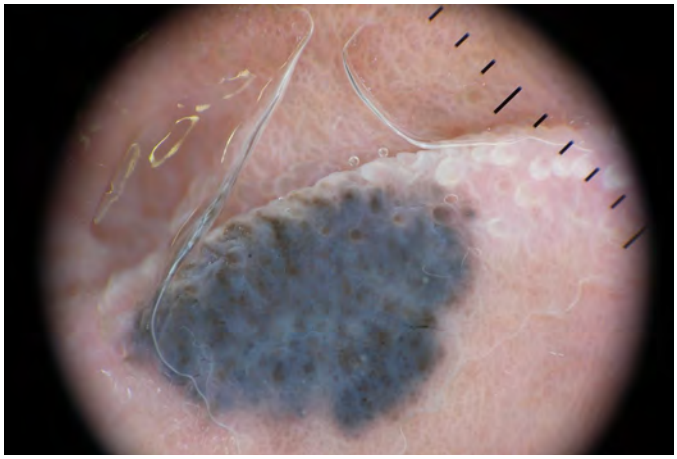

Figure 4: Melanocytic lesion on the glans, with homogeneous globular dermoscopic pattern

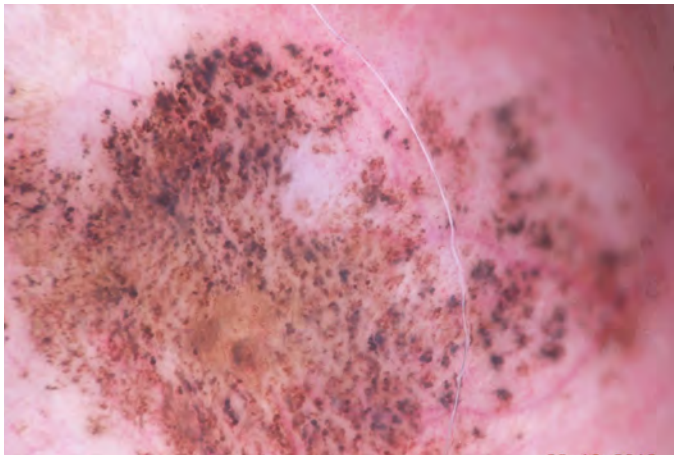

Figure 5: Melanocytic lesion on the glans and foreskin, with globular dermoscopic pattern with granularity and varied appearance of colors indicating pigment in several layers of the skin

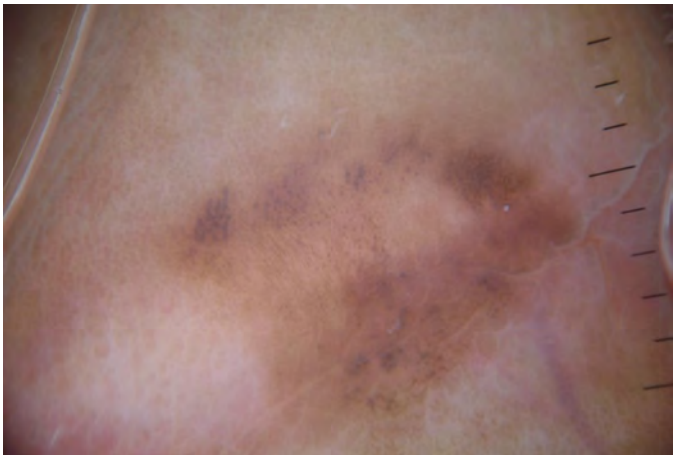

Figure 6: Melanocytic lesion in the balanopreputial sulcus of the penis, with a reticular dermoscopic pattern and granularities represented by a bluish-gray color.

DISCUSSION

The migration of divided nevi occurs at different times during embryogenesis, depending on the site of origin. For the penis, the division occurs between the 11th and 14th gestational week, the external genitalia maturation period, and for the eyelid, around the 24th week.[4,6] Some dermoscopic patterns have already been reported both in pediatric and in adults patients. Among them are the globular and reticular-globular, which presents a pigmented network in the periphery and globules in the center, in addition to the homogeneous pattern, which has some globules in the center – all suggestive of benignity.[4,5]

The low risk of malignant evolution is known. As far as we are aware, only three cases involving eyelids and penis have been reported to date.[6,7,8]

Considering that we found kissing nevus in glabrous and non-glabrous skin, as well as in mucosal and semi-mucosal areas, signs that lead to a clinical suspicion for malignancy should be sought. However, they are sometimes difficult to be assessed in these areas due to their multi-component pattern, containing different colors and structures, absence of structures, and blue-whitish veil.[4,5] None of the patients presented signs suggestive of melanoma.

Among the therapeutic options available in the literature, the most indicated one given the benign lesions is the expectant management (watchful waiting), with clinical and dermoscopic follow-up. Surgical excision with mucosal and/or flap grafts, postectomy, and laser therapy (Nd:YAG, alexandrite, CO_2) should be chosen, considering the patient's functional and psychological aspects.[4,5,9,10] All patients are under clinical follow-up.

The follow-up of these lesions varies in the literature. There are reports of follow-ups every three, six, and 12 months. Some authors suggest a follow-up similar to that of congenital nevi, always considering the dermoscopic pattern of the lesion.[4,5]

CONCLUSION

Knowledge of the dermoscopic patterns of the divided nevus is essential for the proper follow-up of the patient and the biopsy indication, as the sites of onset of this lesion are not so simple to approach and can lead to esthetic, functional, and, mainly, psychological impairment. ●

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Primary oral mucosal melanoma: case report

Melanoma primário de mucosa oral: relato de caso

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ABSTRACT

Oral mucosa melanoma (OMM) represents 0.2% to 8% of melanoma cases. It mainly affects the palate and gums of patients between 40 and 70 years old. It is initially asymptomatic, contributing to late diagnosis and poor prognosis. The treatment of choice consists of surgical resection, and adjuvant radiotherapy and chemotherapy may be used. We report a case in an 80-year-old male patient with primary gingival and hard palate melanoma who underwent tumor resection followed by palate reconstruction. We emphasize the importance of a complete physical examination and active search for lesions in the oral mucosa for early diagnosis.

Keywords: Melanoma; Mouth mucosa; Palate

RESUMO

O melanoma de mucosa oral (MMO) representa de 0,2 a 8% dos casos de melanoma. Acomete, principalmente, palato e gengiva de pacientes entre 40 e 70 anos. Inicialmente é assintomático, contribuindo para o diagnóstico tardio e prognóstico reservado. O tratamento de escolha consiste na ressecção cirúrgica, podendo ser utilizadas radioterapia e quimioterapia adjuvantes. Relatamos um caso em paciente de 80 anos do sexo masculino, com melanoma primário na gengiva e palato duro, que foi submetido à ressecção tumoral seguida de reconstrução de palato. Ressaltamos a importância do exame físico completo e da busca ativa por lesões na mucosa oral para diagnóstico precoce.

Palavras-chave: *Melanoma; Mucosa bucal; Palato*

Case report

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INTRODUCTION

Melanoma is the third most common type of skin cancer; however, it is uncommon in the oral mucosa.[1,2] It mainly affects individuals over 40 years,[3,4] with a slight predominance among men,[5,6] and is located preferentially on the palate and gums. The condition presents a varied morphology, initially without symptoms, which leads to a late diagnosis and poor prognosis.[7,8] The treatment of choice is surgical resection, followed or not by neck dissection, with the option of adjuvant chemotherapy or radiotherapy.[9,10]

We present a case of oral mucosal melanomas and discuss the differential diagnosis, treatment, and prognosis of these lesions.

CASE REPORT

The dentist referred an 80-year-old brown man for evaluation of an asymptomatic pigmented lesion, with four months of evolution, in the hard palate and upper region of the gingiva, on the right. The patient did not use dental prostheses and reported no drinking or smoking.

Oroscopy revealed a blackened plaque on the right hard palate, measuring approximately 1 cm, with an ulcerated area, accompanied by satellite lesions, and a blackened plaque on the right upper gingiva, measuring approximately 2.5 cm (Figures 1 and 2). Clinical examination showed no other suspicious lesions or palpable cervical lymph nodes. Computed tomography of the head, neck, and chest, abdominal ultrasound, and laboratory tests did not show significant findings. We performed an incisional biopsy, which showed an infiltrative growth neoplasm, consisting of anaplastic cells containing a large amount of melanin in the cytoplasm, with an intense degree of pleomorphism and nuclear atypia (Figure 3). The immunohistochemical profile was compatible with infiltrative malignant melanotic melanoma positive for HMB-45 and melan A (Figure 4).

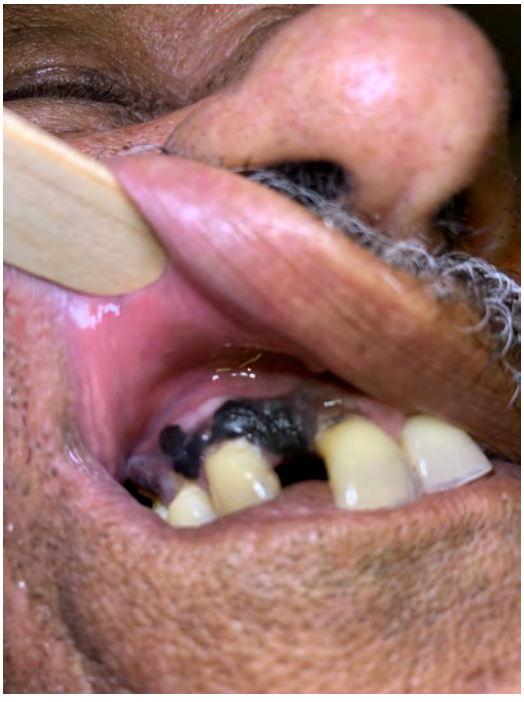

Figure 1: Macroscopic aspect of right gingiva lesion

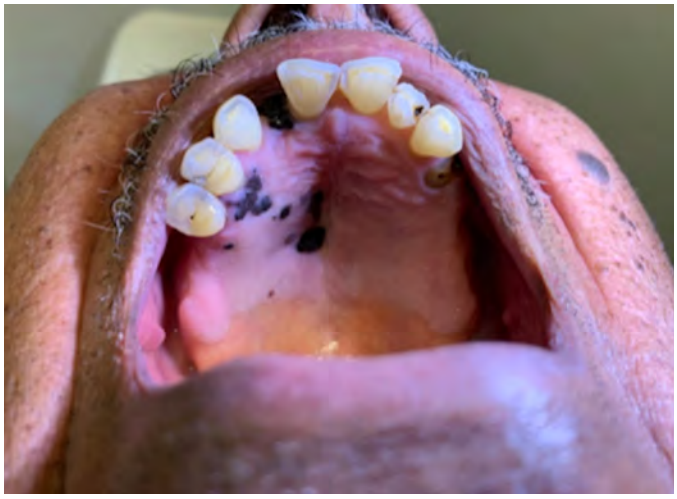

Figure 2: Macroscopic aspect of palate lesions

The patient underwent resection of the hard palate, medial upper gingiva fragment, teeth, and upper alveolar ridge on the right, followed by reconstruction of the palate using a right jugal mucosa flap (Figures 5 and 6). Histopathological examination of the surgical specimen confirmed the previous diagnosis of invasive malignant melanoma, with an extensive in situ component in the periphery of the lesion, ulceration, no perineural and angiolymphatic invasion, and surgical margins free of neoplasia. We chose not to perform cervical lymph nodes dissection and adjuvant treatment. The patient did not show signs of recurrence or dysfunction associated with the surgical procedure during a 12-month follow-up (Figure 7).

DISCUSSION

Oral mucosal melanoma (OMM) results from the uncontrolled growth of melanocytes found in the basal layer of oral mucous membranes.[1-3] It is a rare tumor, representing only 0.2% to 8.0% of all melanomas and only 0.5% of oral malignancies,[4-6] with reports of prevalence in Afro-descendants and Japanese.[7,8] The highest incidence occurs after the age of 40, between the fifth and sixth decades of life, with a slight preponderance among men.[9,10] They are located in 80% of cases in the hard palate and gingiva and 20% of cases in the oral mucosa, lips, tongue, base of the mouth, and uvula.[7,9,10] Its etiology is unknown, as it is not associated with sun exposure.[1,7,8] The condition has been linked to risk factors such as trauma, injuries from ill-fitting dentures, and exposure to alcohol, formaldehyde, and tobacco for long

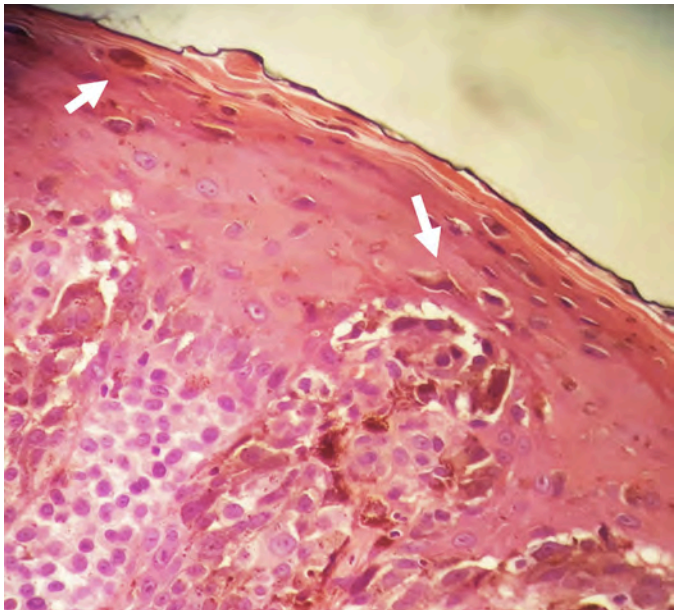

Figure 3: Neoplastic cells with evident red nucleoli. Note neoplastic cells infiltrating the epidermis (arrows)
(Hematoxylin & eosin, 400x magnification)

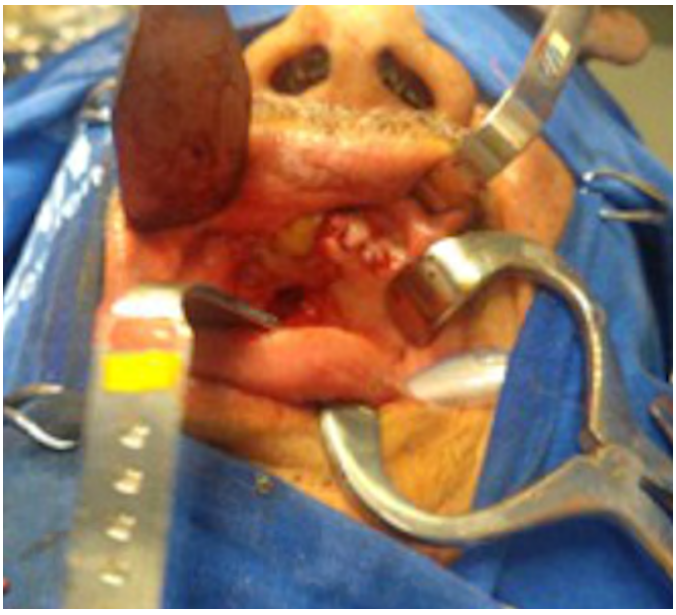

Figure 5: Intraoperative phase after tumor resection

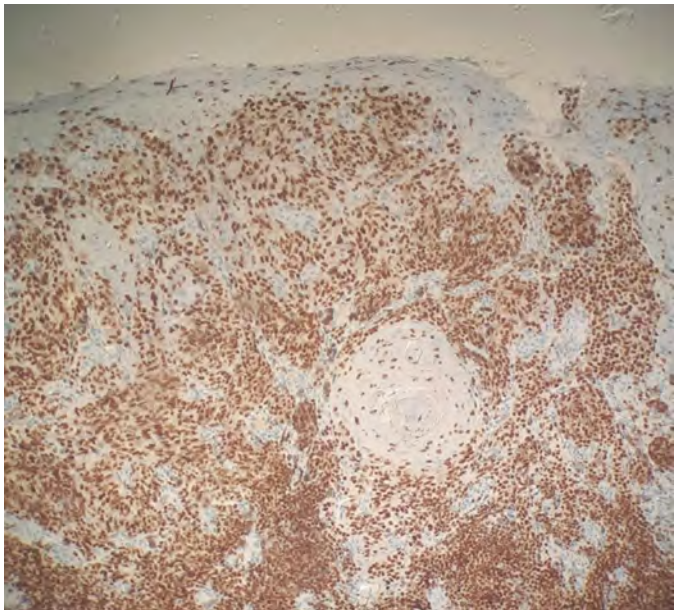

Figure 4: Neoplastic cells with cytoplasm marked with melan-A
(100x magnification)

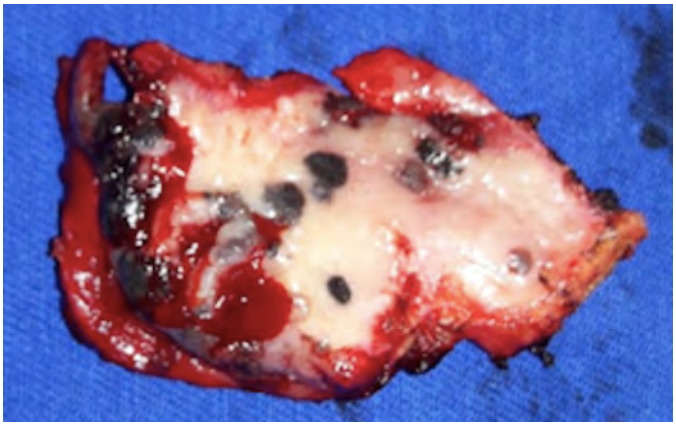

Figure 6: Surgical piece

periods.[3,4,6,10] Although most OMMs arise again, more than a third develop from benign melanocytic lesions.[1,5,8]

Initially, it presents as an asymptomatic macula or plaque that evolves with swelling, ulceration, bleeding, pain, tooth mobility, and the appearance of satellite lesions.[7-10] Its color varies in shades of black, brown, gray, purple, and red. However, a third of the lesions present no pigment.[3] It tends to recur locally and develop metastasis to lymph nodes (33%). In contrast, involvement of the lungs, brain, bones, and liver affects up to 85% of patients.[4,5] Differential diagnosis includes amalgam tattoo, melanoacanthoma, smoking-associated melanosis, post-inflammatory pigmentation, melanocytic nevus, drug-induced melanosis (such as minocycline and antimalarials), Peutz-Jeghers syndrome, Cushing's syndrome, Addison's disease, Kaposi sarcoma, and other various conditions that cause pigmentation in the oral mucosa.[1,2,8,9]

Histologically, tumor cells are characterized by the proliferation of atypical melanocytes. The evaluated parameters include the

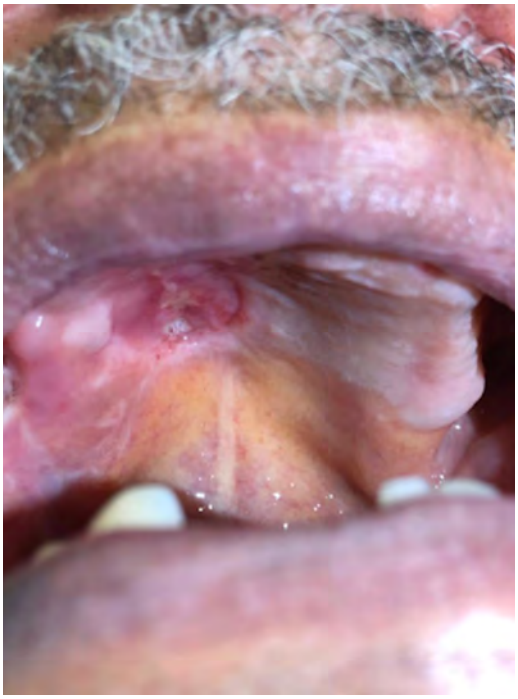

Figure 7: Postoperative result

presence or absence of melanocytes in the tumor; cell morphology (epithelial, spindle, plasmacytoid, or mixed); cellular organization (solid, alveolar, organoid, or pagetoid); presence of necrosis, perineural and perivascular invasion and depth of tumor invasion.[7,10] Due to the lack of analogous histological landmarks between the skin and oral mucosa, the diagnosis of the depth or thickness of tumors, as defined by Clark and Breslow, is not accepted in the daily practice of OMM.[4,7] Therefore, a classification based on the histopathological pattern of the tumor has been implied: melanoma in situ, limited to the epidermis and its junction with the connective tissue (15%); invasive melanomas, extending into the connective tissue (30%); and melanomas with a combined pattern between invasive and in situ (55%).[1,5,8,10] The use of immunohistochemical staining helps confirm the diagnosis.[9] The markers involved in the diagnosis of melanoma are S-100, HMB-45, melan-A, and tyrosinase.[7,8] S-100 is sensitive (97%-100%) but not specific (75%-87%); HMB-45 and melan-A are considered more specific markers.[8]

The TNM system (tumor, lymph node, and metastasis) recognizes three stages for OMM:[1,8]

- Stage I: Presence of only primary tumor (N0M0)

Level I: Melanoma in situ with no evidence of invasion or "microinvasion"

Level II: Invasion to the lamina propria

Level III: Musculoskeletal, bone, or cartilage invasion

- Stage II: Tumor with metastasis to regional lymph nodes (N1M0)

- Stage III: Tumor with distant metastasis (M1)

Currently, the best option for treatment is complete surgical resection of the lesion with 1.5 cm of surrounding healthy tissue, with or without lymph node neck dissection.[7,8,10] Some authors recommend adjuvant radiotherapy to maximize regional control.[3,4,6] Chemotherapy and immunotherapy can prevent distant metastases.[1] Careful monitoring of the patient is essential to check for recurrences.[2]

The prognosis is poor and related to advanced age, tumor extension, low resectability, amelanotic lesions, lymph node involvement, high mitotic rate of atypical melanocytes, and vascular or neural invasion. Five-year survival for OMM is around 15% to 30%.[1,6,10]

CONCLUSION

We report a primary oral mucosal melanoma case in a man who achieved therapeutic success after tumor resection and continues to be followed up in our Service to assess the recurrence or appearance of new suspicious lesions. The authors emphasize the importance of careful clinical examination for early detection of suspicious lesions, as cases of OMM are often initially asymptomatic, and early biopsy plays a fundamental role in the prognosis.

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Hot asphalt burns: case report and therapeutic review

Queimadura por asfalto: relato de caso e revisão terapêutica

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ABSTRACT

Hot asphalt burns are a health threat due to the risk of death and adhesion to tissues.

A 40-year-old man suffered first and second-degree burns by hot asphalt on 20% of the body surface area. The asphalt adhered to the skin was removed on the 4th day of the ICU stay with liquid petroleum jelly, and the burns were treated with healing gel.

Burns caused by hot asphalt are serious and represent 1.4% of hospitalized cases. They affect young people in the skin and airways by inhaling the vapors.

Removing asphalt from the skin is a major therapeutic challenge.

Keywords: Burns. Burns, Chemical. Petroleum. Accidents. Accidents, Occupational

RESUMO

As queimaduras por asfalto quente representam uma ameaça para a saúde devido ao risco de morte e adesão aos tecidos.

Paciente do sexo masculino, 40 anos, vítima de queimadura de 1° e 2° graus por asfalto quente em 20% da superfície corporal. O asfalto aderido na pele foi removido no 4º dia de UTI com vaselina líquida, e as queimaduras, tratadas com cicatrizante tópico.

