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Características Clínicas da Alopecia Frontal Fibrosante no Brasil: Série de 59 Pacientes

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RESUMO – **Introdução**: A alopecia frontal fibrosante (AFF) foi inicialmente descrita em 1994 na Austrália, Europa e América do Norte, e este é o maior estudo sobre as características da AFF na América Latina. **Métodos**: Através de questionários e revisão dos processos clínicos, descrevemos as características de 59 pacientes com AFF, quanto à forma clínica, características individuais e uso de produtos cosméticos. **Resultados**: A idade média dos pacientes foi de 58,4 anos (35-84 anos). A duração da doença variou de seis meses a 20 anos (mediana 5 anos). A maioria das mulheres encontrava-se na menopausa e (83,1%) e era não fumadora (83,1%). Cinco por cento tinham pelo menos uma doença autoimune associada, principalmente hipotireoidismo (13,6%). Seis pacientes (15%) apresentavam líquen plano pigmentoso e dez pápulas faciais (25%). Alopecia dos supracílios ocorreu em 50 (84,7%) e no corpo em 47 (79,7%). Pápulas faciais foram mais prevalentes em mulheres na pré-menopausa. **Conclusão**: Estudar a epidemiologia da AFF pode ajudar a entender a fisiopatologia dessa doença epidémica e este artigo traz algumas semelhanças e diferenças com estudos publicados anteriormente sobre a AFF, como maior frequência em mulheres na pós-menopausa, associação com hipotireoidismo e irritação facial com o uso de produtos cosméticos.
PALAVRAS-CHAVE – Alopecia/epidemiologia; Brasil; Líquen Plano.

Clinical Characteristics of Frontal Fibrosing Alopecia in Brazil: A Series of 59 Patients

ABSTRACT – ***Introduction:*** *Clinical characteristics of frontal fibrosing alopecia (FFA) have been studied since its description in 1994 in Europe, North America and Australia, and the present study is the largest on FFA features in Latin America.* ***Methods:*** *This study, through questionnaire and medical records, describes characteristics of a Brazilian population of 59 patients with FFA, concerning clinical forms, individual features and use of cosmetic products.* ***Results:*** *Mean patients' age was 58.4 years (range 35-84y). Duration of disease varied from six months to 20y (median 5y). Most women were postmenopausal (83.1%) and non-smokers (83.1%). Five percent had at least one associated autoimmune disease, most commonly hypothyroidism (13.6%). Six of 40 patients (15%) had lichen planus pigmentosus and ten had facial papules (25%). Eyebrow alopecia occurred in 50 (84.7%), and body hair loss in 47 (79.7%). Facial papules were more prevalent in premenopausal women.* ***Conclusion:*** *Studying FFA epidemiology may help understanding the pathophysiology of this epidemic disease and this study highlights similarities and differences to previously published studies in FFA, such as greater frequency in postmenopausal women, association with hypothyroidism and facial irritation with cosmetic products.*
KEYWORDS – *Alopecia/epidemiology; Brazil; Lichen Planus.*

INTRODUCTION

Frontal fibrosing alopecia (FFA) is a chronic cicatricial lymphocytic alopecia that turned epidemic in recent years.[1] It affects mainly postmenopausal women, usually starting at the eyebrows or fronto-temporal area of hair implantation.[2,3] The optimal treatment has not been established yet.[3] Clinical and clinicopathologic studies of FFA have been done in Europe, North America and Australia,[3-5] and the present study is the largest on FFA characteristics in Latin America.

The etiopathogenesis of FFA is still unknown. It is assumed

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DOI: https://dx.doi.org/10.29021/spdv.77.4.1119

Recebido/*Received* 2019/10/16 | **Aceite/*Accepted*** 2019/11/25 | **Publicado/*Published*** 2019/12/31

