Clinical-histopathological profile of the frontal fibrosing alopecia: a retrospective study of 16 cases of a university hospital*

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Abstract: Background: Frontal fibrosing alopecia is a condition of unknown origin, histologically similar to classic lichen planopilaris and generally observed in postmenopausal women with alopecia of the frontal-temporal hairline.
Objectives: To describe the clinical, dermatoscopic, and histopathological characteristics and the treatment used in patients who have frontal fibrosing alopecia at the Alopecia Outpatient Clinic in a university hospital.
Methods: Retrospective descriptive study performed by reviewing medical charts and biopsies of the scalp.
Results: Sixteen patients were analyzed, all of them female, 93.75% of them postmenopausal, and 56.25% brown-skinned. All had frontal alopecia (100%), followed by temporal alopecia (87.5%) and madarosis (87.5%). On dermatoscopy, perifollicular erythema and tubular scales were found as a sign of disease activity. Of the patients, 68.75% had associated autoimmune diseases, including lupus, thyroid disease and vitiligo. Of the 13 biopsies from 8 patients, 10 showed microscopic aspects compatible with frontal fibrosing alopecia. Laboratory tests did not show major abnormalities and minoxidil was the most used treatment.
Study limitation: Data collection limited by the study's retrospective design associated to flaws while filling in the medical charts and absence in standards to the collection and processing of the pathology and histopathological examination.
Conclusions: A demographical, clinical, and histopathological description of 16 patients diagnosed with frontal fibrosing alopecia, which remains a challenging disease, of unknown origin, and frequently associated with autoimmune diseases. This study reinforces literary findings. However, more research is needed to establish the pathogenesis and effective treatments.
Keywords: Alopecia; Autoimmune diseases; Retrospective studies; Therapeutics

INTRODUCTION

It is estimated that the scalp has about 100,000 to 150,000 pilosebaceous follicles and hair rarefaction can generate psychological, social and cultural stigmas, and alopecia is a frequent dermatological complaint.

Signs of hair loss may be subtle and the dermatologist should perform a systematic approach to their evaluation, including detailed history, clinical, trichoscopic, laboratory and histopathological examination.

Alopecia can be classified into non-scarring and scarring. The scarring ones constitute a group of diseases that result in permanent loss of hair due to destruction of the hair follicles and their replacement by connective tissue.[1] They can be subdivided into two categories: those in which the follicles appear to be the target of the inflammation (primary) and those in which the process destroys follicular structures in a non-specific way (secondary).[2]

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Frontal fibrosing alopecia (FFA) is a type of primary cicatricial alopecia that affects predominantly postmenopausal women, affects the frontotemporal region, and can extend to the occipital region, being frequent the involvement of the eyelashes and also other sites of the body. Histopathologically, its findings are indistinguishable from those described in lichen planopilaris (LPP), including replacement of follicular units by connective tissue, perifollicular lymphocytic lichenoid infiltrate, basal layer vacuolar degeneration and perifollicular fibrosis, particularly around the infundibulum and isthmus.[1]

The aim of this study is to describe the demographic, clinical, dermatoscopic, and histopathological profile of patients with FFA as well as the treatments used. They were treated at the Alopecia Outpatient Clinic of a university hospital.

METHODS

A retrospective cohort study was carried out based on the analysis of medical charts and review of slides containing histological sections stained by Hematoxylin & Eosin from patients who underwent a scalp biopsy for diagnostic confirmation. The patients studied were seen at the Hospital Universitário Clementino Fraga Filho (HUCFF), Universidade Federal do Rio de Janeiro (UFRJ), between January 2015 and December 2016.

All patients with clinical and/or histopathological diagnosis of FFA were included in the study. Those who did not present sufficient data due to lack of records were excluded.

The variables studied were: gender, age, color/race and menopausal status, comorbidities, associated symptoms (pruritus, pain, burning), area of alopecia, dermatoscopic findings (perifollicular erythema and tubular scales) and histopathological findings (hyperkeratosis, follicular ostium hypergranulosis, acanthosis, superficial perivascular mononuclear inflammatory infiltrate, pigmentary incontinence, vertical dermal fibrosis, perifollicular inflammatory infiltrate, perifollicular fibroplasia, vacuolar degeneration of the basal layer of the follicular epithelium and thinning of the external root sheath), laboratory tests (complete blood count, iron studies, liver function test, lipids, vitamin D, ESR, CRP, ANA, renal and hormonal functions) and treatment used.