As queimaduras por asfalto quente são graves e representam 1,4% dos casos hospitalizados. Acometem jovens nas regiões da pele e vias aéreas por inalação dos vapores.

Remover o asfalto da pele caracteriza-se em grande desafio terapêutico.

Palavras-chave: *Queimaduras. Queimaduras Químicas. Petróleo. Acidentes. Acidentes de Trabalho*

Case report

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INTRODUCTION

Burns result from the direct or indirect action of chemical or physical agents capable of producing large amounts of heat and causing damage to body tissues,[1-3] which characterizes them as one of the most serious traumas among the types of accidents.[2,4]

Many victims are affected by burns worldwide,[4] representing a serious public health problem,[3,4] with high rates of morbidity resulting from physical and psychological sequelae,[1-3] and mortality,[1-3,5-7] including in Brazil.[4] The causes of death are mainly due to infections and systemic repercussions in extensive cases.[1,8-10]

Burns caused by hot asphalt are rare, accounting for about 1.8% of hospitalized cases.[7,11] However, they represent a threat to the health of road pavers and roofers.[7] This is because this product is composed of hundreds of harmful chemical substances, and its handling in construction occurs at high temperatures (approximately 140 °C to 250 °C), producing hot and toxic vapors and fumes and a viscous liquid that adheres to the skin.[6,10,12,13]

Occupational injuries and accidents at the workplace involving hot asphalt are peculiar because they comprise gas inhalation poisoning and severe mucosal and skin burn[6] with adhesion of the asphalt mass,[6,10,12,13] with the risk of infection and total or partial tissue destruction.[10-12]

The initial measures in the care of individuals burned by hot asphalt should be immediate, at the accident site, with the cooling of the asphalt followed by its removal with appropriate substances to avoid worsening the burn damage and its complications.[9,10,14]

This study aims to briefly review the literature on the topic and illustrate its importance with a case report and subsequent discussion.

CASE REPORT

A 40-year-old man was a victim of burns on the face, neck, and hands after an asphalt mixture pipe explosion during a work activity in road construction. His co-workers quickly assisted him with a continuous jet of water to cool the asphalt mixture. The patient was admitted to the emergency room conscious, hypothermic, with low oxygen saturation (85%) on room air, and hemodynamically stable. He presented burns to the airways caused by inhaling the hot gases released in the explosion. He also had burns on the skin, with superficial (first degree) and partial (second degree) thickness in 17% of the body surface (8% in the head, 1% in the cervical region, 5% in the anterior trunk, and 3% in the hands), with bitumen adhered to most of these areas (Figure 1).

The patient evolved with the need for orotracheal intubation, sedation, analgesia, mechanical ventilation, parenteral hydration, according to the Parkland formula, and was referred to the intensive care unit (ICU). He presented a significant improvement in respiratory condition with progression of ventilatory parameters within four days of ICU stay. However, due to the presence of adhered bitumen, mainly on the face, sedation and analgesia interruption was suspended. As this is an unusual situation, a team doctor researched the best treatment and then, together with the nursing staff, used liquid petroleum jelly to remove the bitumen from almost 90% of the compromised surface for approximately three hours (Figure 2). The burns were then treated with a healing ointment.

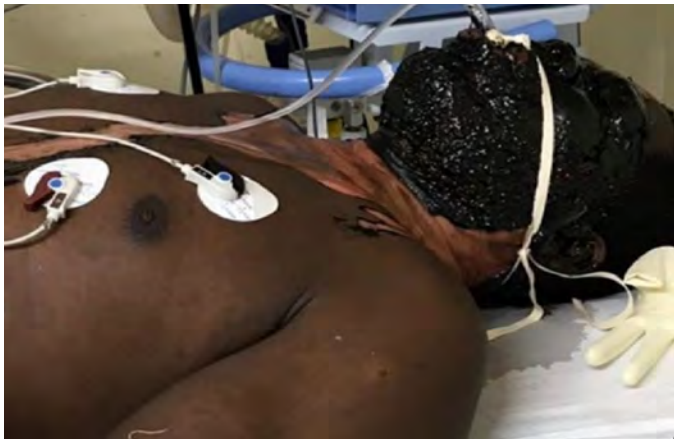

Figure 1: Mechanically ventilated patient presenting adhered bitumen plaque across the face and skin detachment in the cervical and thoracic region

Due to the delay in extubation, the patient developed ventilator-associated pneumonia (VAP), septicemia, and acute renal failure (ARF). A sepsis protocol with broad-spectrum antibiotics, volume expansion, metabolic acidosis correction, and vasoactive drugs was instituted, in addition to conservative treatment with diuretics for ARF. On the 37th day of admission, the patient was discharged from the ICU in good general condition and excellent skin healing (Figure 3).

DISCUSSION

Burns are major health threats, with approximately one million cases a year in Brazil and six million victims annually worldwide, according to a 2015 estimate.[3,4] Mortality from burns occurs in a more significant proportion in developing compared with developed countries.[3] Among the relevant causes of burns, the civil construction environment stands out, as they result in highly complex cases.[15]

Occupational injuries and accidents at the workplace in civil construction represent about 10% to 15% of all work-related accidents in Brazil, with approximately 25% of severe cases, and they are relevant causes of morbidity and mortality.[15,16] The professionals most affected in fatal cases are bricklayers (28%) and construction workers (14%), who are probably subjected to more stressful tasks due to the low level of professional qualification.[17] The leading causes of these accidents are falls (37.3%) and contact with machines and tools (16%).[16] Events associated with

Figure 2: Patient on the 4th day of hospitalization with first and second degree burns on the face after removing the bitumen with liquid vaseline

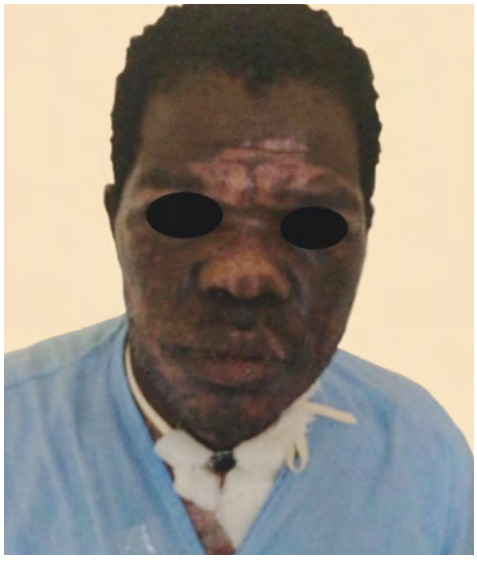

Figure 3: 37th day of hospitalization: patient showing good recovery of general condition and post-healing residual hypochromia in the central and lateral region of the face

explosions or contact with heat sources, as in the present case, are responsible for only 1% to 2% of occupational injuries in civil construction. However, in general, they are serious cases.[16,17] The profile of accidents victims at the workplace in civil construction in Brazil has a significant predominance of men (almost 100%), generally affecting young people aged between 21 and 40 years, with a mean age of 29.6 years (61.4%).[16]

Accidents caused by hot asphalt have a much higher lethality (approximately 7%) than that found in other accidents at the workplace (1% to 4%).[7,18] Among them, 91% occur due to falls or spills, 4% because of hot asphalt pipes rupture (as the case reported), and 2% for traffic accidents.[10] The most frequently affected areas are the upper limbs, followed by the head and/or face (44%), and cornea (11%), showing an average affected body surface of 13.1%.[10] The average length of hospital stay is directly related to the extent of burned body surface, age, comorbidities, inhalation injuries, and associated trauma.[4,10]

It is important to emphasize that, despite bitumen, asphalt, and tar are different substances, the literature often mixes them, and they present a difficult differentiation with similar properties.[10] They're all nonpolar polycyclic aromatic hydrocarbons (PAH), with high volatility and high handling temperature.[20] Understanding this spectrum of information allows similar approaches in emergency care situations,[10] as in the clinical case presented.

Also, occupational injuries involving hot asphalt are peculiar because they comprise gas inhalation poisoning of asphalt fumes and severe skin burns.[6] Intoxication occurs mainly due to the presence of carbon monoxide, hydrogen sulfide, and aliphatic hydrocarbons present in the substance, which can cause serious cardiovascular, respiratory, gastrointestinal, neurological, and ocular consequences.[6]

Regarding burns, which were the most prominent aspect in our report, hot asphalt presents very high temperatures at the time of accidents (approximately 140 °C to 250 °C).[6,12] Inhaling fumes and volatile gases at this temperature burns the mucous membranes of the airways Also, in extensive burns, there is a high pulmonary impairment and high risk of death,$_2$ in addition to complications caused by the hemodynamic repercussions of the fumes toxic effects[6] and the burn extension.[1]

Despite cooling quickly, the heat retained by the hot asphalt can promote burns with varying depths in contact with the skin. It undergoes a solidification process with great adhesion to the skin when cooled, making its removal challenging.[7,10,19] Therefore, it is often impossible to properly visualize the dimension of burns until entirely removing the substance.[6] Furthermore, one of the most frequent complications of this type of burn is infections resulting from loss of continuity of intact skin.[10]

Another relevant consideration to burns from hot asphalt is the long-term risk of developing subsequent neoplastic diseases since the oxidative damage alters the genetic material of the affected tissues.[12,19] Thus, the burn, through direct contact with these hydrocarbons, is a relevant carcinogen marker.[13,20]

This type of burn treatment requires a specialized and early approach to lesions to minimize the risk of complications and reduce morbidity and mortality.[14] The most relevant initial approach is the immediate cooling of the chemical through immersion in water at the time of the accident, still at the site.[6,14] This procedure is recommended as essential to prevent the hot

asphalt heat from causing tissue destruction in greater depth and adjacent regions.[6,14]

Sequentially, the patient must be taken to the hospital emergency room with advanced life support for fluid resuscitation and airway management according to the extent and location of the burn.[7] The clinical case addressed in this article required this care because it presented a burn in 17% of body surface and involvement of the face and airways. In the past, bitumen removal was performed through mechanical debridement, with undesirable results due to the healthy tissue removal and an increase in tissue exposure.[12] Currently, the chemical principle of "like dissolves like"[19] is applied, therefore, using nonpolar solvents to remove through micelle formation effectively.[7,19] Despite the few comparative studies in the literature, the most indicated solvents are vaseline, vegetable oils, butter, and antibiotic ointments.[6,10,19] Other types of chemical solvents, such as alcohol, acetone, kerosene, and gasoline, have been contraindicated in these cases because they are ineffective, irritating, and toxic.[12] The surgical approaches have been necessary in about 42% of cases.[6]

The average time of emulsification to remove the substance adhered to the skin ranged from 20 minutes to a few hours.[6,10,11] Some authors report experiences of clinical cases in which, one hour after the accident, they emulsified the asphalt mixture with an appropriate solvent for 20 minutes. Then, they could remove it without damaging the skin, followed by extubation and treatment completion.[11] Thus, it is essential to emphasize the long period during which our patient was exposed to the substance until its removal, which probably contributed to the infectious disease's complications and consequently prolonged hospitalization. It reflects the challenge of health services in dealing with this type of cases, especially due to the lack of scientific information in the literature.

The prognosis of these patients depends on age, the burn extension, and inhalation injuries. It's worse in individuals over 60 years of age, with severe burns (more than 40% of body surface) and the presence of burns in the airways.[3] To obtain a good quality of life after the accident, optimized and multidisciplinary care is necessary for the acute and late phases of the burn, thus avoiding emotional sequelae and unsightly scars.[1-4,21] The improvement of healing results after removal of asphalt depends a lot on the care with the wound, such as debridement, grafts, and healing therapies.[10]

CONCLUSION

Even with a vast road network in the country, burns caused by hot asphalt mixture are still little discussed in Brazilian and world literature, and its treatment remains undefined. This situation promotes therapeutic challenges in the healthcare system and leads in harm to patients resulting from late management, which prolongs the length of hospital stay and increases treatment costs.

Given the current scenario of increasing road paving and technology evolution, we concluded that there is an emerging need for more discussions on the subject to be fostered and published in the literature. Hot asphalt burns are a condition that is easy to diagnose, simple and inexpensive to treat, but that requires prior and specific learning from the assistant physician. Therefore, the elucidation of cases with clinical presentation, management, and evolution becomes essential for disseminating knowledge on the subject. •

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Infantile melanoma: early diagnosis by total body mapping in dysplastic nevus syndrome

Melanoma infantil: diagnóstico precoce pelo mapeamento corporal total em síndrome do nevo displásico

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ABSTRACT

Melanoma is a rare neoplasm in the pediatric population, and it is even rarer in children under 10 years of age. Total body mapping constitutes a low-cost and non-invasive method that increases diagnostic accuracy in evaluating pigmented lesions, especially in high-risk patients. We reported the case of a 9-year boy with dysplastic nevus syndrome, in which one lesion presented a subtle change (asymmetry of structures) within a 6-months follow-up. Its excision resulted in melanoma with a Breslow thickness of 1 mm and a negative sentinel lymph node. Total body mapping reduces the number of unnecessary excisions. It allows diagnosis of melanomas in early and potentially curable stages, especially in children and patients with risk factors such as dysplastic nevus syndrome. We report this case due to the rarity of the neoplasia in this age group and also to demonstrate the importance of sequential digital dermoscopy in early diagnosis of melanoma in this population.

Keywords: Dermoscopy; Melanoma; Dysplastic nevus syndrome

RESUMO

O melanoma é uma neoplasia rara na população pediátrica, sendo ainda mais rara em crianças menores de 10 anos. O mapeamento corporal total constitui método não invasivo e de baixo custo, capaz de aumentar a acurácia diagnóstica na avaliação de lesões pigmentadas, principalmente em pacientes de alto risco. Relatamos um paciente de nove anos de idade com síndrome do nevo displásico, no qual uma lesão apresentou mudança sutil (assimetria de estruturas) no seguimento de seis meses. A exérese da lesão resultou em melanoma com Breslow 1mm e linfonodo-sentinela negativo. O mapeamento corporal total reduz o número de exéreses desnecessárias e permite o diagnóstico de melanomas em estágios iniciais e potencialmente curáveis, especialmente em crianças e pacientes com fatores de risco como síndrome do nevo displásico. O caso foi reportado devido à raridade da neoplasia na faixa etária e para demonstrar a importância da dermatoscopia digital seriada no diagnóstico precoce de melanoma nessa população.

Palavras-chave: *Dermoscopia; Melanoma; Síndrome do nevo displásico*

Case Report

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INTRODUCTION

Melanoma is the second leading cause of cancer in adolescents and young adults. Its incidence significantly increases with age, but it is infrequent in children.[1]

Interactions between sun exposure, nevi development, and family history are the main determinants of melanoma development during the first decades of life.[1,2] Predisposing factors such as giant congenital melanocytic nevus, xeroderma pigmentosum (XP), or genetic mutations have been reported in rare cases of childhood melanoma.[1,2]

Early recognition is essential to prevent disease progression. Therefore, a high index of suspicion is necessary when evaluating children.[1,3] Dermoscopic examination is vital to visualize pigmented lesions' morphological characteristics and differentiate melanoma from melanocytic nevi.[3] However, early melanomas may show extremely discrete or absent signs on dermoscopy in the first exam, being only detected through morphological changes during the follow-up.[3] Thus, body mapping can detect incipient melanomas.[3]

CASE REPORT

A nine-year-old boy, white, was referred to the Dermatology Service two years ago for follow-up due to multiple melanocytic nevi. The patient denied a family or personal history of melanoma.

During the initial follow-up, dermoscopy presented nevus identity with homogeneous areas without structure, hyperpigmented, in a more centralized location (Figures 1-3). We performed exeresis, whose histopathology was compatible with a dysplastic nevus. The patient was referred to follow-up with body mapping (sequential digital dermoscopy).

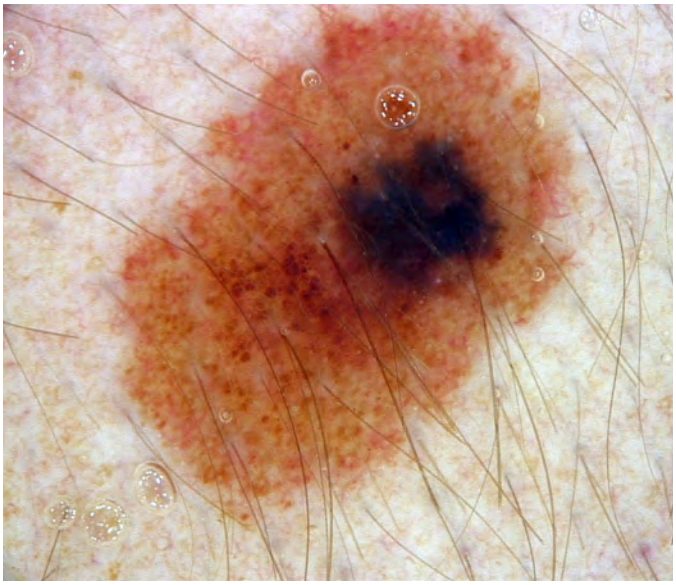

Figure 1: Dysplastic nevus syndrome. Dermoscopy of a lumbar lesion with 20x magnification. Ellipsoid lesion, with homogeneous globular pattern with central hyperpigmentation (fried-egg type)

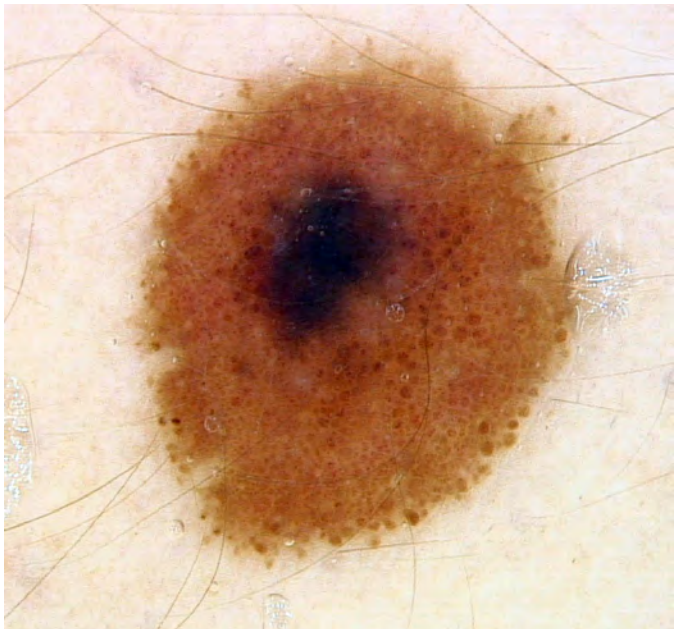

Figure 2: Dermoscopy of a thoracic lesion with 20x magnification. Circular lesion, with homogeneous globular pattern with central hyperpigmentation (fried-egg type)

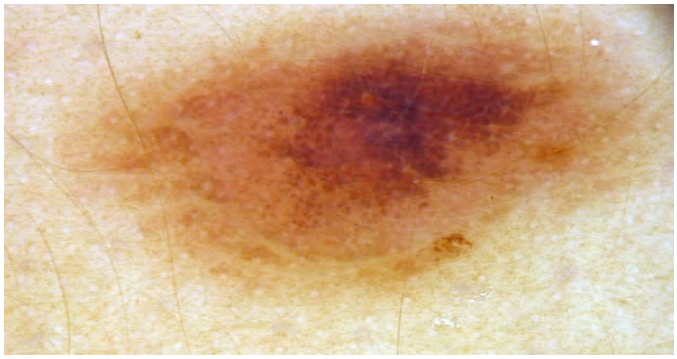

Figure 3: Dermoscopy of dorsolumbar lesion showing an ellipsoid lesion with a homogeneous, symmetrical pattern and central hyperpigmentation (20x magnification)

In the follow-up, the lesion evolved on the lower dorsum, which initially had characteristics similar to its nevus identity, with a homogeneous globular pattern and a central area without a hyperpigmented structure (Figures 4 and 5).

After six months, the lesion evidenced eccentric pigmented blur and atypical central vessels (Figure 6). We conducted the exeresis, and the histopathological examination revealed melanoma in the vertical growth phase, with a Breslow thickness of 1.0 mm, without ulceration, mitosis, or perineural invasion. We performed enlargement of the lesion margins and searched for sentinel lymph nodes, negative for neoplasia.

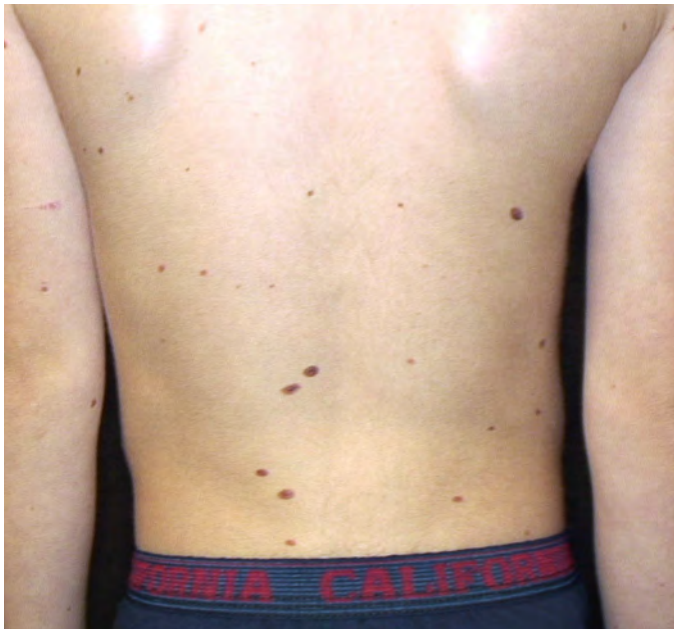

Figure 4: Panoramic photograph of the dorsal region, with no new lesions compared to the previous exam (six months ago)

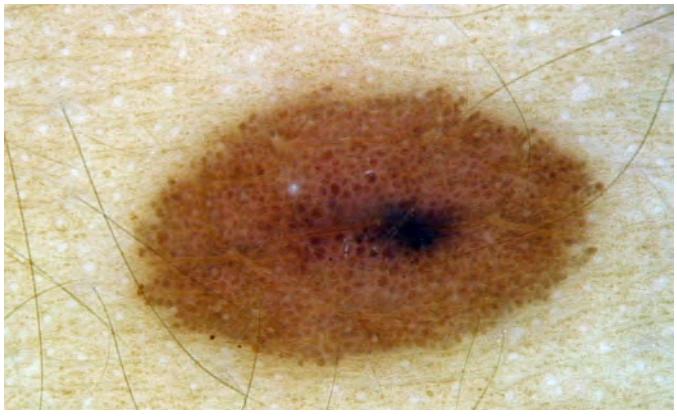

Figure 5: Dermoscopy of the lesion on lower dorsum lesion, six months before the melanoma diagnosis, showing an ellipsoid lesion, with a homogeneous globular pattern with central hyperpigmentation (fried-egg type), consistent with the patient's nevus identity (20x magnification)

DISCUSSION

Melanoma is the most common skin neoplasm in children, although it is infrequent in this population, being even rarer in children under 10 years of age. Diagnosis is often tricky and late due to its rarity in this age group.[3,4]

Compared to adults, children have thicker primary lesions, often nodular and amelanotic, with atypical vascular structures or chrysalis, evidenced only by dermoscopy, in addition to not meeting the traditional ABCDE criteria.[4,5] Furthermore, in contrast to melanoma in adults, a significant proportion of neoplasms arise from preexisting nevus (80%), and regular monitoring of lesions is essential for early diagnosis.[4,5,6]

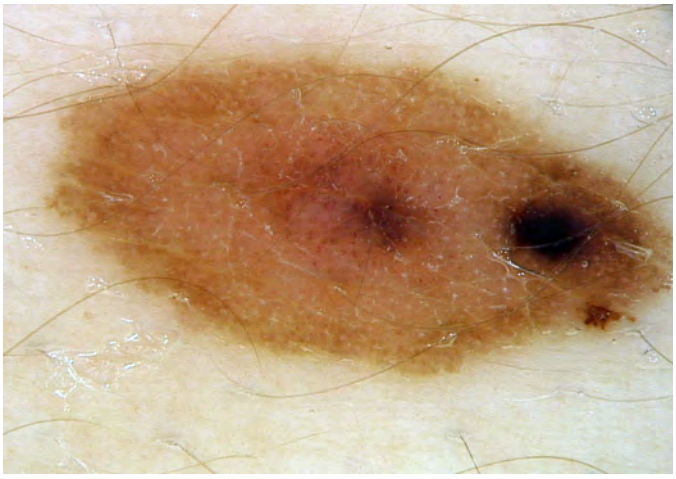

Figure 6: Melanoma in dysplastic nevus syndrome. Dermoscopy of the lesion on the lower dorsum showing an ellipsoid lesion with a homogeneous pattern and asymmetric hyperpigmentation, with a rudimentary atypical focal network, which appeared after six months of follow-up (20x magnification)

Body mapping, or sequential digital dermoscopy, presents as a low-cost and non-invasive method capable of increasing the diagnostic accuracy in assessing pigmented skin lesions.[7] The exam is based on the analysis of digital dermoscopic images sequenced throughout the time to find specific dynamic criteria that indicate a change in the biological behavior of the lesion.[7,8] Thus, body mapping reduces the number of unnecessary excisions and allows the early diagnosis of early-stage and potentially curable melanomas.[7,8]

The importance of the examination is mainly due to young patients in whom the different pigmented lesions do not present typical characteristics at initial dermoscopy.[6,7,8] Thus, when comparing the same lesion at different times, sequential digital dermoscopy allows the early detection of subtle changes that may suggest the diagnosis of melanoma.[8,9]

The nevus identity of the reported patient is composed of several dysplastic lesions with very similar or even more atypical dermoscopic characteristics than the lesion in which melanoma was diagnosed, making early diagnosis even more difficult.