Artigo Original

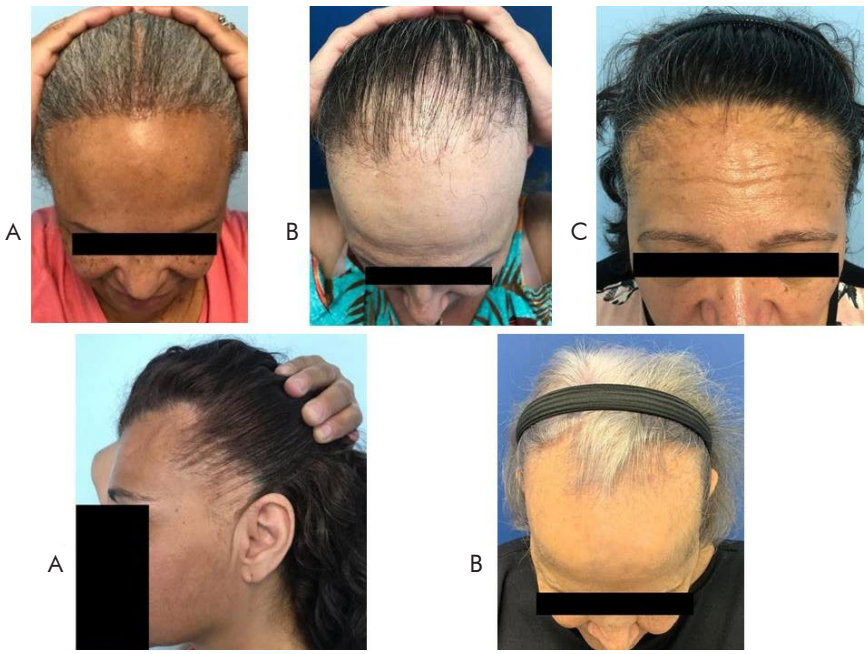

Figure 1

that hormonal, genetic and environmental factors are involved.[6-9] As most patients with FFA are postmenopausal women, in addition to reports of disease improvement with the use of 5-alpha-reductase inhibitors, the hormonal issue was one of the first to be raised.[3]

Familial cases of FFA indicated a possible genetic basis for the disease and have been described since 2008.[10] The genetics of FFA have recently been described. In locus 6p21.[1] there would be an indication that the association is determined by HLA B*07:02, which would confer a fivefold increase in the risk of FFA.[11]

Environmental factors are supposed to be involved in the pathogenesis of FFA, mainly because it is a recently described disease (1994), and it develops in older ages. In 2016, two studies suggested the association of FFA and the use of sunscreens and facial creams.[12,13]

METHODS

All patients with clinical and histological diagnosis of FFA (n=80) observed between 2014 to 2017 (new cases and follow-up) from Dermatology department of Hospital do Servidor Municipal de São Paulo, in Brazil, were invited to respond to 48 questions regarding aspects of the disease and usual habits, especially exposure to personal products (Supplement 1). Fifty-nine accepted to collaborate. The questionnaire was administered by a trained dermatologist. The protocol was approved by the Ethics Committee (CAAE nº 62445116.8.0000.5442).

The clinical patterns (based upon hair line recession)[14-16] (Fig. 1) were defined through patients' photos by a single observer. Clinical data as the presence of lichen planus pigmentosus (Fig. 2), facial papules (Fig. 3), eyebrow and body hair loss, and data on treatment durations, disease stability were

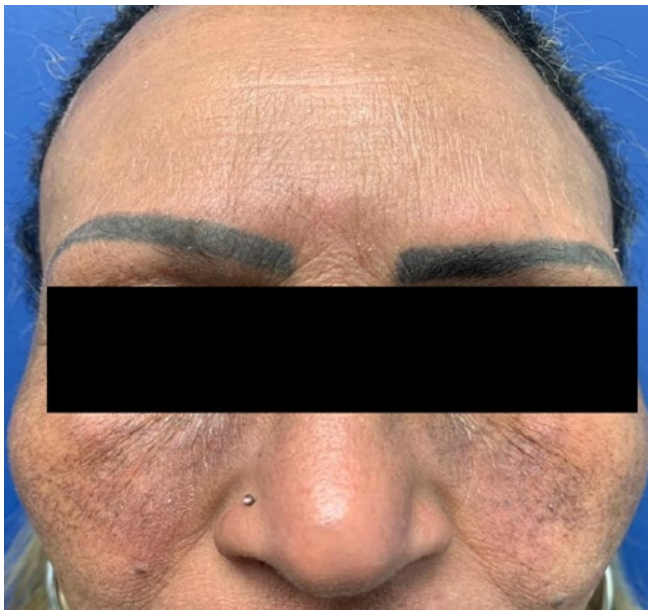

Figura 2

defined through the clinical review of charts. No laboratory or histopathological exams were performed for the study.