The data were tabulated in spreadsheets and descriptive statistics were applied using the Excel program (Microsoft Office, version 2010).

RESULTS

A total of 171 patients were treated at the Alopecia Clinic between January 2015 and December 2016, of whom 112 (65.50%) had non-scarring alopecia, 51 (29.82%) had scarring alopecia and 8 (4.68%) patients with an association of both types.

Sixteen (9.36%) patients were diagnosed with FFA, all were female and the ages ranged from 29 to 80 years, with a mean of the age 62 (Figure 1). Most were postmenopausal (93.75%) and were brown-skinned (56.25%) (Table 1).

Among the comorbidities investigated, 8 patients had discoid and/or systemic lupus erythematosus, 8 had hypertension, 6 had thyroid disease, 5 had lichen planus pigmentosus, 3 vitiligo, 2 patients were diabetic, 1 had psoriasis and 1 oral lichen planus (Table 1).

As for the site of alopecia, all had frontal alopecia and the majority temporal (87.5%) and madarosis (87.5%) (Table 1) (Figure 1). One patient was asymptomatic, 10 reported pruritus, 5 burning and 4 felt pain. Regarding dermatoscopy, 14 cases (87.5%) exhibited perifollicular erythema and 10 (62.5%) tubular scales (Table 1).

Among the laboratory results found in the charts, vitamin D was low in 3 out of 8 of them, reactive ANA in 3/7, elevated TSH in 3/9, elevated CRP in 5/6, elevated ESR in 4/9 patients. Blood count, iron studies, liver function test, lipids, and renal and hormonal functions showed no abnormalities.

Thirteen scalp biopsies were found from 8 patients. Four patients had one sample, three had two samples and one had three samples, one of the biopsies had been performed 8 years before the other two. Vertical serial cuts were performed in 12 samples and horizontal in one sample. Of the 12 biopsies whose vertical sections were analyzed, 9 biopsies presented hyperkeratosis, 9 showed follicular ostium hypergranulosis, 8 exhibited acanthosis and 5 had vertical dermal fibrosis. These findings were not possible to evaluate in the horizontally cut sample. Superficial perivascular mononuclear inflammatory infiltrate was seen in 13 cases and melanophages were found in 3 of them. Perifollicular mononuclear inflammatory infiltrate, in the infundibulum/isthmus area, was seen in 10 of the 13 cases and in 5 of them the inflammatory cells presented lichenoid distribution. In 7 biopsies there was perifollicular fibroplasia, in 4 vacuolar degeneration of the basal layer of the follicular epithelium was observed and in 4 thinning of the follicular epithelium was seen.

The treatment options used are described in table 2, with the majority of patients using 5% minoxidil, 0.1% tacrolimus, 0.05% clobetasol propionate and finasteride.

DISCUSSION

FFA was first described in 1994 by Steven Kossard.[3] It is a primary lymphocytic scarring alopecia mainly characterized by progressive loss of frontotemporal hairline and eyebrows in postmenopausal women, although premenopausal women and men

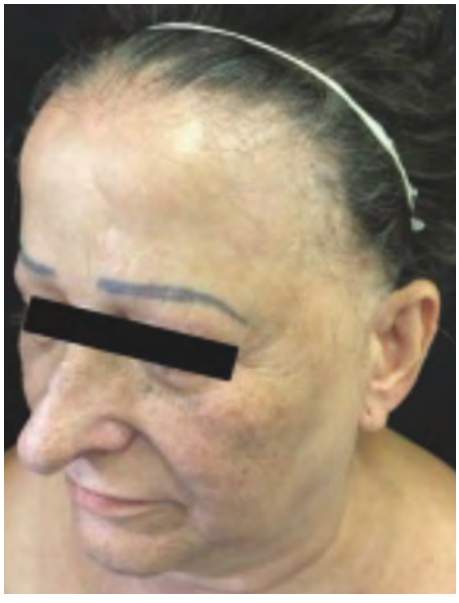

Figure 1: A 69-year-old female patient with frontotemporal alopecia and madarosis