In conclusion, this case confirms the importance of sequential body mapping as a fundamental tool for the early diagnosis of incipient melanoma in this population. ●

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Reconstruction of a full-thickness alar defect using a nasolabial flap combined with hinge flap

Reconstrução de defeito de espessura total em asa nasal utilizando retalho de transposição do sulco nasogeniano combinado com retalho em dobradiça

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ABSTRACT

The nasal region is a frequent site of keratinocyte carcinomas. Its peculiar anatomy, contour, and three-dimensionality make surgical repair challenging. Eventually, in situations of greater complexity, a single technique may not be sufficient to restore the original anatomy, requiring the association of methods. This article describes a strategy for reconstructing a full-thickness alar defect, including the nasal margin, based on the combination of a nasolabial transposition flap with a hinge flap. It is a safe procedure, dependent on the mobilization of local tissue and performed in a single surgical procedure.

Keywords: Surgical flaps. Nose neoplasms. Skin neoplasms. Mohs surgery. Carcinoma, basal cell

RESUMO

A região nasal é local frequente de carcinomas queratinocíticos, e sua anatomia, seu relevo e sua tridimensionalidade peculiares tornam o reparo cirúrgico desafiador. Eventualmente, em situações de maior complexidade, uma única técnica pode não ser suficiente para a restauração da anatomia original, sendo necessária a associação de métodos. Neste artigo, descrevemos uma estratégia para reconstrução de defeito de espessura total em asa nasal, incluindo margem nasal, a partir da combinação de retalho de transposição do sulco nasogeniano com retalho em dobradiça. Trata-se de um procedimento seguro, dependente da mobilização de tecido local e realizado em um único tempo cirúrgico.

Palavras-chave: *Retalhos cirúrgicos. Neoplasias nasais. Neoplasias cutâneas. Cirurgia de Mohs. Carcinoma basocelular*

Case report

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INTRODUCTION

The nasal region is a frequent site of keratinocyte carcinomas. The nose's peculiar anatomy, contour, and three-dimensionality make surgical repair a challenge. The treatment aims to achieve the oncological cure with maximum functional preservation and good aesthetic result since unsightly scars and post-operative deformities can cause psychological impact. The choice of the method for closing the surgical defect will depend on its size and location. Occasionally, in complex scenarios, associating techniques may be necessary to restore the original anatomy.[1,2] In this article, we report the single-stage reconstruction of a full-thickness nasal alar defect, including the nasal margin, combining two techniques: the nasolabial transposition flap and the hinge flap.

CASE REPORT

A 61-year-old woman presented an erythematous plaque, depressed, poorly defined, and infiltrated in the left nasal wing, measuring 0.5 cm x 0.5 cm. The lesion was adjacent to a scar resulting from surgery to remove basal cell carcinoma (BCC), unspecified subtype, in the nasal wing 14 years earlier, approached by conventional technique with bilobed flap closure. Histopathological examination, obtained by incisional biopsy, showed infiltrative BCC with associated perineural invasion. Considering the possibility it was a recurrence, in addition to the aggressive histological subtype, perineural invasion, and high-risk location, we chose the treatment according to the Mohs micrographic surgery (MMS) technique.

The lesion was submitted to MMS, under local anesthesia, with free surgical margins in the second stage, resulting in a full-thickness surgical defect in the left nasal wing, including the nasal margin (Figure 1). Given the complexity and dimensions of the defect, we repaired the lesion combining two techniques: the nasolabial transposition flap, to recompose the nasal roof, and the hinge flap, to reconstruct the nasal floor. For the hinge flap, the Burow triangle provided the "dog ear", formed during the execution of the nasolabial transposition flap. This triangle was incised superiorly to the defect, preserving a deep pedicle in its distal portion. The area that would be neglected was de-epithelialized, and the pedicle was folded back to form the nasal lining. Then, the nasolabial transposition flap was incised according to the usual technique and positioned over the hinge flap, creating the external coverage of the nasal wing. On the nasal margin, both flaps were sutured edge-to-edge (Figure 2).

The patient presented a good postoperative evolution, with satisfactory outcomes from the functional and aesthetic perspectives.

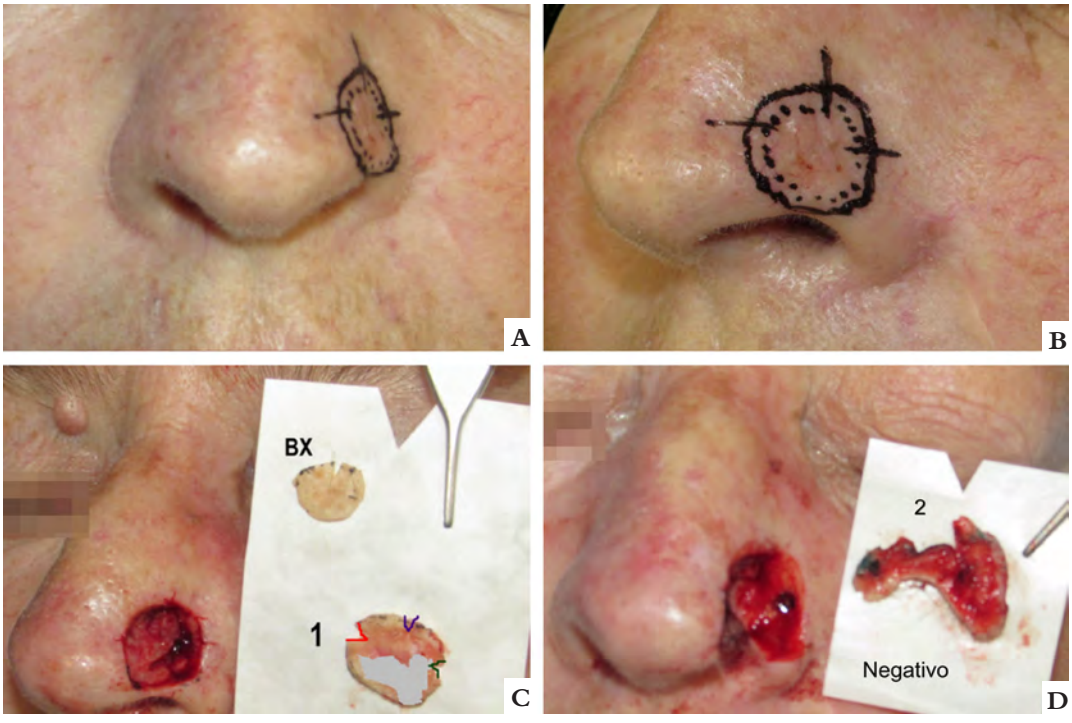

FIGURE 1: A and **B** - Demarcated lesion with dermoscopic aid in the left nasal wing. Marking of 2 mm margin and nicks; **C** - Surgical defect after removing the specimen with a small margin in the first stage, presenting residual tumor; **D** - Final surgical defect, full-thickness, with free margins in the second surgical stage

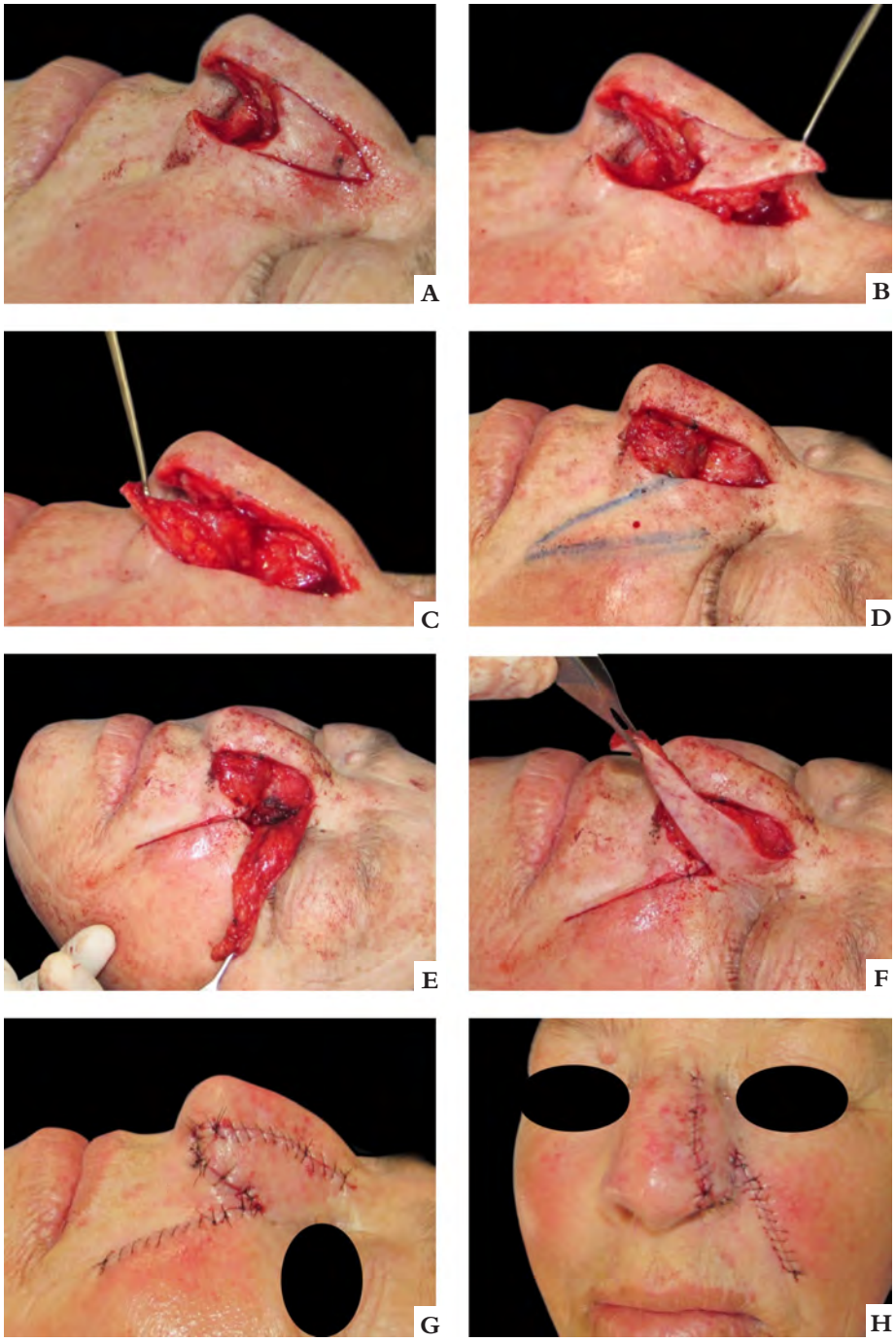

Figura 2: A - Incision of the Burrow triangle, superior to the surgical defect, in a neglected area, with the movement of the transposition flap of the nasogenian sulcus;
B - Detachment of the triangle, maintaining a deep distal pedicle;
C - Triangle hinged to form the nasal floor;
D - After positioning the triangle and suturing the adjacent tissues, the nasolabial transposition flap is programmed;
E - The flap is incised following the nasolabial fold. After releasing the deep planes, the secondary defect is closed by suture planes;
F - Transposition movement of the flap over the nasal floor, created from the hinge flap;
G - After suturing the adjacent tissues, the flap length is corrected and, at the level of the nasal margin, its distal portions were sutured edge-to-edge;
H - Immediate postoperative

DISCUSSION

High-risk keratinocyte tumors, as described in the case, are ideally addressed by MMS. The method allows an assessment of the surgical margins close to 100%, showing higher cure rates and lower recurrence rates when compared to the conventional technique, which uses sample analysis. Also, it provides the preservation of healthy tissue, an essential factor in approaching noble areas.[3,4] However, even when achieving maximum tissue conservation, reconstruction of the nasal region remains challenging. It becomes even more complicated in extensive or complex cases, such as the one reported, where the tumor excision resulted in a full-thickness defect in the nasal wing involving the nasal margin.

Repair of full-thickness nasal defects should include remaking of skin coverage, inner lining, and structural support as

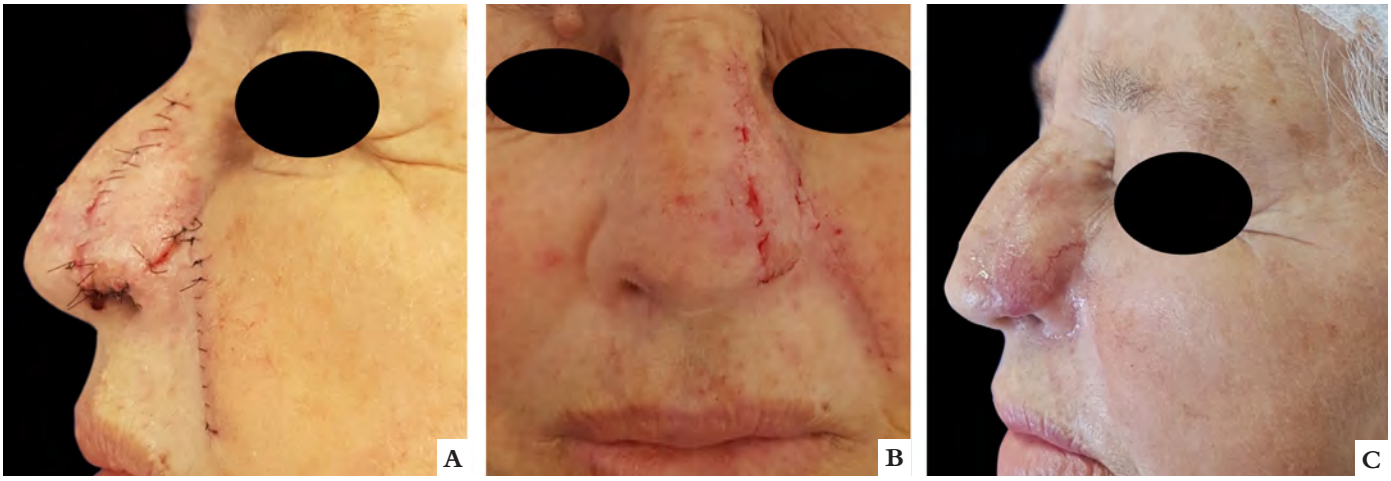

Figura 3: A and **B -** Clinical aspect on the seventh postoperative day, with removal of the stitches. C) Clinical aspect on the fourth postoperative week

needed.[5,6] Failure to provide adequate mucosal support in more significant defects can lead to scar contraction and/or flaws in overlapping flaps or grafts structure, making this step the most critical of the procedure.

Currently, the literature describes several techniques to repair minor defects involving the mucosa, such as the hinge flap, frontal paramedian flap (FPF), full-thickness skin graft (FTSG), and bipedicled vestibular advancement flap. In cases of more extensive involvement, FPF, FTSG with an overlapping FPF, or intranasal flaps (septal mucoperichondrial hinge flap, composite septal chondromucosal flap) are alternatives. Intranasal flaps must be performed under sedation or general anesthesia. However, the other options mentioned can be successfully implemented under local anesthesia in selected cases.[7]

Most procedures include cartilage graft to allow tissue support and prevent nasal valve movement during inspiration. Nevertheless, its use is not mandatory, as in the case used in this report. The hinge flap, with its distal portion sutured to the remaining tissues and folded against the transposition flap to make the nasal fold, promotes an adequate tent effect, allowing free air passage through the nostrils. The tissue layout, forming a "sandwich" by combining the hinge flap with the nasolabial transposition flap to cover the skin, promoted adequate structural rigidity, preventing its collapse during inspiration.[8,9]

Spear et al. described a flap option in 1987, and more recently, Cook published it in detail, which allows reconstruction without cartilage graft. Although it was initially described as a one-time reconstruction, it may require a second surgery for refinement due to tissue thickness that compromises aesthetics and also affects functionality, as narrowing of the nostril impairs breathing.[8,1]

It is essential to emphasize that the hinge flap technique requires a meticulous examination of the donor area. The region must have the least possible actinic damage to avoid neoplasm development in the future since, when being hit to form the nasal floor, it will occupy a complex place to assess and follow-up. Also, it is fundamental to ensure that the margins do not present residual neoplasia not to transfer tumor tissue into the nasal cavity.[5] The approach using the MMS technique, as in the case described, is more likely to achieve this result.

We believe that the reported flap combination offers advantages over other available surgical techniques, including execution in a single surgical procedure, performance under local anesthesia, lower risk of necrosis than skin graft, less bleeding than flaps from the nasal cavity, and relative skin preservation. It saves the tissue reservoir of the forehead, which would be used in the FPF.

CONCLUSION

The combination of the nasolabial transposition flap and the hinge flap represents a good option for reconstructing full-thickness alar defects, including those affecting the nasal margin, with satisfactory aesthetic and functional outcomes. It is a safe method, dependent on the mobilization of local tissue for its execution, and performed in a single surgical time, thus reducing the costs and morbidity inherent to additional procedures. ●

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East-west advancement flap: a useful tool to reconstruct nasal tip defects

Retalho leste-oeste: uma ferramenta útil para reconstruir defeitos na ponta nasal

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ABSTRACT

The reconstruction of nasal defects secondary to non-melanoma skin cancer represents a surgical challenge, especially in the nasal tip, due to its limited local laxity and possible asymmetries. There are multiple techniques to perform this closure, but most are flaps from distant locations that can lead to less aesthetic results. We present two cases of basal cell carcinoma on the nasal tip, where reconstruction with the east-west advancement flap was performed after tumor excision, with a modification of the flap in one of the patients, obtaining a good structural and aesthetic result.

Keywords: Surgical flaps; Carcinoma, basal cell; Nose; Dermatologic surgical procedures

RESUMO

A reconstrução de defeitos nasais secundários ao câncer de pele não melanoma representa um desafio cirúrgico, especialmente na ponta nasal, pela sua limitada frouxidão local e possíveis assimetrias. Existem múltiplas técnicas para realizar esse fechamento, mas a maioria são retalhos de locais distantes que podem levar a resultados menos estéticos. Apresentamos dois casos de pacientes masculinos com carcinoma basocelular na ponta nasal, onde foi feita uma reconstrução com o retalho leste-oeste após exérese do tumor, com uma modificação no retalho em um dos pacientes, obtendo-se um bom resultado estrutural e estético.

Palavras-chave: *Retalhos cirúrgicos; Carcinoma basocelular; Nariz; Procedimentos cirúrgicos dermatológicos*

Case report

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INTRODUCTION

The nose is one of the most common sites for skin cancer, representing a surgical challenge because of its limited local laxity, especially on its tip. It often requires reconstruction with flaps from distant locations, leading to esthetic problems regarding texture, skin color, prominent and visible scars, and possible impairment of the anatomy of the nasal wings' edges. The east-west flap is a horizontal advancement flap, useful for small to medium-sized defects. It is easy to design and execute, with little tissue movement and excellent esthetic results, preserving the nasal architecture and masking the suture lines.[1,2] We present two cases where this flap was successfully performed, with a modification in one of the patients' flaps.

CASE REPORT 1

A 65-year-old man with controlled arterial hypertension consulted the dermatological surgery service due to a nodular basal cell carcinoma on the nasal tip, confirmed by biopsy, with two years of evolution. The tumor measured 1.3 x 1.0 cm, and it was located on the left side of the nasal tip, close to the free edge of the nasal wing (Figure 1). We performed the tumor excision with frozen-section control of surgical margins and repair with an east-west advancement flap.

Regarding the surgical approach, the first step was marking the tumor with a 4 mm margin. Subsequently, we designed the flap with two triangles: the first superior triangle above the defect, and the second inferior one in the nasal midline, in the middle of the columella. After tumescent anesthesia and excision of the lesion, intraoperative frozen section confirmed that the margins were free. Afterward, we removed both triangles and detached the flap. Through a horizontal advancement, the tissue was moved from the nasal tip to the left lateral region of the defect, and the flap was synthesized using a subdermal suture with 5.0 absorbable suture threads and simple stitches on the surface with 5.0 nylon (Figure 2). The sutures were removed within a week, with an excellent esthetic outcome (Figure 3).

CASE REPORT 2

A 57-year-old man without comorbidities was diagnosed with nodular basal cell carcinoma in the nasal supratip region with a slight deviation to the right side (Figure 4). The tumor, measuring 1.0 x 0.9 cm, was excised with frozen-section control of surgical margins and closure with an east-west advancement flap.