Categorical data were expressed as percentage, and numerical data on average +- SD or median with interval between quartiles when appropriate. For numerical data comparison were made through unpaired t-test (normal data) or through Mann-Whitney test (non-normal data). For categorical data, Chi-square test (n>5) or Fisher's exact test (n<5) were used. The level of significance was considered as $p<0.05$.

Epidemiological evaluation of patients treated at the HSPM Trichology Outpatient Clinic from 2014 to 2017

Age ..... years Gender: Woman Men Phototype .....

Profession: ..... Are you currently working on this? Yes No

AFF Running Time: .....

Health problems: .....

Medicinal products in use orally or topically, including vitamins and dietary supplements: .....

.....

.....

Menopausal? Yes No HRT? Yes No

Oral contraceptive? Yes No What? ..... How long? .....

Smoker? Yes No ex-smoker how many years ago? .....

Ethylist? Yes No ex-alcoholist how many years ago? .....

Increased sweating on the face or scalp? ..... (specify where and how long) .....

Proven allergy to any medication? Yes No What? .....

Proven allergy to any cosmetic product? Yes No What? .....

Have you ever undergone chemical peels on your face? Yes No How long ago? .....

Have you had laser treatments on your face? Yes No What? .....

How long ago? ..... How many times? .....

Does your skin become red easily? Yes No When? .....

Do you often use your products at work or leisure, such as chalk, modeling clay, clay, rubbers, ceramics or the like? Yes No Name which: .....

Are you in current treatments for this disease? Yes No How long ago? .....

.....

Have you had previous treatments for this disease? Yes No

What and for how long? .....

.....

Is it itchy at the hair loss site? Yes No Burning? Yes No

Pain? Yes No Loss of body hair? Yes No Where? .....

Loss of eyebrows? Yes No Other skin, mouth or vagina / penis lesions? Yes No

Where? .....

Product Name Current Usage? Use at the time of diagnosis? .....

Facial moisturizers ..... Sunscreens ..... Shampoos .....

.....

Conditioners ..... Hair care products: dyes, straighteners, gels, combing creams .....

.....

Others to remember: .....

.....

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Figura 3

RESULTS

All 59 patients were female, the mean age was 58.4 years (range 35-84y), of whom 31 were Caucasians (52.5%), most of Fitzpatrick's phototype III (45%) and 28 afro-descendants (47.5%). Duration of illness (from onset of patient's perception of the disease until the time of the questionnaire) varied from six months to 20 years, with a median of five years. The mean age at onset of the disease was 52 years and the time to diagnosis was on average six years. Most women were postmenopausal (n= 49; 83.1%), 14 (28.6%) of whom under hormonal replacement therapy, and 49 were non-smokers (83.1%). Five percent had an associated autoimmune disease, most commonly hypothyroidism (13.6%) (Table 1).

As for aesthetic procedures on the face, 11 had already made chemical peels and nine, laser treatments. Thirty-two reported regular use of sunscreen at the time of diagnosis (54.2%) and 33 used facial moisturizers (55.9%). Twenty patients reported intolerance or facial irritation while using cosmetics (33.9%), nine with sunscreens, 13 with moisturizers/anti-aging creams, 8 with foundation and 2 with perfumes.

Thirty-four patients reported facial erythema (57.6%), 19 with sun exposure (32.2%). Twelve patients (20.3%) reported allergies to drugs, mainly to antibiotics; the leading one was penicillin.

Twenty-one (35.6%) had already straightened their hair, 44 had dyed their hair (74.6%) and 16 (27.1%) had already undergone both procedures.

Clinical pattern could be defined in 40 patients by photos, according to Moreno-Arrones *et al*,[14,16] Contin *et al*[16] and Rossi *et al*[15] (Table 2). The most frequently found clinical pattern was diffuse or type 2 (n=19; 47.5%), followed by linear or type 1 (n=9, 22.5%). The patches pattern affected four (10.0%) of the patients, the pseudofringe two (5.0%) and the pattern similar to androgenetic alopecia affected three (7.5%) patients.