Table 1: Demographic and clinical characteristics of patients with FFA

Patient	Age	Skin color	Comorbidities	LPPig	Frontal Alopecia	Temporal Alopecia	Madarosis	Axillary and pubic alopecia	All-over--the-body alopecia	Alopecia on the limbs	Perifollicular erythema	Tubular scales
1	72	White	SAH, SLE, LED	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes
2	80	White	None	No	Yes	Yes	Yes	No	No	No	Yes	Yes
3	70	White	SLE, hypothyroidism, Vitiligo	No	Yes	Yes	Yes	No	No	No	Yes	Yes
4	55	Brown	Vitiligo	Yes	Yes	Yes	Yes	Yes	No	No	No	No
5	60	Brown	SAH, DM, SLE, Hypothyroidism	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6	61	Brown	None	No	Yes	No	Yes	No	No	No	Yes	Yes
7	61	Brown	SLE, Hashimoto's thyroiditis, OLP	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes
8	29	Brown	SLE, LED, vitiligo	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
9	70	Brown	SAH, DM, LED	No	Yes	Yes	Yes	No	No	No	Yes	No
10	53	White	Hashimoto's thyroiditis	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No
11	65	Brown	SAH	Yes	Yes	Yes	Yes	No	No	No	Yes	No
12	73	Black	SAH, LED, Hyperparathyroidism	No	Yes	No	No	No	No	No	Yes	No
13	55	Brown	None	Yes	Yes	Yes	Yes	No	No	No	No	Yes
14	51	White	SAH, LED, psoriasis	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
15	62	Brown	SAH, hypothyroidism	Yes	Yes	Yes	No	No	No	No	Yes	Yes
16	69	White	HAS	No	Yes	Yes	Yes	No	No	Yes	Yes	No
Total (%)	62 (average)	-	-	5 (31,6%)	16 (100%)	14 (87,5%)	14 (87,5%)	6 (37,5%)	2 (12,5%)	5 (31,25%)	14 (87,5%)	10 (62,5%)

SAH: systemic arterial hypertension; **DM:** diabetes mellitus; **SLE:** systemic lupus erythematosus; **OLP:** oral lichen planus. **LED:** discoid lupus erythematosus

may also be affected. Vañó-Galvan *et al* studied 355 patients with FFA being 97% female and 86% postmenopausal, 98.5% Caucasians and with a mean age of 61 years; our results were similar to even though most patients were brown-skinned. [4]

In a study in 2014, with 62 patients with FFA, frontotemporal alopecia was observed in all patients, then the loss of eyebrows (81%) axillary and pubic hair (53%) and in the rest of the body (19%).[5] Similar data have been found in our study and in other publications.[6-9] It is noteworthy that eyebrow loss may be an early presentation and it is recommended that the dermatologist biopsy the site to diagnose FFA early and avoid permanent hair loss.[10]

AFF may have an asymptomatic course, but most patients report burning, itching or pain in the scalp.[5,7] In this study, pruritus was the most reported complaint.

Trichoscopy is an easily accessible, non-invasive and economical tool, being important for the assessment of the severity and for differential diagnoses with other types of alopecia. Signs of local inflammation of hair follicles such as tubular scales at the base of the stems and perifollicular erythema are indications of disease activity and indicate the need for treatment.[1,5] The absence of follicular ostia is seen in the final phase of the disease. According to Fernández-Crehuet *et al,* in a review of 249 cases, the presence of tubular scales at the base of the hair was seen in 89% of the cases, perifollicular erythema in 77% and isolated hairs in 67.9%; our cases showed similar data. [11]

The pathogenesis of FFA is not yet understood. It is suggested to be an immunomediated disease with the participation of cytotoxic T cells in the inflammatory process. The destruction of the follicle would be due to a continuous inflammatory response triggered by proinflammatory cytokines.

Since FFA is frequently concomitant with other autoimmune diseases such as thyroid disease, vitiligo, lupus, Sjogren's Syndrome and psoriasis, it is possible to assume common pathogenic mechanisms for these conditions.[5,8,9,12,13] This association between FFA and autoimmune diseases was found in 30% of patients by Mac Donald *et al,*[8] and, in our study it was observed in 68.75% of the cases. Hypothyroidism was reported more frequently in patients with FFA than the general population (15% to 4.2%).[4] In addition, autoimmune diseases could guide early detection in those patients with a genetic predisposition to the development of FFA, as well as the diagnosis of FFA should guide the investigation of other autoimmune diseases, especially thyroid disease and lupus. Other hypotheses have also been cited by some authors, such as heredity and hormonal factors; however, further studies are needed to define the pathogenesis. [9,14,15]