We chose a surgical approach similar to the first patient; however, we modified the flap design. In this case, the first tri-

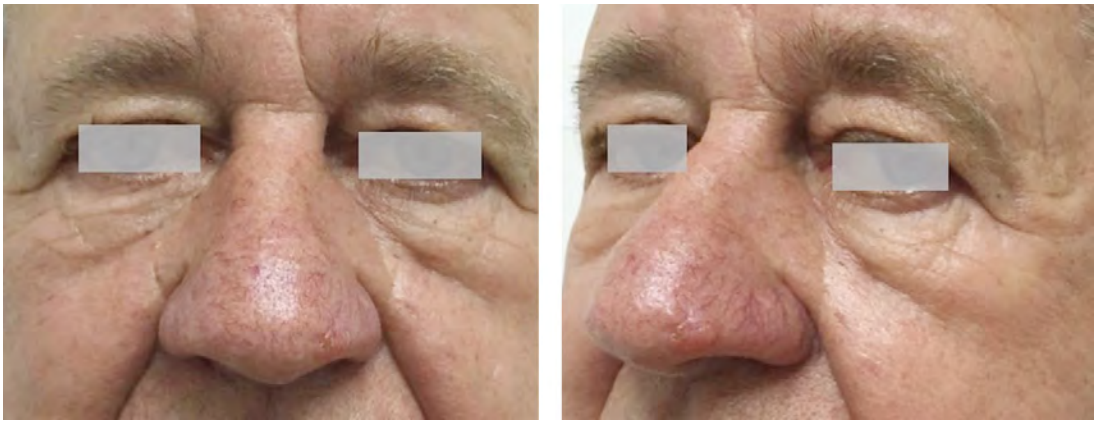

Figure 1: Patient 1. Basal cell carcinoma on the nasal tip on the left side, near the nasal wing

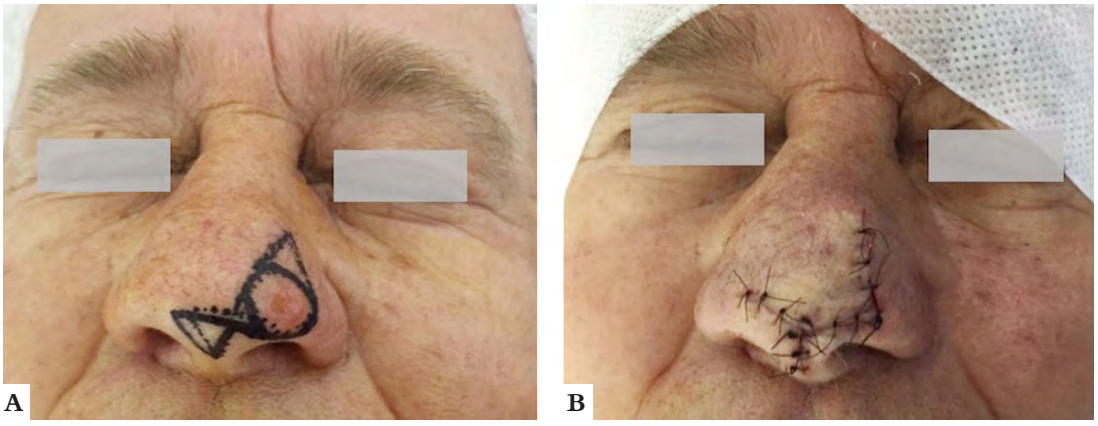

Figure 2: Patient 1.
A - Tumor demarcation and east-west advancement flap design.
B - Immediate results after surgery

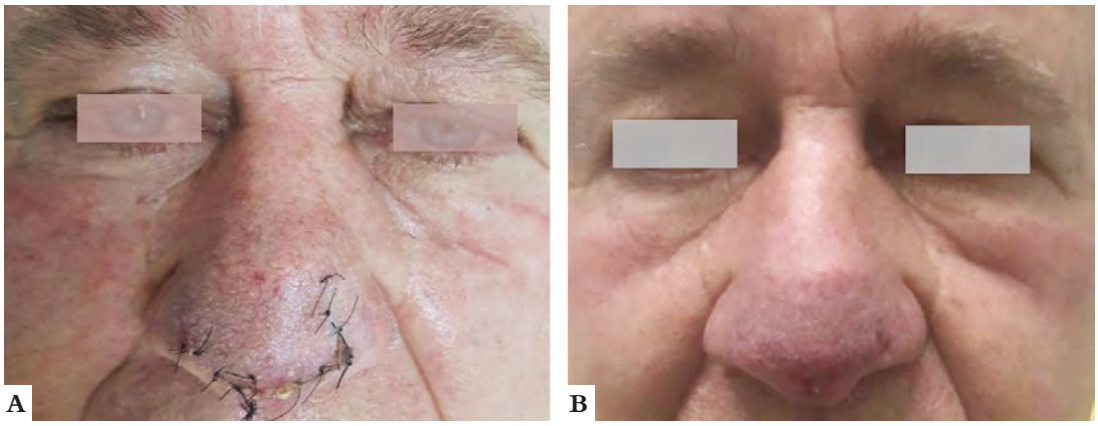

Figure 3: Patient 1.
A - Results one week after surgery with sutures.
B - Without the sutures

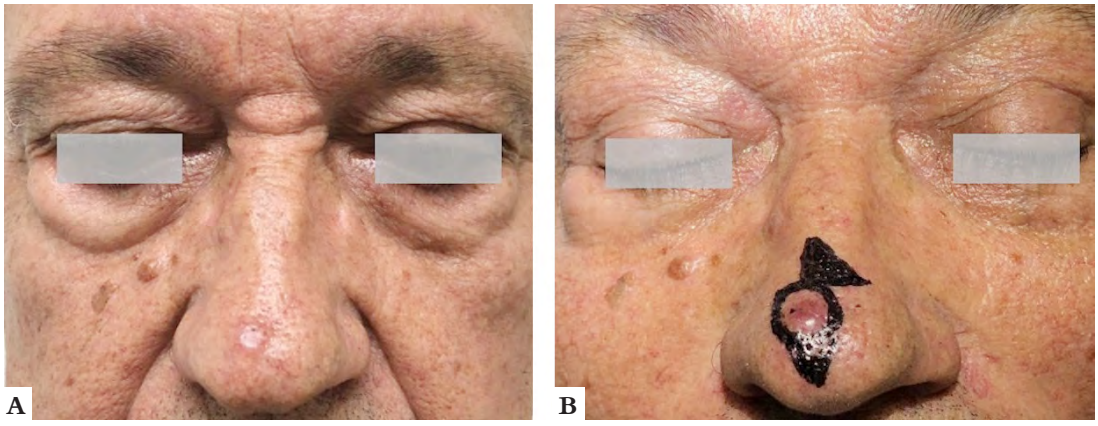

Figure 4: Patient 2.
A - Basal cell carcinoma on the nasal tip.
B - Tumor demarcation and modified east-west advancement flap design

angle was designed on the left side of the defect, starting at the top, and the second inferior one was drawn below, in the nasal midline. After excising the tumor, we removed both triangles with a good detachment, moving the tissues horizontally and bilaterally from the lateral part to the middle of the nasal tip. The defect was closed by tissue synthesis, like in the previous case (Figure 5). The postoperative period, with three months of follow-up, showed an excellent outcome (Figure 6).

DISCUSSION

The east-west flap consists of a horizontal advancement movement. Perry Robins described it, and it uses Burow's triangles to close defects.[1,2] The Burow's triangle advancement flap are half of an A-T advancement flap (also named O-T flap). Some of its advantages are having a pedicle with scarce tissue reserves and being used in challenging areas such as those close to free edges.[3] This condition was evident in the first case, where the defect was very close to the free edge of the left nasal wing. This type of reconstruction prevents its deformity.

In addition to its use in the nasal tip, the approach with Burow's triangles can be performed in other areas such as the nasal ala, upper lip, malar region near the orbital rim (named "J-plasty" by Kouba and Miller), forehead, and temple, among others.[2,3,4]

However, the significance of this flap for nasal tip defects links to the high frequency of skin cancer in this topography, cutaneous tissue difficult mobilization due to its anatomical characteristics, and defects in the center of the face that can radically change the individual's facial and aesthetic characteristics.[1,2,5]

Regarding the making of the flap, the first Burow's triangle (superior) is designed over the surgical defect, with its base tangent to the upper portion of the defect and its vertex towards the nasal dorsum. The second triangle (inferior) is designed in the nasal midline, in the middle of the columella, with its vertex pointing to the lip and its base tangent to a horizontal line drawn from the lower portion of the tumor (Figure 7). This lower triangle is designed medially, so the flap is moved towards a cosmetically more advantageous area.[1,2,6]

In the second case, the flap was adapted due to the location of the basal cell carcinoma. The flap was designed with a triangle inferior to the defect and another superior triangle on the left side due to the tumor's sight deviation tumor to the right side. Thus, the east-west advancement flap can be modified, and its triangles repositioned according to the tumor's position on the nasal tip.

This type of flap is beneficial to repair minor to medium-sized defects (<1.5 cm in diameter) on the nasal tip or

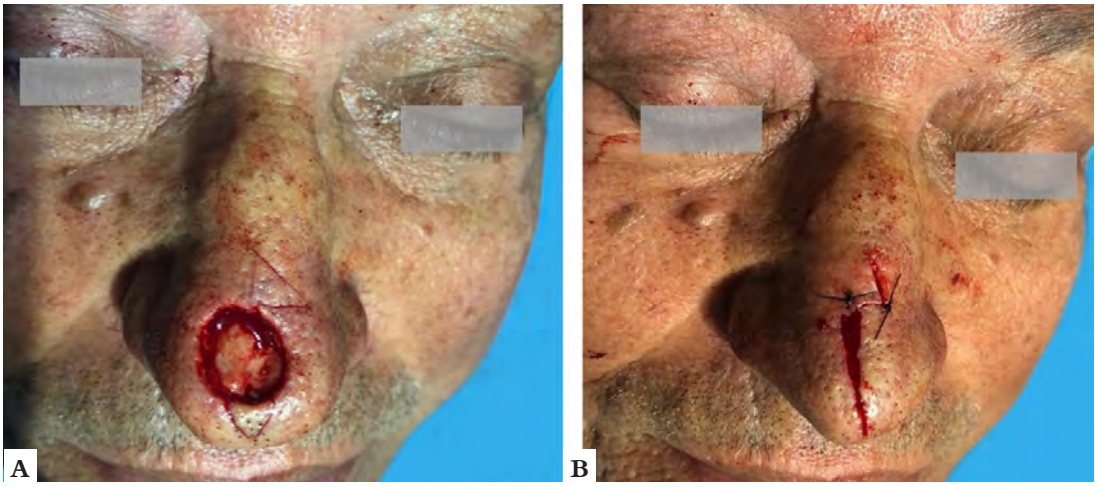

Figure 5: Patient 2.
A - Defect after tumor removal.
B - Key points to approximate the flap

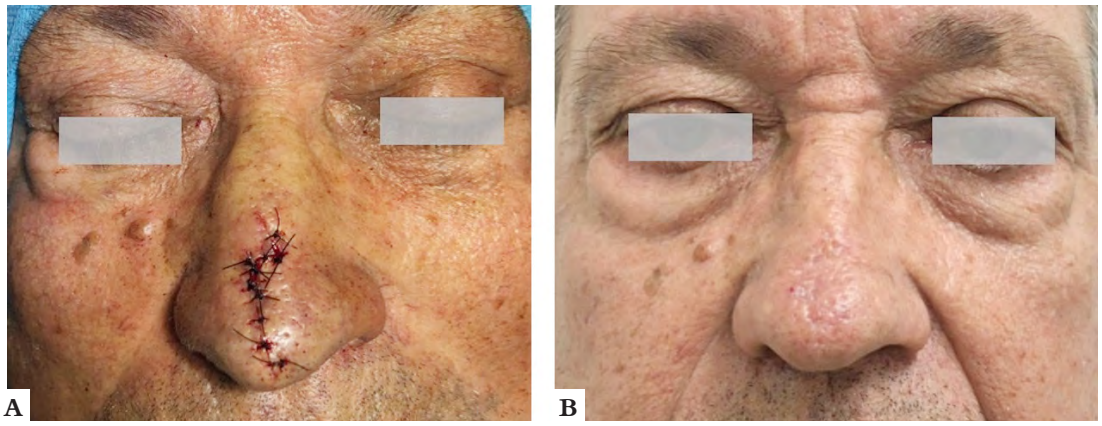

Figure 6: Patient 2.
A - Immediate results after surgery.
B - After three months of follow-up

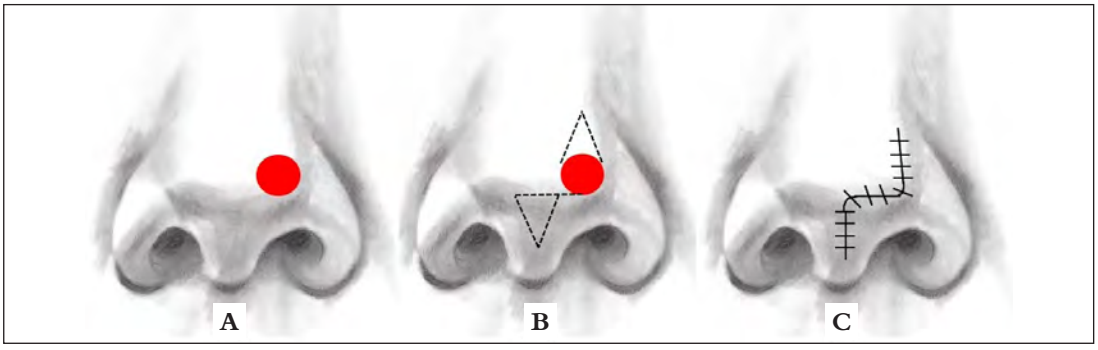

Figure 7:
A - Defect on the nasal tip.
B - East-west advancement flap design, with a Burow's triangle (superior) over the surgical defect and a second triangle (inferior) in the nasal midline, in the middle of the columella.
C - Closure with sutures

dorsum laterally to the nasal supratip, as in the case of the two patients. Its benefits are keeping the reconstruction in the same nasal subunit, preserving the skin's color and texture; excellent vascular supply through the large pedicle, with a lower risk of necrosis; enabling reconstructions without geometric or architectural distortion; not shortening or twisting the nose and not deforming the nasal wing free edge; good camouflage of the suture stitches in the vertical and horizontal axes of the nose.

The advantage of good healing in the region should also be highlighted, as connective tissue constitutes most of the nasal structure, which is rich in sebaceous glands.[1,2,5,6] Both cases evidenced all these benefits, with great esthetic result at one week and three months after surgery, respectively.

However, this study has limitations, such as wide defects, larger than 1.5 cm, because triangles can become very extensive, causing locoregional deformations. Also, the nose size

influences the technique choice, as wider noses carry larger defects, while smaller noses may require movement of distant lateral tissue, resulting in a tight nose appearance. [1,2,6]

CONCLUSION

The east-west advancement flap is an aesthetically excellent repair for small to medium-sized skin cancer defects on the nasal tip. In addition to being easy to design and execute, it requires little tissue movement, hides the suture lines well, maintains the color and texture of the nasal subunit skin, has a large pedicle reducing the risk of necrosis, and does not cause nose distortion. All of these benefits are critical because any defect in this area can seriously affect individual facial features. In well-selected cases, the result of this type of horizontal advancement flap may be superior to the rotation flap, which has long incisions that are difficult to disguise, or the transposition flap, which can cause tissue distortion. ●

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Retroauricular flap: case report

Retalho retroauricular: um relato de caso

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ABSTRACT

Basal cell carcinoma (BCC) can affect the auricular region in several locations and sizes, with or without cartilage involvement. Sometimes resections are small and reconstructions are simple. Other times, when the lesions are more extensive, reconstructions are more complex, considering the limited amount of skin in the area and the peculiarity of the structures involved. We report a case of a retroauricular flap staged in two stages, after the excision of a BCC on the posterior face of the auricle, with partial involvement of the cartilage, showing a great aesthetic and functional result both in the recipient and donor area.

Keywords: Carcinoma, basal cell; Surgical flaps; Skin neoplasms; Ear neoplasms; Rotation

RESUMO

O carcinoma basocelular (CBC) pode acometer a região auricular em diversas localizações e tamanhos variados, com ou sem comprometimento de cartilagem. Algumas vezes, as ressecções são pequenas, e as reconstruções são simples. Outras vezes, em lesões maiores, as reconstruções são mais complexas, considerando-se a restrita quantidade de pele do local e a peculiaridade das estruturas envolvidas. Relatamos o caso de um retalho retroauricular estagiado em dois tempos, após a exérese de um CBC na face posterior do pavilhão auricular direito com comprometimento parcial da cartilagem, evoluindo com ótimo resultado estético e funcional, tanto do pavilhão auricular quanto da área doadora.

Palavras-chave: *Carcinoma basocelular; Retalhos cirúrgicos; Neoplasias cutâneas; Pavilhão auricular; Rotação*

Case report

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INTRODUCTION

Basal cell carcinoma (BCC) is a malignant neoplasm that mostly affects fair-skinned individuals, accounting for 70% of skin tumors.[1,2] It occurs mainly on skin exposed to sunlight and is characterized by a high potential for local invasion and low metastatic risk.[3,4,5]

The auricle can be affected by this neoplastic lesion, which must be surgically removed, especially considering its local destructive potential. The reconstruction is proportional to the size of the lesion and the structures involved, ranging from a simple skin fusiform excision or a skin and cartilage wedge resection to the reconstruction of the entire auricle from cartilage grafting and various operative steps.[5,6]

The anatomy of the ear is quite complex, requiring detailed anatomical knowledge for a good surgical result. Its outer region comprises the auditory meatus and auricle, formed by elastic cartilage and covered by thin skin. They present scarce vascularization and are connected to the perichondrium.[1,6]

CASE REPORT

A 67-year-old man presented an ulcerated and bleeding lesion with raised edges on the posterior face of the right auricle, starting two years ago and increasing progressively. Upon examination, the lesion presented 5 cm in the craniocaudal and 2 cm in the latero-lateral direction, and hardening of the auricle's consistency, suggesting the possibility of cartilage involvement.

The first surgery was performed under general anesthesia to excise the lesion. We conduct the removal with 0.5 cm safety margins on the sides, for the entire thickness of the skin with perichondrium, and partially for the full cartilage length. The frozen section pathology showed all margins free of neoplasia (Figure 1).

We proposed a skin flap in the retroauricular region to cover the defect, measuring approximately 4 cm x 2 cm, with the longest horizontal axis. It was elevated and sutured in the recipient area, respecting a skin island where the retroauricular sulcus resided. Its edges were sutured together, forming a tunnel. The flap remained in this condition for 21 days (Figures 2 and 3).

After this period, the flap was released from its pedicle, and the skin tunnel of the retroauricular sulcus was undone (Figure 4). Thus, the flap was wholly sutured in the recipient area, completing the defect closure (Figure 5). The donor area was closed using a rotation flap, 5 cm in length (Figures 6 and 7). Both flaps evolved with excellent perfusion (Figure 8).

DISCUSSION

Basal cell and squamous cell carcinoma are malignant neoplasms formed from keratinocytes, called "non-melanoma skin cancer". They are the most incident neoplasms, with values still on the rise. Male gender and older age are independent risk factors for developing BCC. Intense and intermittent exposure to solar radiation is associated with BCC development due to mutagenesis caused by ultraviolet radiation, which is exacerbated in individuals with fair skin, red or blond hair, and light eyes.[3,7,8,17,18,19]

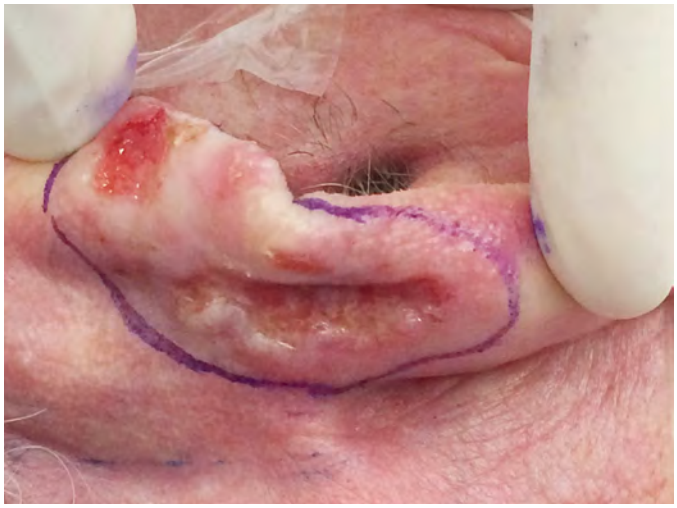

Figure 1: Preoperative evaluation and demarcation of the safety margin

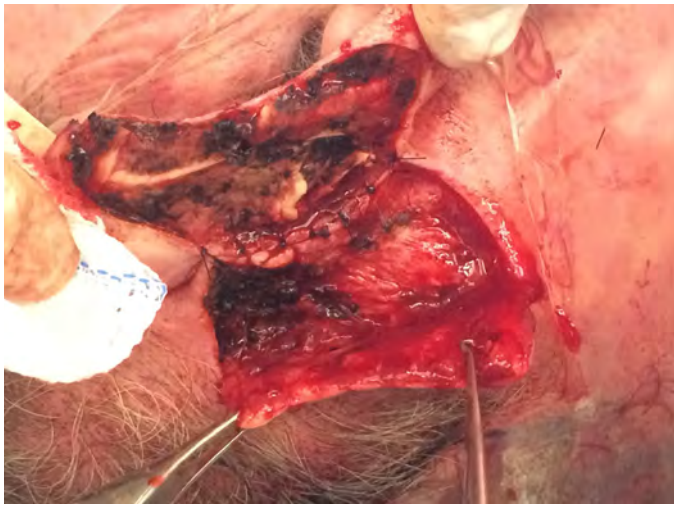

Figure 2: Lesion's resection, including the entire skin's thickness, the perichondrium, and the affected cartilage. Retroauricular flap's elevation and skin island's synthesis in the retroauricular sulcus

The most common clinical presentation of BCC is a pearly papule or nodule with telangiectasias and raised borders. In some cases, crusts or central ulceration may appear. Patients may complain of a non-healing, sometimes bleeding, asymptomatic, or itchy wound. Biopsy of the site is the standard procedure for diagnosing BCC. Some lesions may exhibit more than one histopathological pattern, and the nodular and micronodular forms are the most common. Morpheaform and infiltrative subtypes and lesions with micronodular or basosquamous histopathological changes are more aggressive variants.[3,7,17,18]