Regarding the characteristics of the disease, six of 40 patients (15%) had lichen planus pigmentosus, and ten had papules on the face (25%). No patient presented lesions of lichen planus in other regions.

Concerning disease symptoms, six (10%) patients presented pain and/or burning, and 31 (51.5%) reported pruritus. Eyebrow alopecia occurred in 50 (84.7%), and body hair loss in 47 (79.7%), mainly in the upper limbs.

Respecting treatment, 16 (27.1%) patients are not currently being treated, and the most commonly used medications were doxycycline, hydroxychloroquine and finasteride, in various combinations, with topical drugs as well. Single drug treatment did not occur.

Response to treatment could be assessed in 41 patients through medical records and photos, with stabilization of the clinical picture in 11 patients (26.8%).

DISCUSSION

In search for its etiopathogenesis, the number of published articles on FFA has grown, and environmental factors have been suggested.[5,12,13]

This study, through questionnaire and medical records, describes the characteristics of a Brazilian population of 59 patients with FFA, concerning clinical forms, individual characteristics and use of cosmetic products.

When comparing present data with the literature, we observed a balanced division between Caucasians and Afro-descendants ($p>0.05$), which should reflect the great miscegenation of our population, as it can be seen in another Brazilian study.[17]

Our data reflects a slightly earlier age of onset of FFA (52y) compared to the literature.[4,18] As in previous studies, most patients are postmenopausal, but unlike these, the prevalence of women under hormone replacement therapy is lower (28.6%) compared some reports.[19]

Eyebrow alopecia was very frequent in our series, as well as hair loss in the limbs and genital region. Facial papules were more prevalent in premenopausal women, but with no difference in relation to ethnicity, differently from Mervis *et al*.[20] The predominant clinical pattern was diffuse FFA (II) similarly to Moreno-Arrones *et al*.[14]

The use of moisturizers and anti-aging creams was less frequent than in Moreno-Arrones study,[5] but the use of sunscreens was larger.

As for comorbidities, hypothyroidism was common among patients with FFA, with a lower prevalence than in other studies,[4,19] but similar to Brazilian studies.[17,21] In the authors experience, patients who were treated for FFA with doxycycline, hydroxychloroquine or finasteride had a slightly better control of the symptoms and clinical signs, such as positive pull test and pruritus, but progression seems to have its natural way and is limited to the natural history of the disease, which is still unknown.[7] Loss of body hair did not seem to be reversed

Table 1 - Clinical profile of Brazilian 59 FFA patients compared to literature.