Lichen planus pigmentosus is a macular variant of lichen planus characterized by brown, hyperchromic and reticulate patches in photoexposed areas and flexures. In 2013, Dlova reported the concomitance of LPPig with FFA in 54.54% of the patients studied, most of them in pre-menopause and with high phototype; in our study, it was found in 31.6% of the cases. [16]

There are few reports in the literature of laboratory abnormalities; however, Vañó-Galván *et al* recommend investigating the presence of associated thyroid disease.[4,7,9] In our series, laboratory

Table 2: Treatments used by patients with FFA

Patient	Minoxidil 5%	Clobetasol 5%	Prednisone	Tacrolimus 0.1%	Hydroxychloroquine	Finasteride	Doxycycline	Dapsone
1	X	X		X		X	X	
2				X	X	X		
3	X	X	X	X	X	X	X	
4	X	X						
5	X			X		X		
6	X		X	X			X	
7	X	X						
8	X			X	X	X		
9	X	X		X	X	X		
10	X	X		X	X	X	X	
11	X			X	X	X		
12	X	X			X			
13	X			X		X		
14		X		X		X	X	X
15	X	X						
16	X	X						
Total (%)	14 (87.5%)	10 (62.5%)	2 (12.5%)	11 (68.75%)	7 (43.75%)	10 (62.5%)	5 (31.25%)	1 (6.25%)

data were not available for all the patients, due to the fact that this is a retrospective study. Despite that, positive ANA, increased CRP, ESR and TSH; and low vitamin D were found.

The histopathological picture of FFA was described by Kossard in 1994 after analysis of scalp biopsies of 6 postmenopausal patients.[3] Samples were obtained from the frontal hairline and showed a lymphocytic inflammatory infiltrate concentrated around the follicular isthmus/infundibulum and perifollicular fibrosis, which are indistinguishable from those observed in lichen planus pilaris. These aspects were confirmed by subsequent reports and are in accordance with the data observed in the present study, in which 10 of the 13 samples analyzed presented perifollicular inflammatory infiltrate in the isthmus/infundibulum area and 7 of them had associated perifollicular fibrosis.[17,18]

There is no standardized therapy for FFA. The treatment aims to reduce inflammation, decrease sequelae and slow the progression of the disease. Rácz *et al* carried out a literature review of the treatments used in 114 patients and observed that 5-alpha reductase inhibitors were used most of the time, resulting in a good clinical response in 45% of them. However, it is questioned whether its effectiveness could be due to the improvement of associated androgenetic alopecia.[19] The same questioning is required for the use of minoxidil, since it increases capillary density in the treated area, but does not seem to modify the course of the disease. Other options include hydroxychloroquine/chloroquine, cyclosporine, doxycycline/minocycline, mycophenolate mofetil, topical and oral corticosteroids, and calcineurin inhibitors.[1,4,5,9,19] Rakowska *et al* have recently shown good results with retinoids, isotretinoin and acitretin.[20] Minoxidil was therapy used in our study. The use of immunobiologics may be an alternative in the future and there is a report of complete resolution of LPP in a patient with chronic juvenile arthritis treated with rituximab (anti-CD20 antibody).[21] Hormone replacement therapy shows no efficacy.[3] Fertig and Tosti suggested that oral finasteride associated with hydroxychloroquine, topical inhibitors of calcineurin (tacrolimus) and Excimer Laser would have positive results in the treatment of FFA.[22] However, controlled and randomized clinical trials are still required.

CONCLUSION

FFA remains a challenging disease, of unknown origin, histologically similar to classic LPP and is commonly seen in postmenopausal women. Although clinically characterized as frontotemporal hairline alopecia, madarosis and perifollicular erythema, there is no established effective therapy. We present the demographic, clinical and histopathological description of 16 patients diagnosed with FFA, mostly treated with minoxidil. It should be noted that most of them had concomitant autoimmune disease, such a finding could possibly serve as an indicator for investigation in the setting of AFF. Randomized and controlled multicenter trials are needed to attempt to establish the pathogenesis and an appropriate treatment.❑