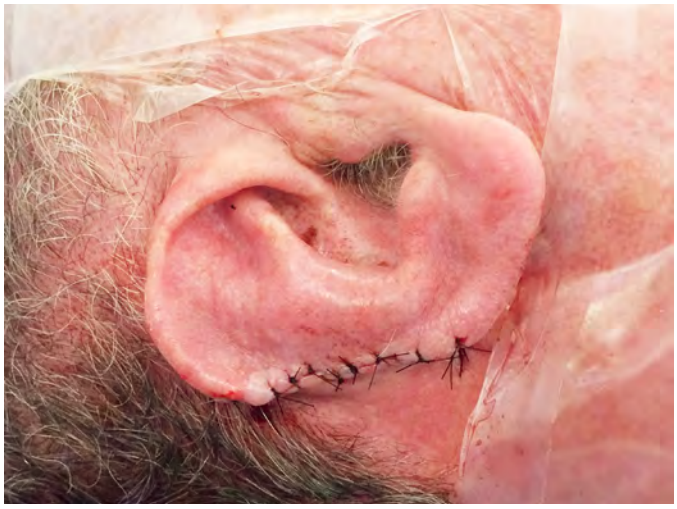

Figure 3: Suture of the interpolation flap in the lateral edge of the ear helix

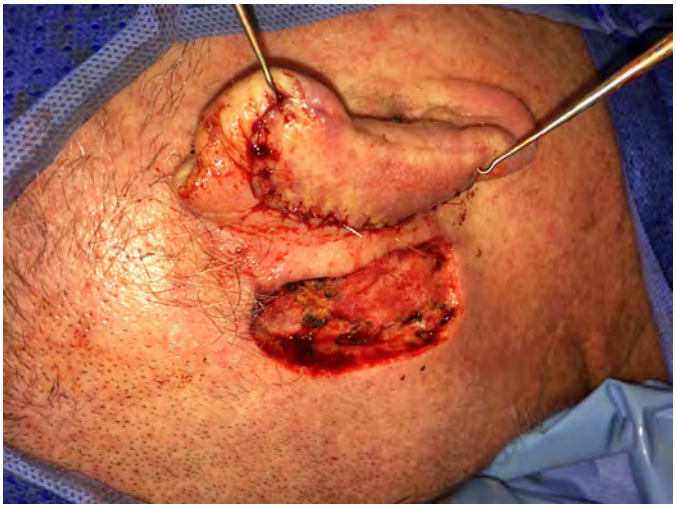

Figure 5: Complete closure of the primary defect and exposure of the donor area

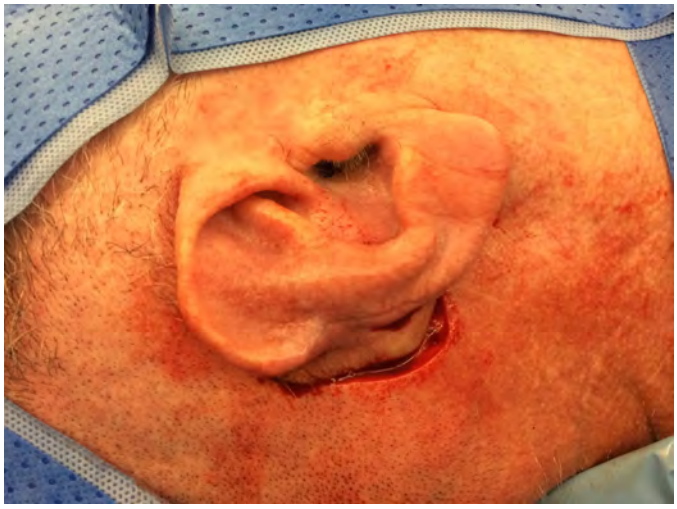

Figure 4: Re-approach after 21 days and release of the pedicle

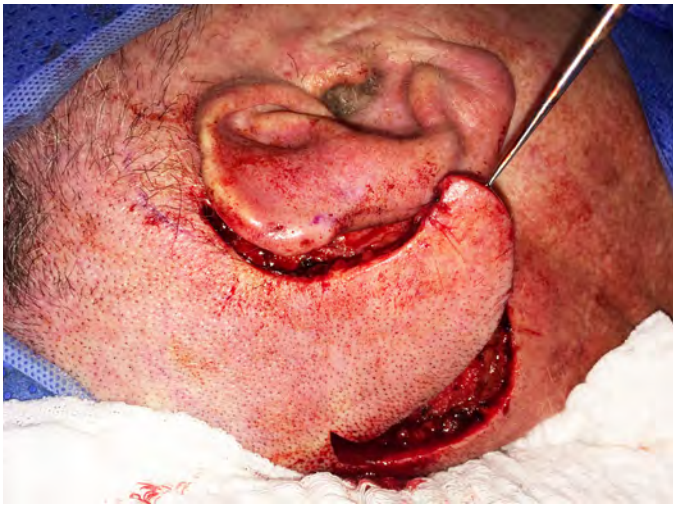

Figure 6: Rotation flap for closing the donor area

While most BCCs grow indolently concerning local invasion, a small portion progresses to locally advanced and metastatic tumors, usually due to neglect.[7,17,18]

Defects related to skin cancer represent one of the most common reasons for ear reconstruction surgery. The rotation flap is an alternative to the primary closure since the latter can deform the auricle. [6,9,20,21]

The option of reconstructing the auricle with the staged retroauricular flap (SRF) is based, above all, on the abundant blood supply at this site, coming from the posterior auricular, superficial temporal, and occipital arteries. We agree with this hypothesis because there is an extensive vascular distribution in the scalp. Irrigation of the retroauricular flap can come from the posterior auricular artery or superficial temporal artery, depending on how the flap is used. Even though staged rotation is necessary, as in the case reported, the quality of the retroauricular skin is beneficial for facial reconstructions, considering the tissue's color, texture, and thickness. Also, the donor area in the posterior region of the ear is hidden and presents, for the most part, good healing.[11,12,22,24,25]

The first surgical stage performs an interpolation flap when an intact skin island between the donor and recipient area

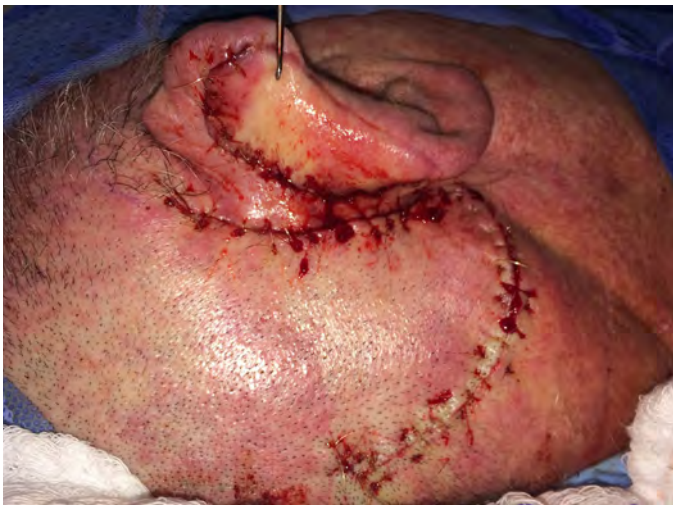

Figure 7: Immediate aspect of the reconstruction

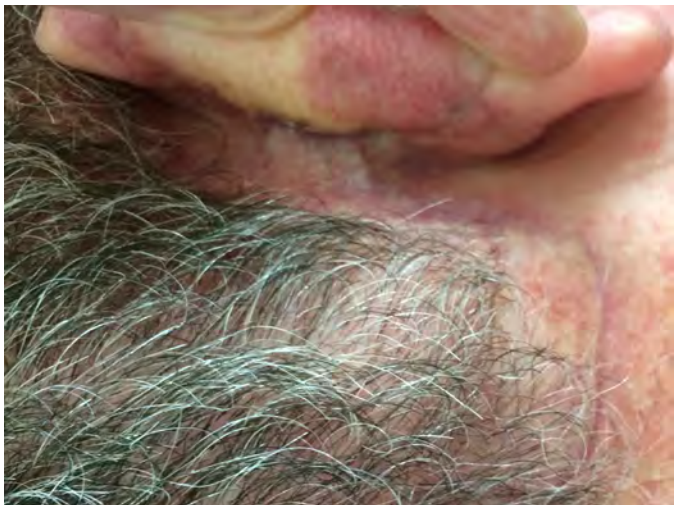

Figure 8: Late aspect of the reconstruction

is responsible for maintaining as much of the original anatomy of the site as possible. The procedure keeps a healthy skin island in the auricular sulcus between the donor and recipient area.[1,13,23,24] This procedure is performed because, after 21 days, the flap no longer depends on its pedicle, with the new recipient area being responsible for the irrigation of this tissue.

The second surgical stage establishes the rotation flap, consisting of the curvilinear displacement of tissue adjacent to the surgical defect, originating from the scalp. Also, the flap can stretch the elastic tissues to cover the defect, redirecting the closing tension, as its points of greater tension run along its distal edge instead of its length.[14,15,16,26,27]

The need for scalp rotation flap to close the donor area of the retroauricular flap is commonly criticized. However, this procedure easily closes the area simultaneously by releasing the pedicle of the retroauricular flap. Also, the flap could be expanded in its dimension in cases of even more extensive defects.[23,24,26,27]

Other flap options could be used for reconstruction. Still, it is necessary to pay attention to the possibility of compromising the retroauricular sulcus or using skin with very different characteristics from the auricle tissue.[10,20,21,24]

Another way to use this flap is vertical, being pedicled in the lower region. Nevertheless, it is believed that it is more vulnerable regarding vascularization and, in addition, the donor site would not close primarily, requiring a hair flap in the glabrous skin area. Note that the release of the pedicle would also be necessary, therefore, requiring two surgical stages.

Analyzing the anatomy of the perforating arteries in this region, we could prepare a flap that could be transposed in a single stage. However, in practice, we do not believe that any scalp flap would reach the recipient area, even using helix rotation.

CONCLUSION

The two-stage interpolation flap, followed by a rotation flap, is an effective method for reestablishing the auricle. This procedure is capable of maintaining the anatomy of the donor and the recipient area of the flap. ●

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Combined CO2 laser and intense pulsed light therapy in the treatment of vascular lesions

Terapia combinada de laser de CO2 e luz intensa pulsada no tratamento de lesões vasculares

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ABSTRACT

Congenital vascular lesions can be subdivided into tumors and malformations. Hemangiomas are benign vascular tumors resulting from the abnormal proliferation of endothelial cells, whereas port-wine stains are vascular malformations of a possible autosomal dominant inheritance. To date, there are no studies associating the use of intense pulsed light and CO2 laser as a therapeutic form for these pathologies. We present a series of 10 cases of vascular injuries treated with the combination of these forms of irradiation. This combined therapy can be effective in reducing the thickness of the lesions or in attenuating the color.

Keywords: Hemangioma; Lasers, gas; Laser therapy; Intense pulsed light therapy; Vascular malformations

RESUMO

As lesões vasculares congênitas podem ser divididas em: tumores e malformações. Os hemangiomas são tumores vasculares benignos decorrentes da proliferação anormal de células endoteliais; já as manchas em vinho do Porto são malformações vasculares de provável herança autossômica dominante. Até o presente momento, não há estudos sobre a associação entre luz intensa pulsada e laser de CO2 como forma terapêutica destas patologias. A presente série de casos apresenta 10 casos de lesões vasculares tratadas com a combinação destas formas de irradiação. Conclui-se que esta terapia combinada pode ser efetiva na redução da espessura das lesões ou na atenuação da coloração.

Palavras-chave: *Hemangioma; Lasers de gás; Terapia a laser; Terapia de luz intensa pulsada; Malformações vasculares*

Case report

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INTRODUCTION

Congenital vascular lesions can be divided into tumors and malformations. Hemangiomas are benign vascular tumors resulting from the abnormal proliferation of endothelial cells. They are the most common type of vascular tumor in childhood. They can affect any part of the body, but they occur more frequently in the scalp.[1,2,3] Contrarily, port-wine stains are vascular malformations of probable autosomal dominant inheritance. They usually occur on the face or neck, alone or in association with syndromes.[4,5] The emission of radiation using hemoglobin as a chromophore has become a therapeutic option due to its exclusively local action. Neodymium-doped yttrium aluminum garnet (Nd: YAG) and pulsed-dye laser (PDL), types of laser,[6,7] and Intense pulsed light (IPL), a form of divergent polychromatic white light, can be used to treat vascular lesions. We present a series of ten cases of vascular lesions, followed up and treated with combined therapy using fractional CO_2 laser and intense pulsed light (IPL).

RESULTS

We describe ten clinical cases with their respective characteristics and results after performing fractional CO_2 laser followed by IPL in the same procedure (Box 1).

Three dermatologists assessed the outcomes using photographs taken before and after the last sessions.

Overall, hemangiomas, women, and cephalic lesions predominated. Also, there was an improvement in texture, thickness, and tone of injuries. We observed a slight percentage reduction in the extension and diameter of lesions (Figures 1 to 5).

Regarding patient satisfaction with the result, all reported being satisfied with the clinical aspects after treatment. No adverse events or complications were described during or as a result of the procedures.

Box 1: Treatment methods, patterns, and clinical outcomes

	Diagnosis (hemangioma or port-wine stain – PWS)	Age and gender	Location and number of sessions (CO_2 + IPL)	IPL (filter); pulse duration (ms); frequency (J/cm²)	CO_2 (Watts); Dual time (µs); Spacing (µm)	Improved tone	Improved extension and diameter	Improved texture and thickness
Patient 1	Hemangioma	26 years; man	Left hemiface; six sessions	570; 12; 12	30; 1.000; 700	Yes	No	No
Patient 2	PWS	46 years; woman	Left hemiface; five sessions	570; 10; 15	30; 800; 800	Yes	No	Yes
Patient 3	PWS	22 years; woman	Forehead, nose, upper right lip; two sessions	570; 12; 14	800 30; 800;	Yes	No	No
Patient 4	Hemangioma	48 years; woman	Infraorbital and right supralabial; eight sessions	570; 10; 15	30; 800; 800	Yes	No	Yes
Patient 5	Hemangioma	43 years; man	Left mandibular region; five sessions	570; 7; 60	30; 800; 600	Yes	Yes	Yes
Patient 6	PWS	53 years; woman	Right hemiface and lip; 16 sessions	570; 12; 12	30; 700; 900	Yes	No	Yes
Patient 7	Hemangioma	27 years; woman	Right breast region; five sessions	570; 15; 8	30; 500; 800	Yes	No	Yes
Patient 8	Hemangioma	50 years; woman	Hemiface and left region; nine sessions	570; 10; 12	30; 1.000; 700	Yes	No	Yes
Patient 9	Hemangioma	69 years; woman	Left hemiface; 13 sessions	570; 12; 15	30; 1.000; 600	Yes	No	Yes
Patient 10	Hemangioma	58 years; woman	right upper lip and malar region; six sessions	570; 10; 12	30; 1.100; 600	No	No	Yes

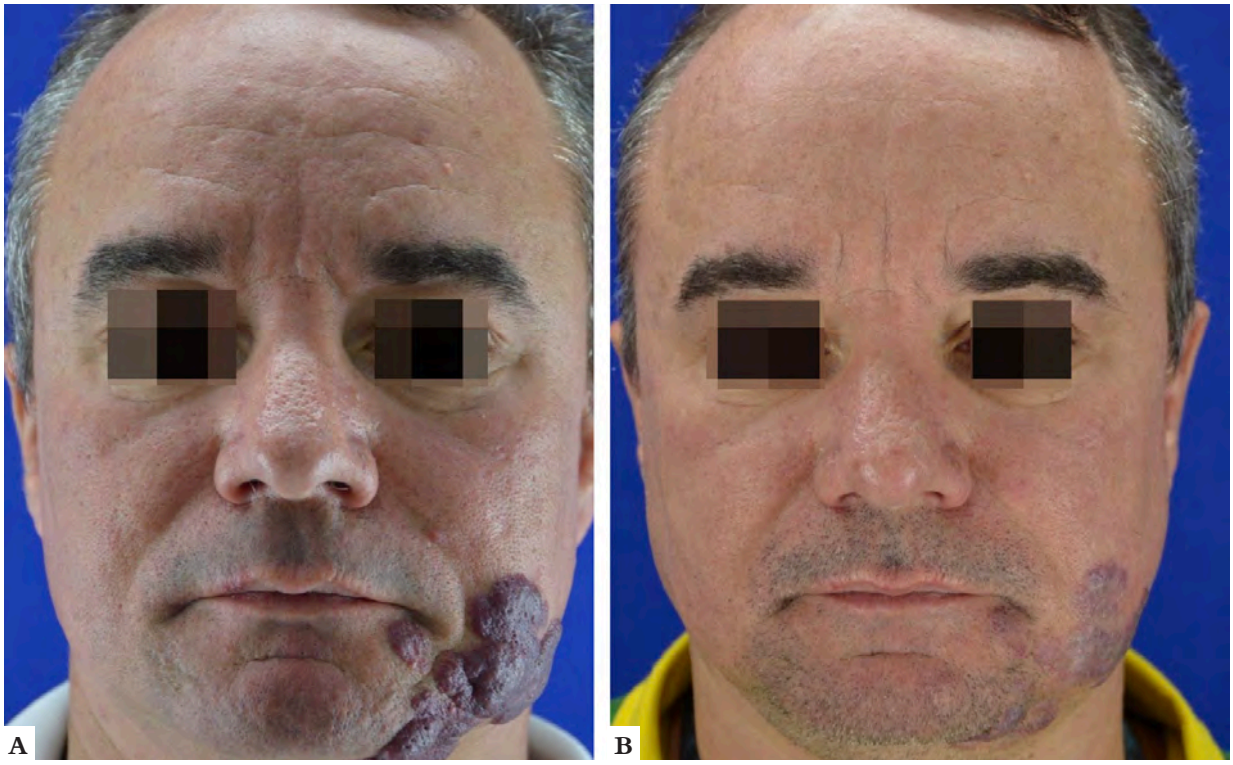

Figure 1: A - Patient 5, man, 43 years old, with hemangioma in the left mandibular region. **B -** Important tumor reduction and tone attenuation after treatment

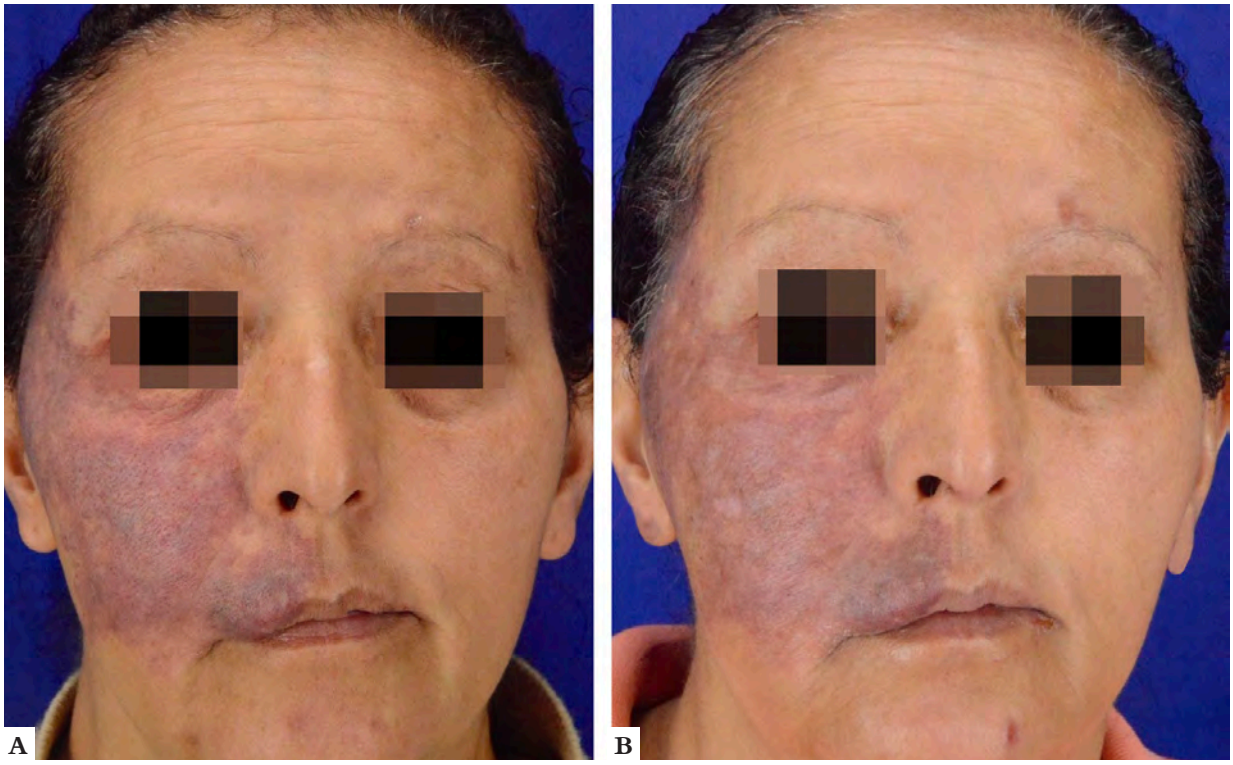

Figure 2: A - Patient 6, woman, 53 years old, with port-wine stain on the right hemiface. **B -** Homogeneous tone reduction and volumetric decrease of lip lesion after combined therapy

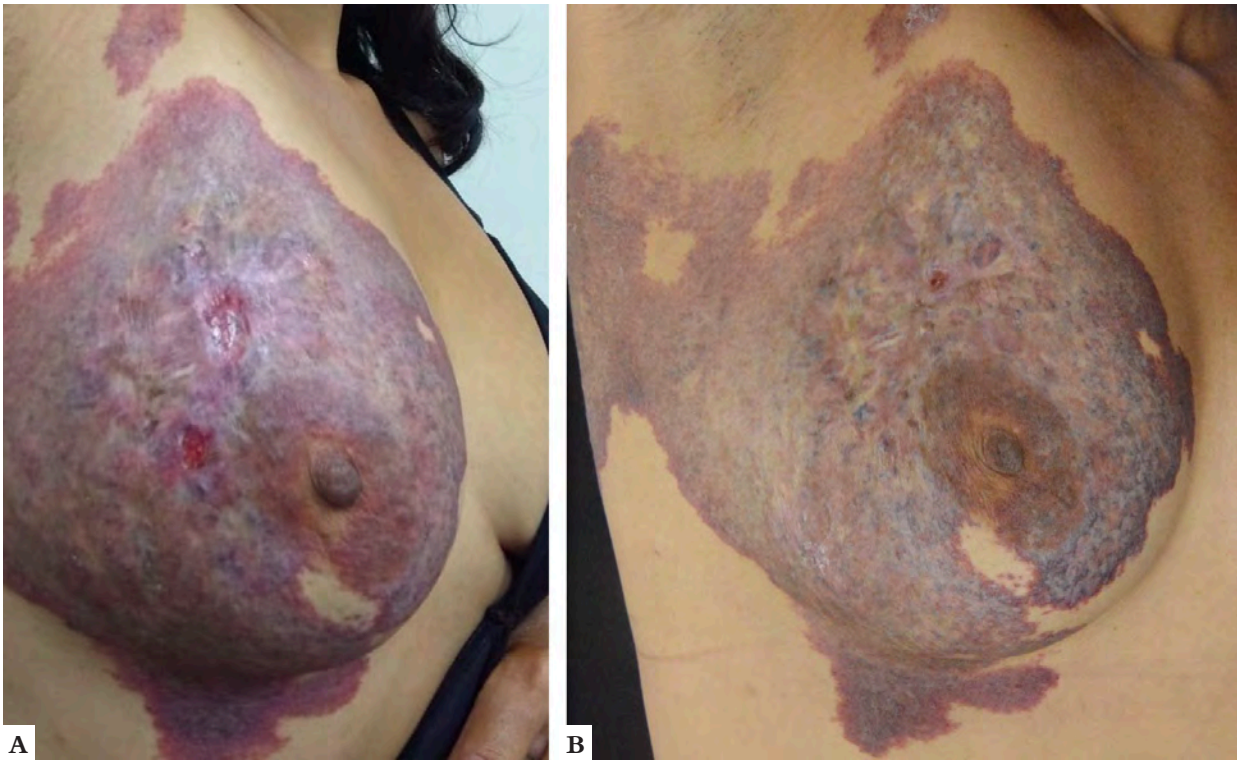

Figure 3: A - Patient 7, woman, 27 years old, with extensive hemangioma in the right breast region, with ulcerations and atrophic scars. **B -** Color homogenization and thickness reduction after treatment