Study	This study	JDD review[4]	Vaño-Galvan[3]	Chile[18]	Mayo Clinic[19]	Secchin, Brazil[17]	Kusano, Brazil[21]
Number of patients	59	932	289	27	148	16	38
Sex	59 F	96.9% F	289 F	26 F/1 M	148 F	16 F	38 F
Age	mean 58.4 y (35-84)	---	60 y (32-91)# p=0.433		---	mean 62 y # p=0.233	61 y # p=0.239
Age at onset	52.02 y	55.6 y	---	57.5 y	---	---	44 y / 59 y**
FFA duration	median 5 y	3.7 y	---	---	---	---	---
Age at diagnosis	---	60.6 y	---	---	62.1 y	---	---
Race	white 30 (50.8%) black 29 (49.2%)	white 86% p<0.001 black 12% p<0.001	---	---	white 89.2 p<0.001 black 5.4% p<0.001	black 56.3% p=0.648	
Post-menopausal	49 (83.1%)	84.14% p=0.832	---	---	87.2% p=0.442	15 (93.8%) p=0.283	---
Pre-menopausal	10 (16.9%)	15.6% p=0.790		---	---	---	---
HRT	14/49 (28.6%)	---	19% p=0.123	---	63.3% p<0.001	---	16 (42.1%) p=0.188
Comorbidities							
Hypothyroidism	8 (13.6%)	1.4% p=0.004	20.8 p=0.204	---	44.6% p<0.001	3 (18.8%) p=0.603	11 (28.9%) p=0.064
SAH	20 (33.9%)	5.9 % p<0.001	---	---	37.2% p=0.656	8 (50%) p=0.238	18 (47,4%) p=0.093
DM	12 (20.3%)	---	0.3% p<0.001		3.4% p<0.001	2 (12.3%) p=0.475	2 (5.3%) p=0.039
Dyslipidemia	7 (11.9%)	10.2% p=0.677	---	---	45.3% p<0.001		14 (36.8%) p=0.004
Autoimmune diseases	3 (5%) SLE 1, PM-1 Hepatitis 1	3.1% p=0.422	---		41 (27.7%)*** SLE 5(3.4%) p=0.598	14 @ SLE 4 (25%) p<0.001	& SLE 1(2.6%) p=0.753
Osteoporosis	4 (6.8%)	4% p=0.297	---	---	15.5% p<0.093	---	1 (2.63%) p=0.367
Clinical symptoms and signs							
Pruritus	31(51.5%)				66.7% p=0.042	10(62.5%) p=0.478	
Pain	6 (10.2%)				27.7% p=0.007	4 (25.0%) p=0.122	
Facial erythema	22(37.3%)						
Alopecia							
Eyebrows	50(84.7%)	70.4% p=0.036			60.1% p=0.004	14 (87.5%) p=0.782	34 (89.5%) p=0.505
Axillae	15(25.4%)	15.2% p= 0.093			15.5% p=0.963	6 (37.5%)	21 (55%) p=0.003
Genital	11(18.6%)	11.7% p=0.203			7.4% p=0.036		
Limbs	41(69.5%)	7.4% p<0.001			9.5% p<0.001	5 (31.25%) p=0.005	
Eyelashes	1 (1.7%)	1.4% p=0.820					
Lichen planus pigmentosus	5 (8.5%)				18.2% p=0.143	5(31.6%) a p=0.018	1 (2.6%) b p=0.244

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Table 1 - Clinical profile of Brazilian 59 FFA patients compared to literature. (Cont.)

Study	This study	JDD review[4]	Vaño-Galvan[3]	Chile[18]	Mayo Clinic[19]	Secchin, Brazil[17]	Kusano, Brazil[21]
Number of patients	59	932	289	27	148	16	38
Environemental factors							
Cosmetic use (Current %)							
Moisturizers	17 (28.8%) Past – 7	---	89.6 $p<0.001$	---	---	---	---
Sunscreens	46 (77.9%) Past – 30	---	48.1 $p<0.001$	---	---	---	23 (60.5%) $p=0.064$
Antiaging/ antiwrinkle	25 (42.4%) Past – 22	---	78.5 $p<0.001$	---	---	---	---
Hair dyes	38 (64.4%) Past – 32	---	---	---	---	---	33 (86.4%) $p=0.05$
Hair straightener	12 (20.3%) Past – 13	---	---	---	---	---	---
Cosmetic "allergy"	20 (33.4%)	---	---	---	---	---	---
Smoking	10 (16.9%)	---	---	---	---	---	---
Medications (n=130)							
Chloroquine	13 (22%)	7 (5.4%) $p<0.001$	---	26% $p=0.684$	---	7 (43.8%) $p= 0.082$	27 (71.1%) $p<0.001$
Minoxidil	18 (30.5%)	---	---	55.6% $p=0.026$	---	14 (87.5%) $p< 0.001$	---
Isotretinoin	1 (1.7%)	---	---	0 $p=0.496$	---	---	---
Topical steroids	8 (13.6%)	33 (25,4%) $p<0.001$	---	100% $p<0.001$	---	10 (62.5%) $p< 0.001$	---
Intralesional steroid	1 (1.7%)	21 (16.2%) $p=0.004$	---	0 $p=0.496$	---	---	---
Doxycycline	21 (35.6%)	---	---	---	---	5 (31.8%) $p=0.746$	---
Finasteride Dutasteride	17 (28.8%)	20 (15.4%) $p=0.032$	---	29.6% $p=0.940$	---	10 (62.5%) $p=0.13$	17 (44.8%) $p=0.110$
Tacrolimus	8 (13.6%)	---	---	---	---	11 (68.8%) $p< 0.001$	---
Methotrexate	1 (1.7%)	---	---	---	---	---	---
Clinical Stability	28/39 (71.8%)	---	---	---	40/95 (42.1%) p=0.002	---	20 (52.6%) $p= 0.083$