REFERENCES

1. Bolduc C, Sperling LC, Shapiro J. Primary cicatricial alopecia: Lymphocytic primary cicatricial alopecias, including chronic cutaneous lupus erythematosus, lichen planopilaris, frontal fibrosing alopecia, and Graham-Little syndrome. J Am Acad Dermatol. 2016;75:1081-99.
2. Sperling LC. An atlas of hair pathology with clinical correlations. Boca Raton: Parthenon Publishing Group; 2003.
3. Kossard S. Postmenopausal frontal fibrosing alopecia. Scarring alopecia in a pattern distribution. Arch Dermatol. 1994;130:770-4.
4. Vañó-Galván S, Molina-Ruiz AM, Serrano-Falcón C, Arias-Santiago S, Rodrigues-Barata AR, Garnacho-Saucedo G, et al. Frontal fibrosing alopecia: a multicenter review of 355 patients. J Am Acad Dermatol. 2014;70:670-8.
5. Banka N, Mubki T, Bunagan MJ, McElwee K, Shapiro J. Frontal fibrosing alopecia: a retrospective clinical review of 62 patients with treatment outcome and long-term follow-up. Int J Dermatol. 2014;53:1324-30.
6. Chew AL, Bashir SJ, Wain EM, Fenton DA, Stefanato CM. Expanding the spectrum of frontal fibrosing alopecia: a unifying concept. J Am Acad Dermatol. 2010;63:653-60.
7. Samrao A, Chew AL, Price V. Frontal fibrosing alopecia: a clinical review of 36 patients. Br J Dermatol. 2010;163:1296-300.
8. MacDonald A, Clark C, Holmes S. Frontal fibrosing alopecia: a review of 60 cases. J Am Acad Dermatol. 2012;67:955-61.
9. Esteban-Lucía L, Molina-Ruiz AM, Requena L. Update on Frontal Fibrosing Alopecia. Actas Dermosifiliogr. 2017;108:293-304.
10. Anzai A, Donati A, Valente NY, Romiti R, Tosti A. Isolated eyebrow loss in frontal fibrosing alopecia: relevance of early diagnosis and treatment. Br J Dermatol. 2016;175:1099-101.
11. Fernández-Crehuet P, Rodrigues-Barata AR, Vañó-Galván S, Serrano-Falcón C, Molina-Ruiz AM, Arias-Santiago S, et al. Trichoscopic features of frontal fibrosing alopecia: results in 249 patients. J Am Acad Dermatol. 2015;72:357-9.

12. Miteva M, Aber C, Torres F, Tosti A. Frontal fibrosing alopecia occurring on scalp vitiligo: report of four cases. Br J Dermatol. 2011;165:445-7.
13. del Rei M, Pirmez R, Sodré CT, Tosti A. Coexistence of frontal fibrosing alopecia and discoid lupus erythematosus of the scalp in 7 patients: just a coincidence? J Eur Acad Dermatol Venereol. 2016;30:151-3.
14. Tziotzios C, Stefanato CM, Fenton DA, Simpson MA, McGrath JA. Frontal fibrosing alopecia: reflections and hypotheses on aetiology and pathogenesis. Exp Dermatol. 2016;25:847-52.
15. Navarro-Belmonte MR, Navarro-López V, Ramírez-Boscà A, Martínez-Andrés MA, Molina-Gil C, González-Nebreda M, et al. Case series of familial frontal fibrosing alopecia and a review of the literature. J Cosmet Dermatol. 2015;14:64-9.
16. Dlova NC. Frontal fibrosing alopecia and lichen planus pigmentosus: is there a link? Br J Dermatol. 2013;168:439-42.
17. Kossard S, Lee MS, Wilkinson B. Postmenopausal frontal fibrosing alopecia: a frontal variant of lichen planopilaris. J Am Acad Dermatol. 1997;36:59-66.
18. Feldmann R, Harms M, Saurat JH. Postmenopausale frontale fibrosierende Alopezie. Der Hautarzt. 1996;47:533-6.
19. Rácz E, Gho C, Moorman PW, Noordhoek Hegt V, Neumann HA. Treatment of frontal fibrosing alopecia and lichen planopilaris: a systematic review. J Eur Acad Dermatol Venereol. 2013;27:1461-70.
20. Rakowska A, Gradzińska A, Olszewska M, Rudnicka L. Efficacy of Isotretinoin and Acitretin in Treatment of Frontal Fibrosing Alopecia: Retrospective Analysis of 54 Cases. J Drugs Dermatol. 2017;16:988-92.
21. Erras S, Mouna Z, Akhdari N, Belaabidia B, Essaadouni L. Rapid and complete resolution of lichen planopilaris in juvenile chronic arthritis treated with rituximab. Eur J Dermatol. 2011;21:116-7.
22. Fertig R, Tosti A. Frontal fibrosing alopecia treatment options. Intractable Rare Dis Res. 2016;5:314-5.

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