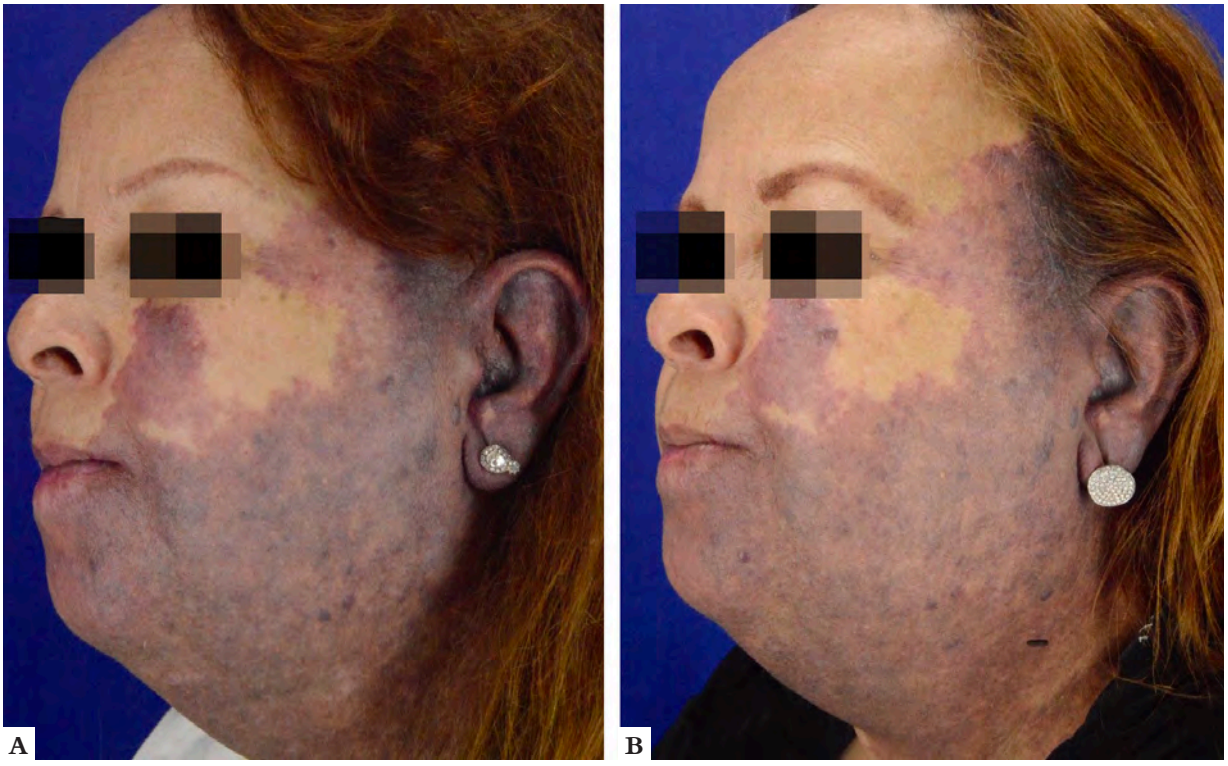

Figure 4: A - Patient 8, woman, 50 years old, with large hemangioma in the left hemiface and left lateral cervical. **B -** Texture attenuation and a slight improvement in tonality after nine sessions

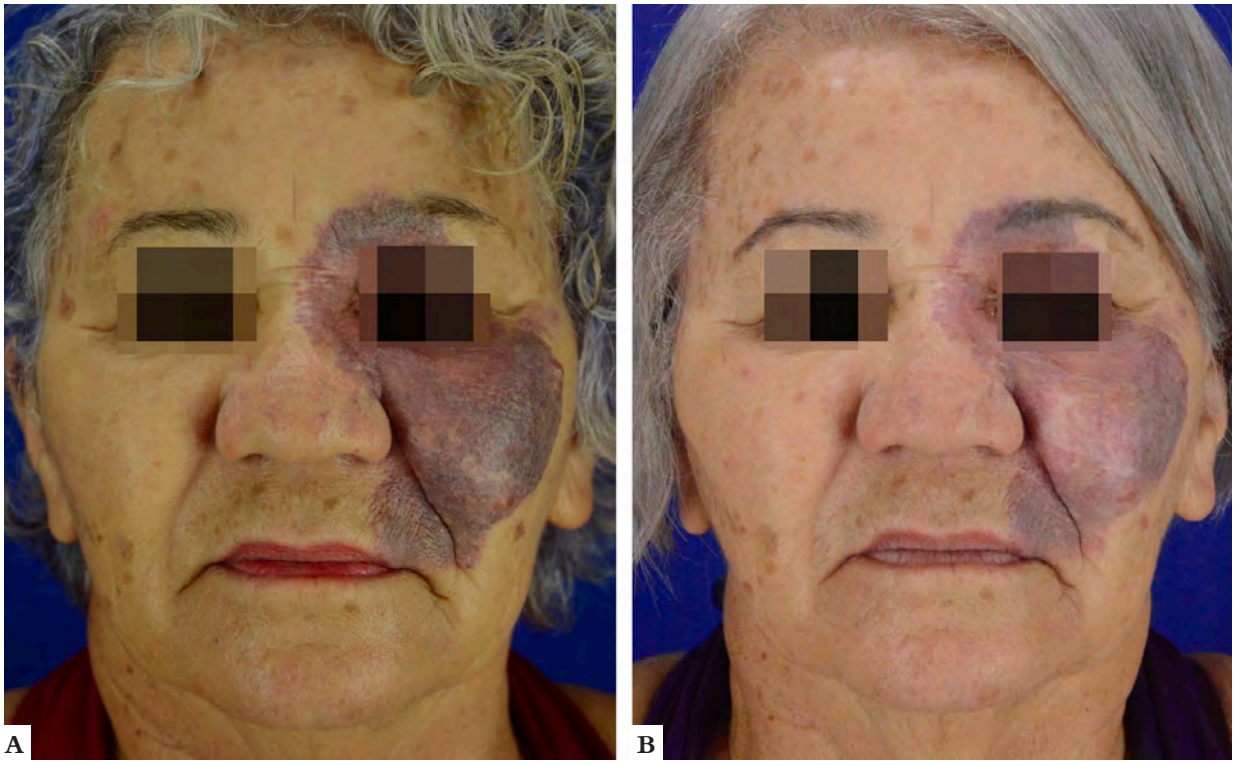

Figure 5: A - Patient 9, woman, 69 years old, with hemangioma on the left hemiface.
B - Post-procedure with combined therapy presenting tone improvement and thickness reduction

DISCUSSION

Hemangiomas are benign vascular tumors. They are the most common type of vascular tumor in childhood – their incidence can reach up to 10% in Caucasian children – and appears to be prevalent in children with a history of prematurity and low birth weight. This disorder affects more women than men (2.1:1) and results from the abnormal proliferation of endothelial cells and vascular components. The lesions can affect any part of the body, but it is more common in the scalp, neck, and trunk. In general, these vascular lesions appear after the first month of birth and tend to regress spontaneously, still in the first year of life (lesions decrease about 10% per year, and most of them fully regress by age 12). Despite its benign behavior, it may not progress with spontaneous regression and present, in about 5-10% of cases, ulceration, bleeding, local pain, atrophic or fibrotic scars formation, and deformities (mainly in deep and larger diameter tumors). These variants may signal resolution in childhood.[1,2,3]

Among systemic and topical drug therapies, the literature currently describes options such as propranolol (assessed as the systemic treatment of choice for children); topical beta-blockers as timolol; imiquimod; and intravenous medications such as steroids and bleomycin. Laser treatment is initially indicated for superficial hemangiomas that regressed spontaneously, or residual lesions after other treatments. Cases resistant to less invasive approaches may need surgical approaches.[1,3]

Port-wine stain is the second most common congenital vascular malformation. It is characterized by capillary and venous ectasia in the dermis. Clinically, it presents a dark red or purple skin patch, which may progress to darker tones and present nodules or constitute a hypertrophic appearance. Unfortunately, therapeutic options have been limited to performing laser therapy (Pulsed Dye Laser as the gold standard) or surgical procedures in recent decades.[4,5]

Among the different types of laser, the Nd:YAG laser (in long pulse, KTP, or Q-switched modes) and the Pulsed Dye Laser (PDL) have selectivity for vascular lesions (using hemoglobin as a chromophore and "selective photothermal interaction").[6] A recent study demonstrated the effects of irradiation (Nd:YAG laser and IPL) on hemangioma endothelial cells, changing cytokine signaling pathways and apoptotic rate due to the inhibition in the production of several endothelial growth factors. This phenomenon lasted until a few days after the treatment and not just immediately after irradiation.[7] Although the CO_2 ablative laser (10,600nm wavelength) uses water as a chromophore, some studies already reported its success in reducing vascular lesions, especially in infantile hemangiomas with airway involvement.[3]

As a form of white, divergent, non-coherent, and polychromatic radiation, IPL has a wavelength from 500nm to 1,200nm, depending on the filters used. The selectivity of mel-

anin and hemoglobin chromophores and the ability to damage the vascular walls according to established parameters justify its application in vascular lesions of the face.[8,9]

CONCLUSION

The worldwide dermatological literature has not yet described the association between IPL and CO_2 laser for treating vascular lesions. Therefore, we concluded that combining two different types of irradiation can effectively manage vascular lesions, with possible secondary indications when it's not possible to perform Nd:YAG or Pulsed Dye Laser. Device parameters must be further defined to explore the best aesthetic and functional result. ●

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How to prepare a trichogram with transparent enamel base coat?

Abordagem dos aspectos técnicos no preparo da lâmina de tricograma com base de esmalte incolor

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ABSTRACT

The trichogram is an easy and semi-invasive method, useful for evaluating different types of hair loss in daily practice. To date, there is no standardized methodology on how to collect and perform the exam. The use of a liquid interface between the slide and the coverslip to read the trichogram under optical microscopy varies widely in the literature. Among the alternatives, transparent enamel base coat is an inexpensive, accessible, and practical option, providing the examiner with proper visualization of the hair shafts with minimal air bubbles formation.

Keywords: Alopecia; Hair diseases; Scalp dermatoses

RESUMO

O tricograma configura-se em método semi-invasivo de fácil aplicabilidade e baixo custo, útil na avaliação dos diversos tipos de queda capilar no consultório dermatológico. Até o momento, não há padronização da técnica para coleta e realização do exame. A utilização de meios de interface entre lâmina e lamínula para a leitura do tricograma à microscopia óptica varia amplamente na literatura. Dentre as alternativas, a utilização de base de esmalte incolor configura-se em opção de baixo custo acessível e prática, além de permitir a visualização das hastes capilares com mínima formação de artefato.

Palavras-chave: *Alopecia; Dermatoses do couro cabeludo; Doenças do cabelo*

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INTRODUCTION

The recent expansion of knowledge in trichology challenges the physician in searching for a more detailed and objective medical evaluation. However, cutting-edge technologies for the assessment of hair and scalp are not always available. In this context, the trichogram is a semi-invasive method with easy application and low cost, accessible to every dermatologist dedicated to studying hair disorders.

DISCUSSION

After Trotter (1989-1991) described the hair growth cycle, most studies on follicular dynamics were conducted based on the microscopic evaluation of hairy roots (HR).[1] The technique for this assessment, later called trichogram, still helps to interpret various disorders of the hair growth cycle and has practical value since it is a semi-invasive method with easy applicability and low cost.[1,2,3]

The exam consists of collecting 50 to 100 hair strands, usually from two scalp regions (parietal and occipital), and subsequently adjusting the hairy roots on a glass slide.[1,4] A coverslip is generally superimposed on the hair shaft to facilitate reading under an optical microscope, using a liquid medium to fix the hair strands when conducting the evaluation is recommended.

To date, no standardization defines the best way to fix the hair shafts for reading under the microscope. A review of 76 articles indexed in PubMed with the keywords "trichogram" and "technique" published from 1970 to 2021 showed that only 14 studies (18.4%) mentioned some liquid or other fixation midia when conducting the technique. Of these, one used formaldehyde (7.15%),[5] two used a drop of Canadian balsam (14.28%),[6,7] three used only a thin glass slide cover (21.42%),[8,9,10] two used double-sided tape (14.28%),[4,11] five used adhesive tape (37.71%),[2,12,13,14,15] one used unspecified liquid (7.15%),[16] and 62 (81.57%) did not mention or did not use any form of fixation of the hair strands.

A mixture of 45% acrylic resin and 55% xylenes (Eukitt®) can be used for fixing and reading the trichogram with excellent results (Figure 1A). It provides little formation of air bubbles (artifact) and facilitates exam interpretation, especially for inexperienced examiners. On the other hand, this technique is a more expensive option, and it's more challenging to be found in some parts of Brazil. In turn, the use of liquids that do not promote adherence of the hair strands to the glass slide – such as formaldehyde, 0.9% saline solution, and distilled water - facilitate the movement of hair strands on the slide, making it difficult to visually analyze and count the hairy roots in different optical fields.

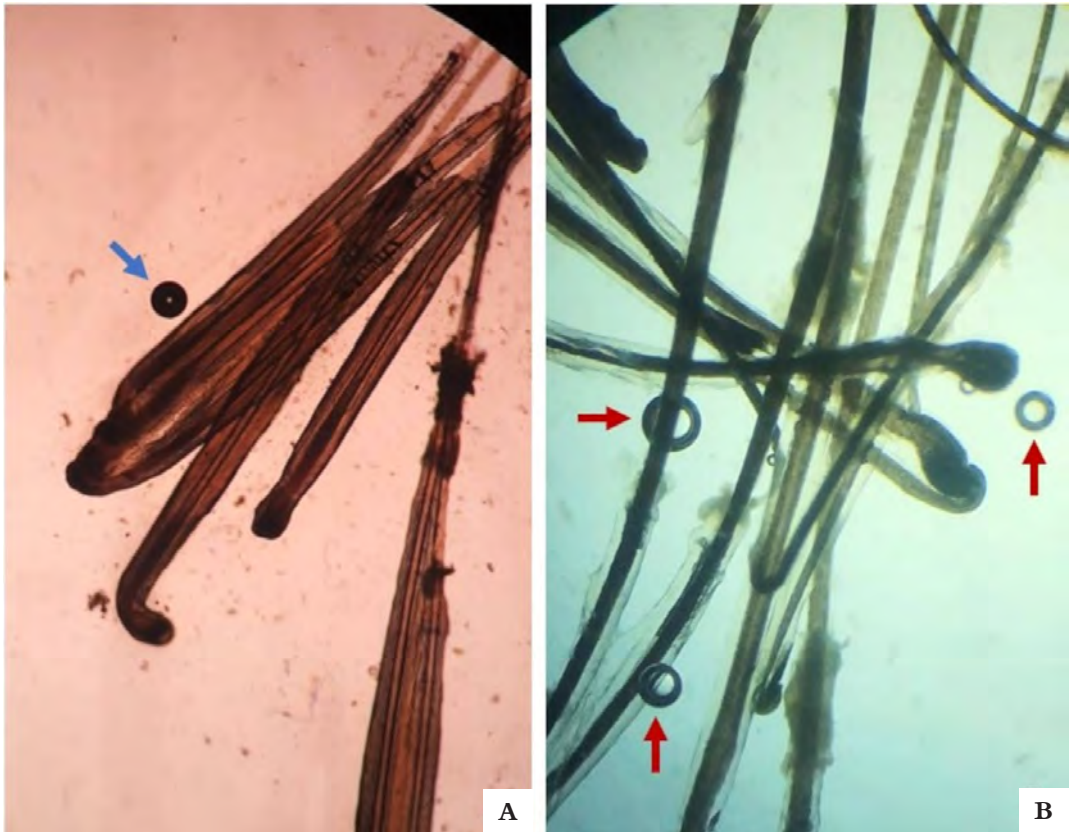

FIGURE 1: Trichogram: assessment of hair shafts under an optical microscope (4x).
A - Evaluation with Eukitt®: transparent medium with minimal air bubbles formation (blue arrow).
B - Evaluation based on enamel: few air bubbles that do not affect the final assessment of the exam

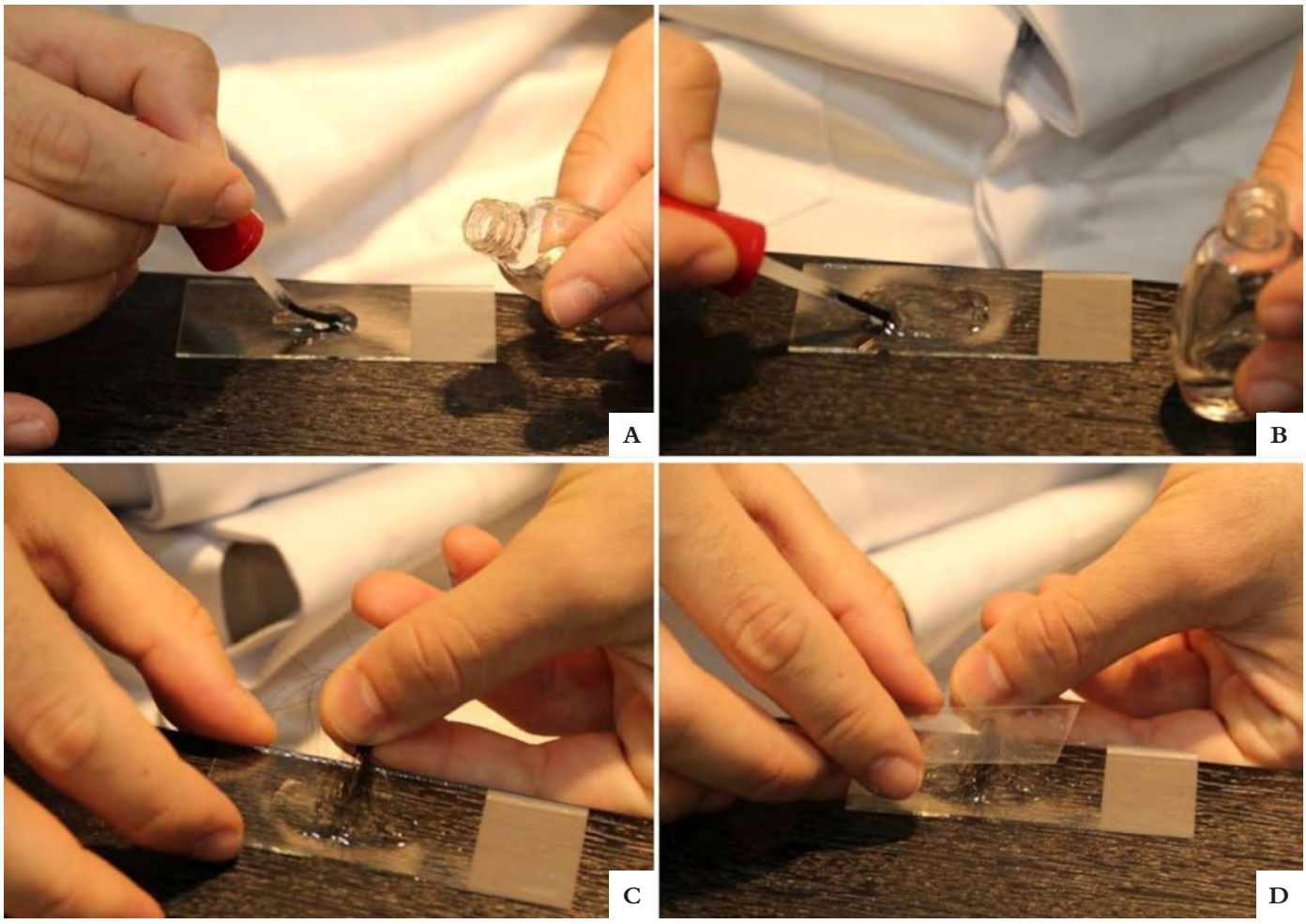

FIGURE 2: Preparation of enamel-based slide for trichogram reading. A good amount of base coat must be applied so that all hair shafts are fully soaked in the liquid **A** and **B -** Fixation must be quick, before the base coat dries, and a coverslip helps with further reading **C** and **D.**

In the authors' experience, using a transparent enamel base coat is a cheap, easy-to-access, and helpful strategy when preparing the hair shafts for the trichogram. However, we haven't found it in the literature among the various options. When opting for this strategy, the examiner must place the hair strands on a previously prepared slide with a generous amount of enamel base coat and then cover with a coverslip glass slide (Figures 2A - 2D). Drying is quick, and fixation is adequate, with minimal air bubbles formation (artifact) (Figure 1B). Also, the material can be kept for analysis on subsequent days.

CONCLUSION

Trichograms can be performed with or without liquid media, and to date, there is no standardization. However, using a colorless enamel base coat in exam preparation is a good practical option. It allows excellent fixation of the hair strands in the slide/coverslip interface, generates few air bubbles, and has fast drying and low-cost wide range availability nationwide. ●

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Hematoma in aesthetic surgery: tips to avoid unaesthetic results Hyaluronidase and hematoma drainage

Hematoma em cirurgia cosmética: dicas para evitar resultados inestéticos a partir da hialuronidase e drenagem de hematomas

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ABSTRACT

Hematomas are common following cosmetic surgery. When minor, they are treated with observation only as they are most often reabsorbed. However, even with small collections of blood, if no early intervention is adopted, poor aesthetic outcomes may occur. Early drainage has been especially described in otorhinolaryngology and radiology journals. The authors present an approach to early treating hematomas. Special emphasis is given to the use of hyaluronidase, which is well known by dermatologists and plastic surgeons for its ability to dissolve hyaluronic acid, but its utility in the treatment of hematomas is not so commonly known by these experts.

Keywords: Hyaluronoglucosaminidase; Hyaluronic Acid; Hematoma; Fibrosis

RESUMO

Hematomas são comuns após cirurgias cosméticas. Quando pequenos, são conduzidos de maneira conservadora, pois, na maioria das vezes, são reabsorvidos. No entanto, mesmo pequenas coleções, quando não ativamente abordadas, podem resultar em maus resultados estéticos. A drenagem precoce tem sido especialmente descrita em revistas de Otorrinolaringologia e Radiologia. As autoras apresentam uma abordagem para o tratamento precoce de hematomas. Ênfase especial é dada ao uso da hialuronidase, bem conhecida pelos dermatologistas e cirurgiões plásticos por sua capacidade de dissolver o ácido hialurônico, mas sua utilidade no tratamento de hematomas não é amplamente difundida entre esses especialistas.

Palavras-chave: *Hialuronoglucosaminidase; Ácido Hialurônico. Hematoma; Fibrose*

How do I do?

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INTRODUCTION

Hematoma is a localized collection of blood. [1] It is relatively common after cosmetic surgeries. Unaesthetic results can be avoided if early interventions are performed to evacuate them. Small hematomas are usually reabsorbed spontaneously,[2] but in some cases, they may induce poor aesthetic results. [2,3]

The hematoma course comprises 3 stages:

Stage I (early formation): The wound is swollen, warm, and fluctuant and requires immediate intervention.

Stage II - (gelatinous): formation of clotting.

Stage III - (organization): Blood clots within the hematoma.

Stage IV - (liquefaction): Fibrinolysis. Needle aspiration or puncture followed by manual expression may be considered.[1]

Hyaluronidase degrades hyaluronic acid. It has been used to treat fluid collections such as injected drugs and contrast media.[4,5] Recently, it has been used to correct adverse events from hyaluronic acid fillers,[6,7] but few studies have investigated its utility for treating hematomas.[4,8]

The goal of this article is to discuss how to treat post-procedure hematomas with the purpose of shortening the recovery time to prevent complications.