Note: # standard deviation estimated by amplitude / 4
* "Allergy" to cosmetics was documented with the patient's report of some reaction to the use of cosmetic products. It does not mean true allergy. Patch test was not performed. ##- no current smokers
** Age of onset in pre- and postmenopausal patients
*** Sjögren syndrome 6 (4.1%), scleroderma 2 (1.4%), psoriasis 11 (7.4%), IBD 8 (5.4%), celiac disease 3 (2%), rheumatoid arthritis 2 (1.4%)
@ 5DLE, vitiligo 3 (18.8%), psoriasis 1 (6.3%), Hashimoto's thyroiditis 2 (12.3%)
& vitiligo 2 (5.3%), psoriasis 1 (2.6%)
[a]- 1 case of oral lichen planus (6.3%); [b]- 1 case of nail lichen planus (2.6%)
DLE (discoid lupus erythematosus); DM (diabetes mellitus); HRT (hormone replacement therapy); IBD (inflammatory bowel disease); LPPig (lichen planus pigmentosus); s. (syndrome); SAH (systemic arterial hypertension); SLE (systemic lupus erythematosus); PM (polymyositis)

Table 2 - Clinical patterns of the FFA Brazilian patients (40 patients evaluated out of 59) compared to literature.

Clinical pattern	Our study 40 patients	Moreno-Arrones[5] 242 patients	Statistical difference
Only eyebrow alopecia	1 (2.5%)	-	
Patches	4 (10.0 %)	-	
Linear (type 1)	9 (22.5 %)	118 (48.8 %)	p=0.002
Difuse (type 2)	19 (47.5 %)	109 (45.0 %)	p=0.769
Pseudofringe (type 3)	2 (5.0 %)	15 (6.2%)	p=0.768
AGA like	3 (7.5 %)	-	
No defined pattern	2 (5 %)	-	

Table 3 - Presence of facial papules in our study (40 patients evaluated) compared to literature.

	Mervis[20]	Our study	*p*
With papules	24 (26%)	10/40 (25%)	0.760
Premenopausal with papules	12/30 (40%)	4/7 (57.1%)	0.410
Postmenopausal with papules	11/57 (19%)	6/33 (18.2%)	0.938
Total	87	40	

or affected by treatment. Some patterns seem to have a better prognosis than others, like the patchy, masculine and pseudo-fringe types. Others, like FFA type two and patients with other autoimmune diseases, such as lupus erythematosus, polymyositis and autoimmune hepatitis, seem to have a more aggressive behaviour.

We used hydroxychloroquine and 5-alpha-reductase inhibitors similarly to Chileans18 and Secchin in Brazil,[17] but the former less frequently and the latter more frequently than reported in Valesky *et al*,[4] and Kusano in Brazil.[21] In our series, the use of topical corticosteroids and intralesional infiltration of corticosteroids was lower as compared with most other studies.[4] This may reflect the current fear of atrophy with injectable corticosteroids in Brazil.

Comparing FFA treatments with the literature is still a difficult task. Each research centre uses a stability parameter (photos, LPPAI, ruler measurement etc.) and single treatments are not attempted. Indeed there are multiple treatment protocols, which makes comparisons fragile.

Possible limitations of this study are recall bias, the retrospective nature of the study and lack of generalization.

FFA presents certain peculiarities in each of the population groups studied. Particular features in this group are a greater frequency in post-menopausal women, association with hypothyroidism and facial irritation with cosmetic products usually used. Studying epidemiology of FFA may help understanding the pathophysiology of this epidemic disease and the present study shows similarities and differences from previously published studies.

Conflitos de interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Suporte financeiro: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Proteção de pessoas e animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.

Conflicts of interest: *The authors have no conflicts of interest to declare.*
Financing support: *This work has not received any contribution, grant or scholarship.*
Confidentiality of data: *The authors declare that they have followed the protocols of their work center on the publication of data from patients.*
Protection of human and animal subjects: *The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).*

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Proveniência e revisão por pares: Não comissionado; revisão externa por pares
Provenance and peer review: *Not commissioned; externally peer reviewed*

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