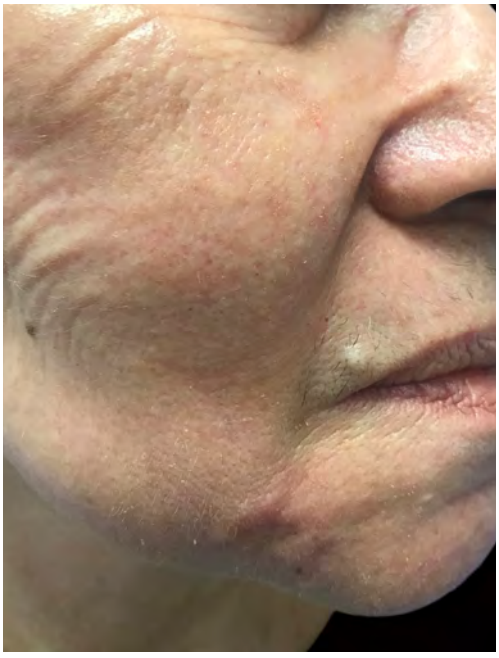

Figure 1: Day 12 post-op: firm nodule

MATERIAL AND METHODS

Case 1: Subcision

A 62-year-old woman underwent subcision to treat marionette lines. The needle was moved back and forth to form close parallel tunnels at dermal level, according to a subcision technique variant called "dermal tunneling".[9] On day 12 post-op she presented with firm local bumps on the treated area (Figure 1), which were punctured with a 22G needle and the blood was drained.

Case 2 Hematoma after face-lift surgery

A 65-year-old woman underwent face-lift surgery and developed larges hematomas. She asked for our evaluation and intervention. On Day 12 post-op, the pre-auricular area was tender and partial scar dehiscence and necrosis had occurred. Although theoretically liquefaction phase was ongoing,[1] the drainage was difficult to perform. Hyaluronidase was indicated to help break down the hyaluronic acid within the coagulated hematoma.[4] Therefore, 2ml of hyaluronidase, reconstituted with 5 ml of diluent to a final concentration of 400u/ml, were injected into the indurated areas followed by fingertip massage. The skin was then punctured with a 22G needle and manual expression of the blood was made (Figure 2).

Case 3. Hematoma causing compression and tissue impending necrosis

A 30-year-old woman had her lips injected with hyaluronic acid. Right after the procedure, the injecting physician noticed an area of impending necrosis characterized by pale skin on the right side of her lower lip, suggesting vascular occlusion. Hyaluronidase was immediately injected through several punctures and improvement of the pale area was observed. However, this procedure induced vascular injury and a large new hematoma emerged. The hematoma pressure was collapsing the vessels, leading to – once again –impending skin necrosis. In order to dissolve the hematoma and improve local blood flow, 2 ml of hyaluronidase (400u/ml) were injected, with 25G cannula. Fingertip massage was performed to help hyaluronidase break the clot and enhance fluid absorption.[4]

RESULTS

Case 1

Within 6 weeks, there were no more nodules and local improvement of wrinkles and laxity could be observed (Figure 3).

Case 2

Immediately after treatment, the patient felt less discomfort. The wound started to heal on the following days. Two weeks later, small areas of localized blue-colored skin indurations were punctured again. Immediately after the procedure, the bluish color disappeared as well as the indurations (Figure 4).

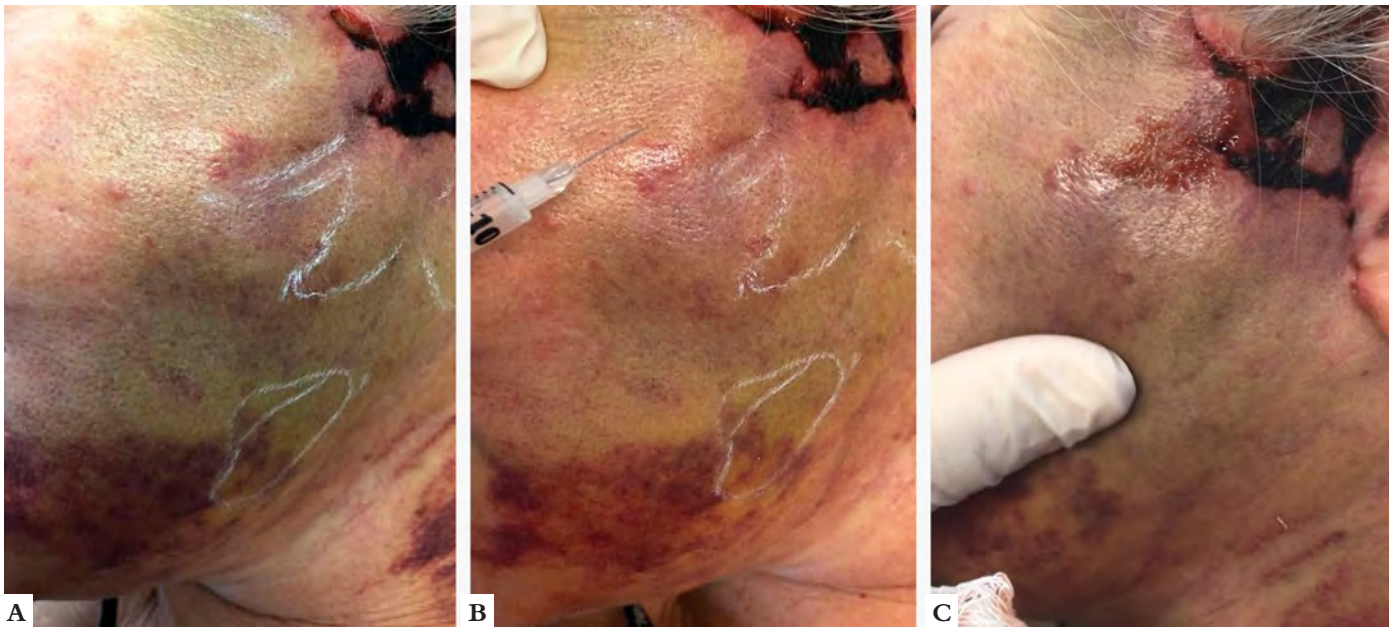

Figure 2: A - Day 12 post-face-lift surgery: Hematoma with skin irregularities and flap suffering. **B -** Hyaluronidase injection to break down consolidated hematoma. **C -** Blood being drained

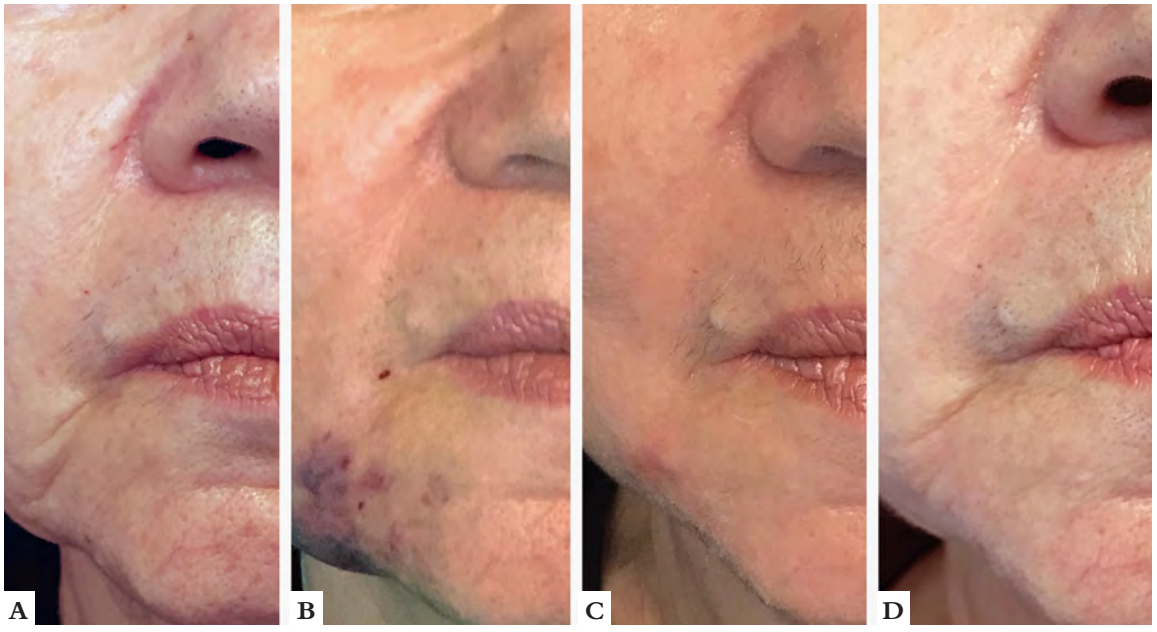

Figure 3:
A - Before subcision.
B - Day 7 post-op: local ecchymosis and hematoma.
C - Day 12 post-op: firm nodule.
D - Final outcome 6 weeks from drainage

Case 3

One hour after the hyaluronidase injection, the purple color on her lip cleared and 24 hours later, almost complete resolution of the hematoma occurred (Figura 5).

DISCUSSION

Subcision is a procedure used to release fibrous attachments. Indications are correction of acne scars, cellulite dimples, and wrinkles, inducing formation of connective tissue through normal physiological healing. [9,10,11] One of its adverse effects are residual indurations. Around 5-10% of patients develop hypertrophic response within 2-4 weeks post-operatively,[9] especially in the glabellar region. This happens due to an exaggerated wound healing response or to an unrecognized and untreated hematoma [3] that can evolve to hypertrophic scars. Hence, the

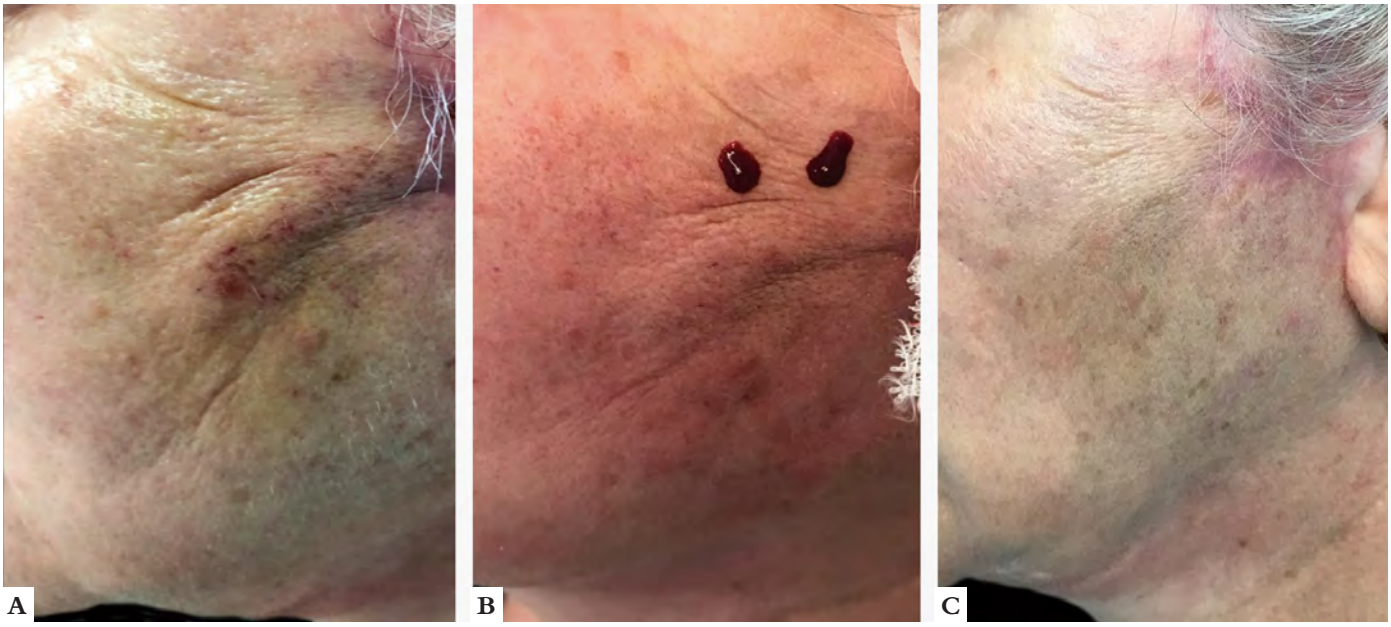

Figure 4: A - Two weeks later, remaining bluish areas of induration. **B -** Drainage of dark blood after puncture with a 22G needle. **C -** Final result

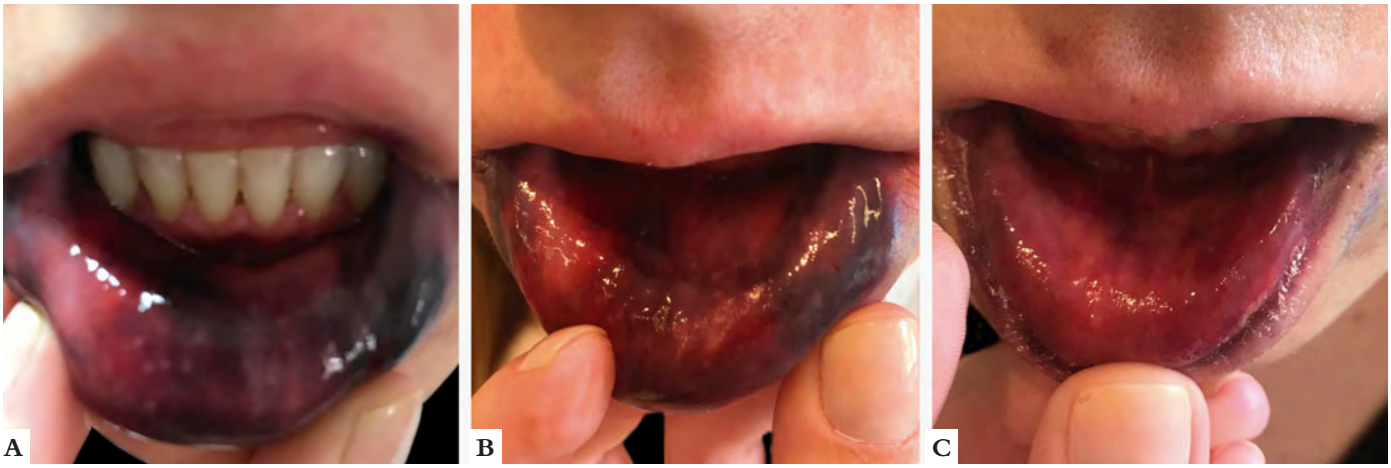

Figura 5: A - Bilateral lower lip hematoma formed following hyaluronidase injection using a needle. **B -** One hour from hyaluronidase injection for hematoma absorption using a cannula. **C -** 24 hours from hyaluronidase injection, almost complete clearing of the lower lip hematoma

importance of recognition and early treatment of hematomas to prevent nodule formation.

Some authors advocate that patients are not bothered by the bumps.[11] This is not our experience. We recommend early drainage of local hematomas in order to prevent or reduce the duration of these residual bumps, preventing posterior fibrosis, thus enhancing patient´s satisfaction.

Hematomas may lead to flap necrosis after face-lift surgeries, resulting in unaesthetic scars.[2] Even being of small size, they may jeopardize the flap viability, leading to knots, necrosis, skin irregularities, hyperpigmentation and prolonged healing time.[2]

The ideal moment to drain the hematoma is when it is in the liquefaction phase.[1]

Hyaluronidase has been used for several years to enhance the absorption of extravasated fluids, [4,5,8] and recently, to correct HA adverse events. [7] But it would also degrade the hyaluronic acid deposited throughout the consolidated hematoma and extracellular matrix. [4] Thus, hyaluronidase may help break down the coagulated hematoma and facilitate the fluid drainage by

creating outflow channels in the extracellular matrix, even when it is in its firm or gelatinous form. [4]

Although this usage is off label, we feel it could help avoiding complications.

In an experimental study, Chuang injected blood in a dog's abdominal wall to simulate bilateral hematomas. One side was treated with hyaluronidase injection and the other was left as a control. One hour from injection, the treated side showed 70% reduction of its size when compared with the control. The favorable results in animals allowed the use of hyaluronidase to treat patients with moderate-to-large hematomas following arterial catheterization in angiographic procedures. Positive effects were observed as early as 5-10 minutes from injection, while most patients responded after one hour by showing reduction and softening of the hematomas.[8] Nelson et al. suggested using hyaluronidase as a tool to allow early reabsorption of facial and neck hematomas.[4]

Hyaluronidase was very useful in our post-rhytidectomy hematoma case, by inducing blood clot liquefaction, allowing its early release, and keeping flap viability.

It was also very effective in dissolving the lip hematoma that occurred after filler injection. To our knowledge, the use of hyaluronidase to make the reabsorption of lip hematomas easier had not been described before.

Hyaluronidase may help treat hematomas at early gelatinous and consolidation phases, thus reducing the risks of complications as well as patient's downtime.

CONCLUSION

Hematoma is a frequent occurrence following surgical procedures. Observation is often adopted. But, in some cases, they may course with complications. The authors propose early intervention with drainage when in the liquefaction phase or by hyaluronidase injection when consolidated in order to reduce patient discomfort, downtime and to prevent poor aesthetic outcomes. Although the use of hyaluronidase is reported in other specialties journals, such use is still little known by dermatologists and plastic surgeons, who would benefit from this new indication. ●

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Cryosurgery with liquid nitrogen versus trichloroacetic acid in the treatment of human papillomavirus (HPV) penile wart: a randomized controlled trial

Criocirurgia com nitrogênio líquido versus ácido tricloroacético no tratamento de verruga peniana por papilomavírus humano (HPV): um ensaio clínico randomizado

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ABSTRACT

Background: Anogenital warts are the most prevalent sexually transmitted infection (0.5%) among dermatological consultations. Cryotherapy with liquid nitrogen (LN) and therapy with trichloroacetic acid (TCA) are remarkable among the treatment strategies.

Objective: To evaluate the effectiveness of LN versus TCA in to treat penile warts in patients from a Brazilian public institution.

Methods: Open, parallel, randomized clinical trial. Following randomization, the warts were counted and submitted to cryotherapy (10s) or case therapy (TCA 80%) in each visit. The primary dependent variable was the lesion count before and after four weeks of treatment. We assessed the following variables: complete clearance, age, immunosuppression, smoking, topography, and education.

Results: 142 treatments were evaluated in 52 participants. There was a predominance of young adults, and the main topography affected was the penis shaft. The mean reduction rate per session was 48% for LN and 26% for TCA (p=0.11). 42 (81%) participants achieved complete clearance, with 39 (75%; 95% CI: 64-85%) reaching clearance in up to three sessions. Age was associated with a worse therapeutic response rate (ß =-0.09; p<0.01).

Conclusions: LN and TCA proved to be effective to treat penile warts, without difference between treatments. Age was associated with a worse therapeutic response.

Keywords: Trichloroacetic acid; Cryosurgery; Sexually transmitted diseases; Papillomavirus infections; Warts

RESUMO

Introdução: *verrugas anogenitais são a infecção sexualmente transmissível prevalente (0,5%) entre atendimentos dermatológicos. Dentre as estratégias de tratamento, destacam-se a crioterapia com nitrogênio líquido (NL) e causoterapia com ácido tricloroacético (ATA).*

Objetivo: *avaliar a eficácia do NL versus ATA no tratamento de verrugas penianas em pacientes de instituição pública brasileira.*

Métodos: *ensaio clínico aberto, paralelo e randomizado. Em cada visita, as verrugas foram contadas e submetidas à crioterapia (10s) ou à causoterapia (ATA 80%), após randomização. A principal variável dependente foi a contagem de lesões antes e após quatro semanas de tratamento. Foram analisados: eliminação completa, idade, imunossupressão, tabagismo, topografia e escolaridade.*

Resultados: *foram avaliados 142 tratamentos em 52 participantes. Houve predominância de adultos jovens, menor escolaridade, e a principal topografia afetada foi a haste. A redução percentual média por sessão foi 48% para o NL e 26% para o ATA (p=0,11). Clearance completo foi atingido por 42 (81%) participantes, sendo que 39 (75%; IC95%: 64-85%) atingiram o clearance em até três sessões. A idade associou-se à pior taxa de resposta terapêutica (β=-0,09; p<0,01).*

Conclusões: *NL e ATA mostraram-se eficazes na terapêutica das verrugas penianas, sem diferença entre os tratamentos. A idade foi associada à pior resposta terapêutica.*

Palavras-chave: *Ácido tricloroacético; Criocirurgia; Doenças sexualmente transmissíveis; Infecções por papillomavirus; Verrugas*

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INTRODUCTION

Despite the vaccination campaign, anogenital warts (AGWs) remain a prevalent sexually transmitted infection (0.5%) among dermatological care.[1] The human alpha papillomavirus (HPV) causes AGWs, usually genotypes 6 and 11. It has a low-oncogenic risk but may present co-infection with high-risk genotypes. In addition to the critical link between contagion and impact on quality of life, HPV can induce epithelial neoplasms, especially in immunocompromised individuals.[2,3]

Among the therapeutic strategies used in AGW treatment, clinical therapy (e.g., imiquimod, podophyllotoxin) and surgical options, especially electrocoagulation, cryotherapy with liquid nitrogen (LN), and treatment with trichloroacetic acid (TCA) 80-90% stand out due to their accessibility and no need for anesthesia. There is no hierarchy of treatments, and few randomized studies compare the effectiveness of different strategies in AGW treatment. LN is associated with a 44-87% cure rate and TCA with 56-94%.[4]

This study aims to assess the effectiveness of LN versus TCA to treat penile warts in patients from a Brazilian public institution.

METHODS

It is an open, parallel, randomized clinical trial involving patients with penile AGW. At each clinical visit, the AGW were counted and submitted to treatment with LN (10s) or TCA 80%, according to computerized randomization. Patients were re-assessed after four weeks, AGWs were recounted, and patients were re-enrolled in the study under further randomization if new treatments were needed. The primary dependent variable was AGW lesion count, assessed after acetoscopy (with acetic acid 5%), before treatment, and after four weeks. We also analyzed complete clearance, age, immunosuppression, smoking, topography (penis glans, shaft, foreskin), and education. The numerical variation of the lesions was evaluated using a generalized linear mixed-effect model (negative binomial). Outcomes were assessed by intention to treat (ITT). Participants who did not attend the re-evaluation visit were considered a therapeutic failure, and the mixed model imputed their results. Significance was defined as p values <0.05. The project was approved by the Research Ethics Committee (n. 4418.2012).

RESULTS

We assessed 142 treatments in 52 participants: 13 (9%) of the cases did not return for re-evaluation (drop out). Table 1 shows the primary clinical and demographic data of the sample. There was a predominance of young adults, low education, and the main affected topography was the penis shaft. Cauterization with TCA was indicated in 63 (44%) of the treatments, and 59 was completed; NL was indicated in 79 (56%) of the treatments, with 70 completed, with no difference between the groups regarding the drop out rate (p=0.82).

Table 1: Main clinical-demographic characteristics of the studied sample.

Variable		Results
Age (years)*		28 (10)
School – n (%)		
	Elementary School	20 (43)
	High School	21 (45)
	University	6 (13)
HIV positive – n (%)		4 (8)
Smoking – n (%)		10 (19)
Topography of the lesions – n(%)		
	Penis shaft	91 (64)
	Penis foreskin	32 (23)
	Penis glans	19 (13)
Number of pre-treatment lesions **		3 (1-5)
Number of post-treatment lesions **		0 (0-3)

** means (standard deviation); ** median (p25-p75)*

Figure 1 represents the AGW counts for each group and treatment time. There was a significant reduction in the median (p25-p75) of AGWs for both groups: TCA (3 [2-9] to 1 [0-4]; p<0.01) and LN (2 [1-4] to 0 [0-2]; p<0.01), with no differences between treatments (p=0.11). The mean percentage reduction in each session was 48% for LN and 26% for TCA.

Complete clearance (absence of acetowhite areas) was achieved by 42 (81%) study participants during follow-up, with 39 (75%; 95% CI: 64-85%) of all included participants achieving clearance within up to three monthly sessions. As the participants were re-included at each return in different treatment groups, assessing the complete clearance linked to each treatment was impossible.

When we assessed clinical-demographic elements as predictors of a general response to treatments, age (β= -0.09; p<0.01) was associated with the worst response rate. However, HIV carriers (p=0.99), education (p=0.51), smoking (p=0.17), and the topography of the lesions (p=0.24) did not interfere in the therapeutic response.

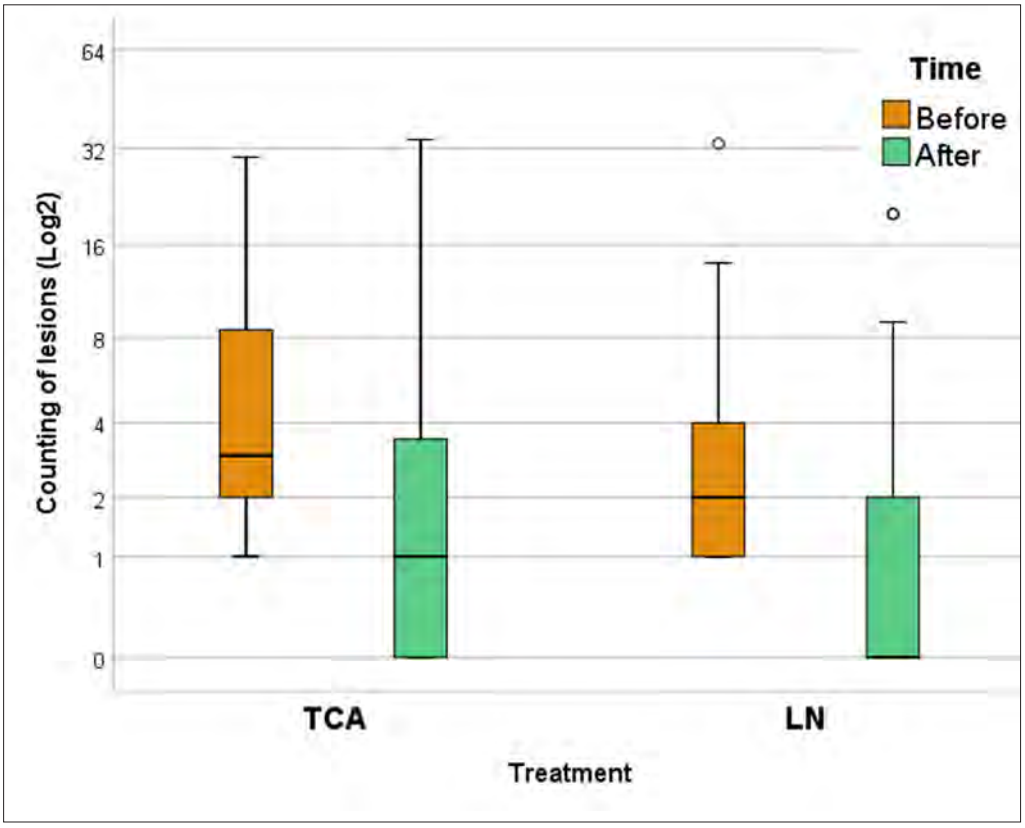

Figure 1: Representation of the count of penile anogenital warts before and after four weeks of each treatment session with trichloroacetic acid solution (TCA) 80% or liquid nitrogen (LN)

DISCUSSION

In a randomized clinical trial analyzing TCA 90% versus LN (swab) in lesions in both sexes, complete clearance in up to six sessions of TCA was 64%, and LN was 70%.[5]

A systematic review of randomized studies identified complete clearance of 72% for TCA therapy (six studies) versus 58% for LN (12 studies). However, the LN application regimen (spray versus swab), TCA concentration (80% versus 90%), and the number of sessions were not weighted.[4]

The present study has limitations because it is monocentric, depends only on clinical diagnosis, shows loss to follow-up of 9% of subjects included, does not have a quantitative assessment of immunity, and does not protocol follow-up with the same treatment type for each participant. Prospective studies should compare whether the combination of treatments (e.g., TCA+LN, TCA+imiquimod) or different regimens of LN or TCA 90% can lead to more robust results, reducing the number of sessions needed to clear genital HPV.

CONCLUSIONS

LN and TCA proved to be effective in treating AGW, with no difference between treatments. Age was a factor associated with a worse therapeutic response. ●

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Seasonal and daylight saving time fluctuations in Google searches for scalp seborrheic dermatitis

Flutuações sazonais e do horário de verão nas pesquisas do Google para dermatite seborreica do couro cabeludo

Letter

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ABSTRACT
Scalp seborrheic dermatitis, or dandruff, is thought to worsen during the winter when there is later sunrise and less daylight. This study investigates trends in search engine interest for the term "dandruff" as they relate to changes in daylight, sunrise, and seasonality. We investigated the search interest in several countries of varying latitudes over a five-year period, and we explore the effect of daylight saving time on disease interest within two cities in the United States. We discuss our findings in the context of hormonal changes and skincare/behavior.
Keywords: Hair; Dandruff; Dermatitis; Hair diseases; Light; Sunlight

RESUMO
Acredita-se que a dermatite seborreica do couro cabeludo, ou caspa, piore em gravidade durante o inverno, quando ocorre o nascer do sol tardio e menos luz do dia. Neste estudo, investigamos as tendências no interesse do mecanismo de pesquisa pelo termo "caspa", visto que se relacionam com as mudanças na luz do dia, nascer do sol e sazonalidade. Analisamos o interesse de pesquisa em vários países de latitudes variáveis em um período de cinco anos e exploramos o efeito do horário de verão sobre o interesse por doenças em duas cidades dos Estados Unidos. Discutimos nossas descobertas no contexto de mudanças hormonais e cuidados com a pele/comportamento.
Palavras-chave: *Cabelo; Caspa; Dermatite; Doenças do cabelo; Luz; Luz solar*

INTRODUCTION

Contributing factors to scalp seborrheic dermatitis (dandruff) development are increased sebum, by-products of microorganisms like *Malassezia yeasts*, and allergic sensitivity. Dandruff is thought to worsen in severity during the winter,[1] when there is later sunrise and less sunlight. We aimed to evaluate potential seasonal fluctuations of search engine interest for "dandruff" and the possible correlation with daylight, sunrise, and DST shifts.

METHODS

We assessed the frequency of search-engine queries for scalp seborrheic dermatitis over five years (2015-2019) to investigate a possible relationship between sunlight and search interest in the United States, Brazil, South Africa, and Colombia. The United States experiences more intense sunlight in June, July, and August; while South Africa and Brazil experience more intense sunlight in December, January, and February. In Colombia, the sunlight intensity is distributed more evenly throughout the year. We selected English-speaking (United States, South Africa) and non-English-speaking countries (Colombia and Brazil). Lay terminology matching the condition and language of each country was used. Google Trends[2] was used to determine the search frequencies (SF) each week relative to the maximum weekly searches each year. Average monthly frequency was taken over five years, and it was used to plot the average relative search interest in a year cycle (Figure 1). To investigate the specific effects of sunrise in the United States, we compared search trends for New York City (NYC, observes DST) and Phoenix (ST) for the year of 2018 (the most recent year without the effect of COVID-19 pandemic) (Figure 2). In the United States, searches for dandruff were estimated to be one hundred thousand to one million per month.

RESULTS

When evaluating interest as compared to daylight, it spiked in the late winter (low sunlight) of both northern (United States) and southern (Brazil, South Africa) locations (Figure 1). Dandruff interest occurred throughout the year along the equator (Colombia), with a reduced interest in the two Equinoxes (March and September). In the context of sunrise time, searches increased in the winter when sunrise was later in both NYC and Phoenix. However, searches decreased in March in NYC but peaked again in April, after "springing forward" (unexpected increase). In contrast, the peak followed a typical reduction as the winter faded in Phoenix, without a spring peak. The peaks of interest followed the sunrise time pattern (Figure 2), suggesting that luminosity in the morning might be protective for dandruff.

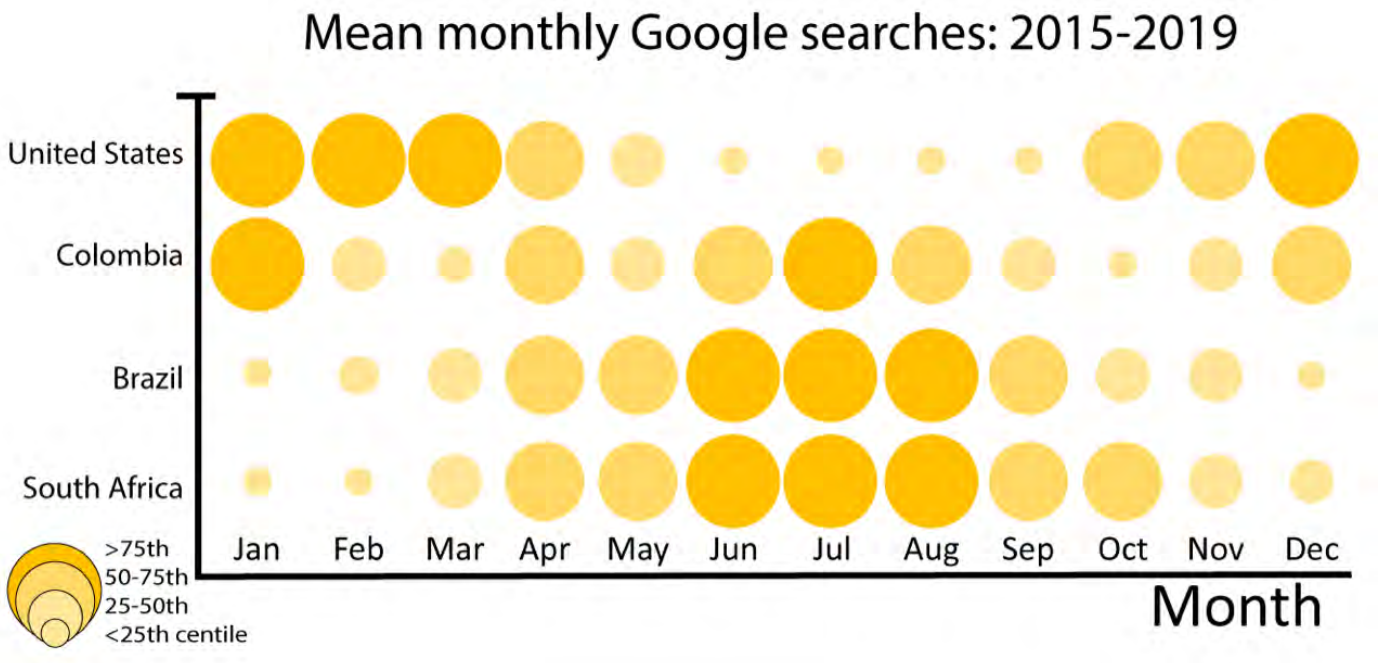

FIGURE 1: Average monthly Google search frequency (2015-2019) of terms related to scalp seborrheic dermatitis in the United States (dandruff), Brazil (caspa), Colombia (caspa), and South Africa (dandruff) over a representative one-year period. Circles are sized in quartiles to show monthly frequency relative to maximum interest.

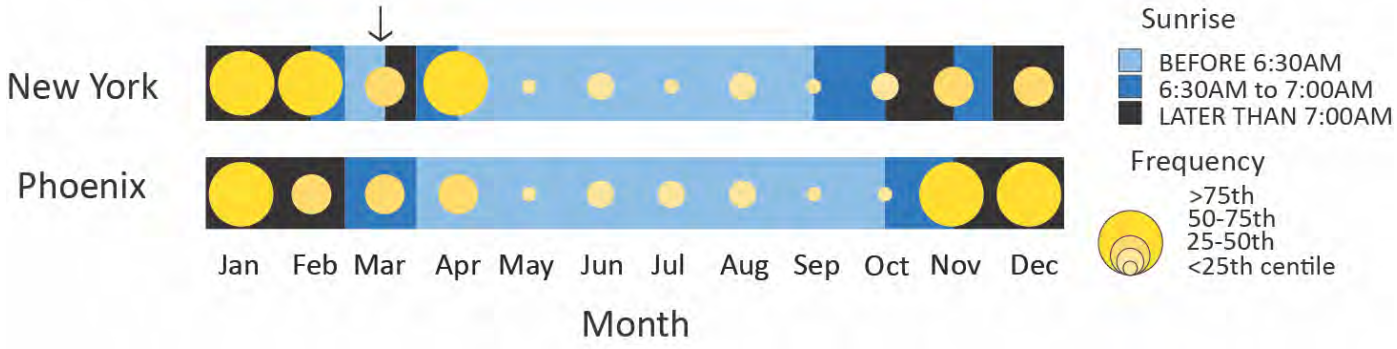

FIGURE 2: Average monthly Google search frequency of "dandruff" in New York City, NY, USA and Phoenix, AZ, USA in 2018. Background coloring represents sunrise time (two-week periods). Daylight saving time changes for New York City occurred on March 11 and November 4. Monthly search frequencies are depicted and sized in quartiles to show monthly frequency relative to maximum interest. Increased interest in dandruff is observed during later sunrise. Increased interest occurs in New York City in April, following the March 11 "spring forward" arrow.

DISCUSSION AND CONCLUSION

During daylight saving, "springing forward" simulates winter mornings, and the interest in dandruff returns to the winter trends. Natural morning light occurs earlier in the summer and later in the winter, which may influence hormone/androgen levels[3] and contribute to the seasonal variations in dandruff, as increased sebum production can occur via increased androgen levels.

This research has several limitations. Our study measured interest (Google searches), not necessarily disease. Other factors could also explain these findings, such as reduced hair washing, increased wintertime interest, or increased media advertising during particular seasons. We could not evaluate hair washing behavior or advertisement trends. Nevertheless, we observe a trend with sunrise/daylight and dandruff search interest. This study suggests that further research should be conducted to assess the correlation between sunlight, sunrise, and dandruff. It could open avenues for the development of sunlight-based therapies for dandruff. ●

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Myomodulation with hyaluronic acid for correction of gummy smile

Miomodulação com ácido hialurônico para o tratamento do sorriso gengival

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ABSTRACT

The "gummy smile" occurs when more than 3-4 mm of gingiva appears during the act of smiling. It is considered unattractive and causes aesthetic disharmony. It has a multifactorial etiology, with several techniques described for its correction. Myomodulation with hyaluronic acid is a non-surgical alternative with immediate and lasting results. In this article, we present a case of myomodulation with hyaluronic acid to correct "gummy smile" in a 31-year-old patient.

Keywords: Hyaluronic acid; Gingiva; Smile

RESUMO

O sorriso gengival ocorre quando há exposição de mais de 3-4 mm de tecido gengival durante o ato de sorrir. É considerado pouco atraente e causa de desarmonia estética. Possui etiologia multifatorial com diversas técnicas descritas para sua correção. A miomodulação com ácido hialurônico é uma alternativa não cirúrgica, com resultados imediatos e duradouros. Neste artigo nós apresentamos um caso de miomodulação com ácido hialurônico para correção do sorriso gengival em uma paciente de 31 anos.

Palavras-chave: *Ácido hialurônico; Gengiva; Sorriso*

Letters

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INTRODUCTION

The discomfort caused by the excessive gingival display, or a "gummy smile", is an increasingly common complaint in dermatology practice. The choice of therapeutic approach must rely on a detailed analysis of the underlying factors.[1] Botulinum toxin is the most popular intervention. However, in some cases, the limitations on the natural movement of the facial muscles cause patient discomfort.[2] In these situations, myomodulation with hyaluronic acid (HA) is an effective alternative that yields immediate and longer-lasting results.[2,3]

This article presents a detailed video analysis of the case of a 31-year-old woman with a gummy smile treated with myomodulation of the involved muscles.

Anatomical evaluation and proposed course of treatment:

Diagnostic assessment: (Figure 1)

Figure 1 analysis shows a gummy smile with an anterior pattern due to hyperactivity of the levator labii superioris/alaeque nasi muscles.[3] Conversely, when the facial muscles are at rest, the corner of the mouth is projected downwards, creating a sullen expression ("sad mouth"). The descended mouth corner causes in this patient are a hyperactive depressor anguli oris muscle, ptosis of the zygomatic retaining ligaments (the attachment points of the main elevation muscles of the mouth, i.e., the zygomaticus major and minor), and deflation of the lateral suborbicularis orbiculi fat (SOOF), which acts as a pulley to facilitate the lifting action of these muscles.[4] There is also some hyperactivity of the depressor septi nasi muscle, as seen in Figure 2.

Proposed treatment: (Figure 2)

1. Supraperiosteal and infrazygomatic lifting and anchoring (using the lift technique[5]) and replacement of SOOF volume to increase the contractile power of the zygomatic muscles and facilitate mouth corner elevation.
2. Reduction of muscle hyperactivity through deposition of hyaluronic acid over the levator labii superioris alaeque nasi and levator labii superioris muscles. We used the same technique to decrease hyperactivity of the depressor septi nasi and correct ptosis of the nasal tip while smiling.
3. Myomodulation of the depressor anguli oris muscles will be performed at a later date.

Treatment steps as shown in the video:

1. Lidocaine 2% with vasoconstrictor is infiltrated into the infrazygomatic region with subsequent puncture using a 21G needle to introduce the cannula;
2. Lifting and anchoring of the zygomatic retaining ligament (using the lift technique[5]) with a 22G rigid cannula and supraperiosteal deposition of three 0.1 mL boluses of high G prime HA on each side. Then, the cannula is placed in the SOOF, and 0.2 mL of HA is deposited on each side, totaling 1 ml of filler.
3. The cannula is oriented toward the ala nasi through the superficial fat pads into the same puncture site.
4. The cannula traverses the nasolabial ligament and reaches the pyriform aperture.

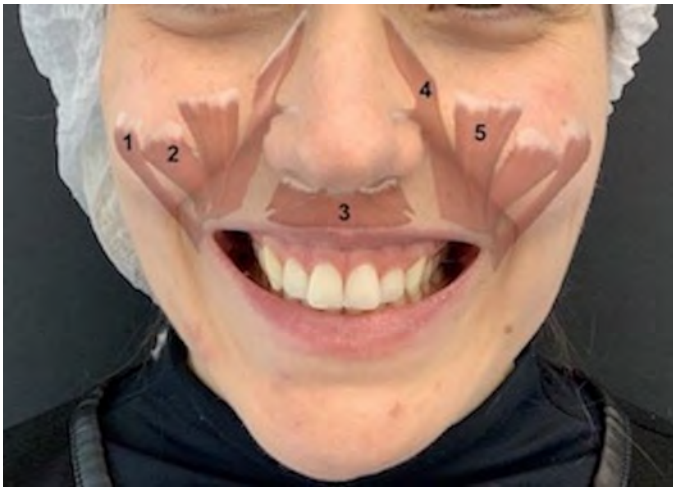

Figure 1: Diagnostic analysis
1. Zygomaticus major m. - **2.** Zygomaticus minor m. - **3.** Orbicularis oris m. **4.** Levator alaeque nasi m. - **4.** Levator labii superioris m.

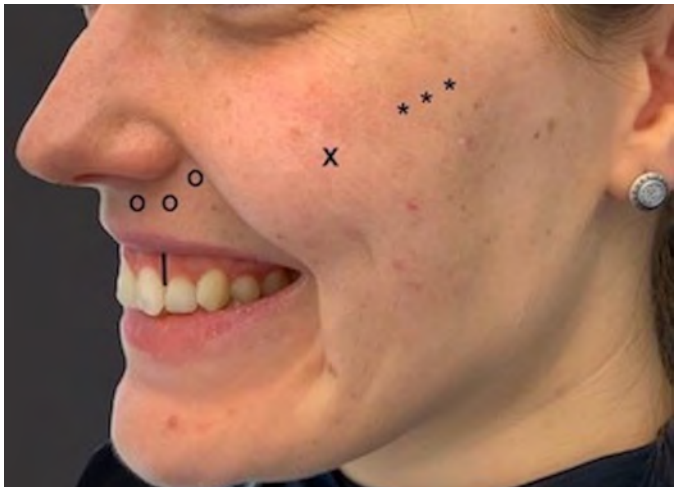

Figure 2: Proposed treatment

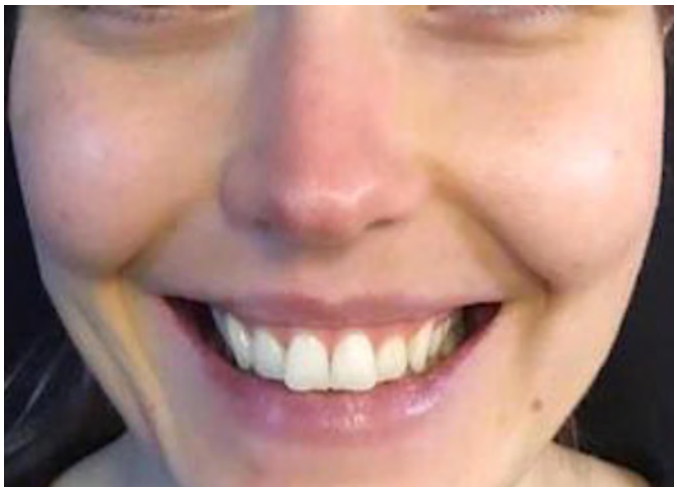

Figure 3: Frontal image after the procedure

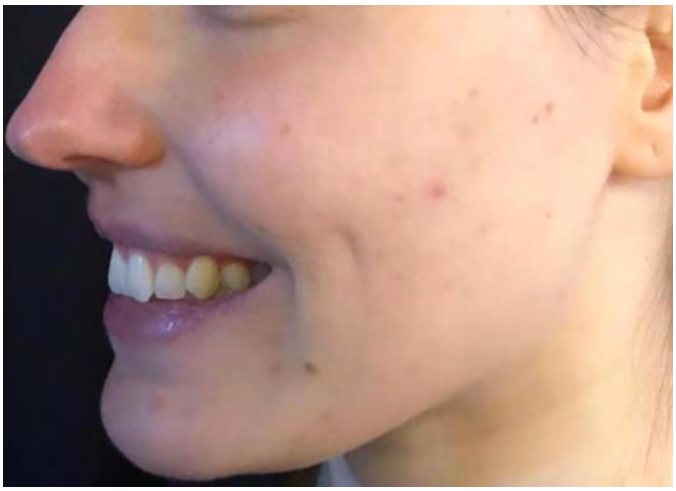

Figure 4: Lateral image after the procedure

5. Intermediate G prime HA was deposited over the levator labii superioris and depressor septi nasi to create a mechanical barrier to their hyperactivity. The volume deposited was 0.3 mL on each side. The filler was infiltrated slowly in microbolus increments of no more than 0.05 mL, to reduce the risk of extrinsic vascular compression. Aspiration of the cannula was always performed before HA deposition.

CAUTION: It is of paramount importance to note that the region of the pyriform aperture is considered to be at high risk of arterial occlusion due to its proximity to the angular artery. We suggest that applications in this region be performed with a 22G cannula, with 8 seconds of aspiration before each slow infiltration of a microbolus (maximum volume 0.05 mL).

6. Immediately after the procedure, there is a noticeable reduction of the gingival display, the elevation of the mouth corners, and improvement of ptosis of the nasal tip while smiling (Figures 3 and 4).

CONCLUSION

Knowledge of anatomical structures and the development of hyaluronic acid-based myomodulation techniques have increased the precision and optimized the outcomes of dermal filler procedures. We believe HA should be considered for correcting the gummy smile in cases where botulinum toxin has yielded unsatisfactory results and when the patient is searching for an immediate, longer-lasting effect. ●

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