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Frontal fibrosing alopecia (FFA): Report on four cases and review of the literature

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Abstract

Frontal fibrosing alopecia was recently described by Kossard, et al. as a progressive symmetrical recession of the frontal-temporal-parietal hairline affecting particularly postmenopausal women. Besides affecting the scalp, there are some cases in the literature with partial or total loss of the eyebrows, also involving the trunk, and superior extremities. Because the clinical, histological, and immunochemical findings are indistinguishable from those seen in lichen planopilaris, frontal fibrosing alopecia is now considered a localized variant of lichen planopilaris. We report four cases of Mexican postmenopausal women with this kind of dermatosis evaluated at the Dermatological Center Dr. Ladislao de la Pascua. (Gac Med Mex. 2016;152:91-7)

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Introduction

Frontal fibrosing alopecia (FFA) was described by Kossard et al. in 1994 in six female postmenopausal patients who showed a cicatricial-type alopecic band, with bilateral and symmetric progressive recession of the frontotemporal hairline [1]. It is a dermatosis that can be accompanied by eyebrows and facial and/or pubic hair loss[2].

Clinical cases description

Clinical cases are presented of 4 postmenopausal women who attended the Dr. Ladislao de la Pascua Dermatological Center presenting with progressive hair loss and hairline recession of 2 to 8-year evolution, together with partial to total loss of the lateral third of the eyebrow, and bilateral loss of axillary hair in two cases (Table 1).

Dermatologic examination revealed head-localized monomorphic-looking dermatosis affecting the scalp of the frontoparietal region at hairline, consisting of an alopecic band-shaped plaque with cicatricial aspect, uniform paleness, absence of follicles, some areas with perifollicular erythema (cases 1, 3 and 4; Figures 1, 3 and 4), and fine scaling at the perilesional area, with chronic and asymptomatic evolution. The glabellar-frontal distance in all 4 patients was increased up to a maximum of 10 cm in case 3. The rest of the skin, oral mucosa and nails showed no anomalies, except for case 4, where the patient had the diagnosis of generalized vitiligo and had achromic patches on the axillae, under treatment with psoralens.

The reason for consultation in all cases was hair loss around 1-2 years after menopause, which was progressive

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Table 1. Female androgenetic alopecia (FAGA)

Case	Age (years)	Time of evolution (years)	Post-menopause	FAGA	Frontotemporal recession/ glabellar-frontal distance	Eyebrow extension	Other areas	Perifollicular erythema at fibrous band periphery	Association with lichen planus	Dermatoscopy	Histopathology	Jacquet's sign
1	58	3	Yes	No	Yes/9.8 cm	Yes	No	Yes (preauricular region)	No	No follicles. Perifollicular erythema	Fibrotic foci/ lymphocytic infiltrates	Negative
2	64	8	Yes	No	Yes/8.0 cm	Yes	No	No	No	No follicles	Fibrotic foci	Negative
3	50	2	Yes	No	Yes/10 cm	Yes	Yes (axillae)	Yes	No	No follicles. Perifollicular erythema	Fibrotic foci	Negative
4	55	2	Yes	No	Yes/9.5 cm	Yes	Yes (axillae)	Yes	No	No follicles	Fibrotic foci/ lymphocytic infiltrates	Negative

and refractory to different commercial topical treatments. With the presumptive diagnosis of FFA, performing an incisional biopsy was decided in order to rule out concomitant conditions and arrive to diagnosis by clinicopathological correlation. Cases 1, 3 and 4 were initially treated with high-potency topical steroids for a 2-month period, and arrest of the progressive recession of the hairline alopecic band on the frontal-parietal-temporal zone was achieved; subsequently, calcineurin inhibitors (0.1% tacrolimus ointment) were topically administered twice daily in the maintenance phase. In case 2 (Fig. 2), care was expectant. In no case was follicle growth achieved.

Epidemiology

Cases reported in the literature so far show an age range between 50 and 85 years[3]. In 2014, a multi-center review of 355 FFA-diagnosed patients was published, out of which 343 were females and only 12 were males. Reported average age was 61 years, ranging from 23 to 86 years[4]. Geographical zones where higher number of cases are found are Central Europe and North America, with low incidence in Asian countries[5]. Characteristically, this dermatosis occurs in postmenopausal women, although there are cases in premenopausal females (16%) reported in the literature[4,6]. The recent increase in the number of cases of this dematosis may be owing to its intended search or probably to some not yet determined environmental factor[9]. Still, many women older than 60 years do not consider frontotemporal region hair loss to be abnormal, as shown by the case series of Poblet and Jiménez, where in 50% of the studied patients FFA was not the main reason for consultation[10]. At the Dr. Ladislao de la Pascua Dermatological Center, over the period from January 2009 to August 2014, 17 FFA cases were recorded; 100% corresponded to the female gender, with an average age of 43 years at presentation.

Etiopathohenesis

Etiopathogenesis of this condition is unknown. There are several theories proposing the hormonal factor as a causative agent, given the higher prevalence in menopausal women, together with a lichenoid-type tissue reaction that selectively destroys the androgen-dependent hair follicle[5,11]. Others propose that frontotemporal region follicles are genetically predetermined to suffer apoptosis with postmenopausal changes, with

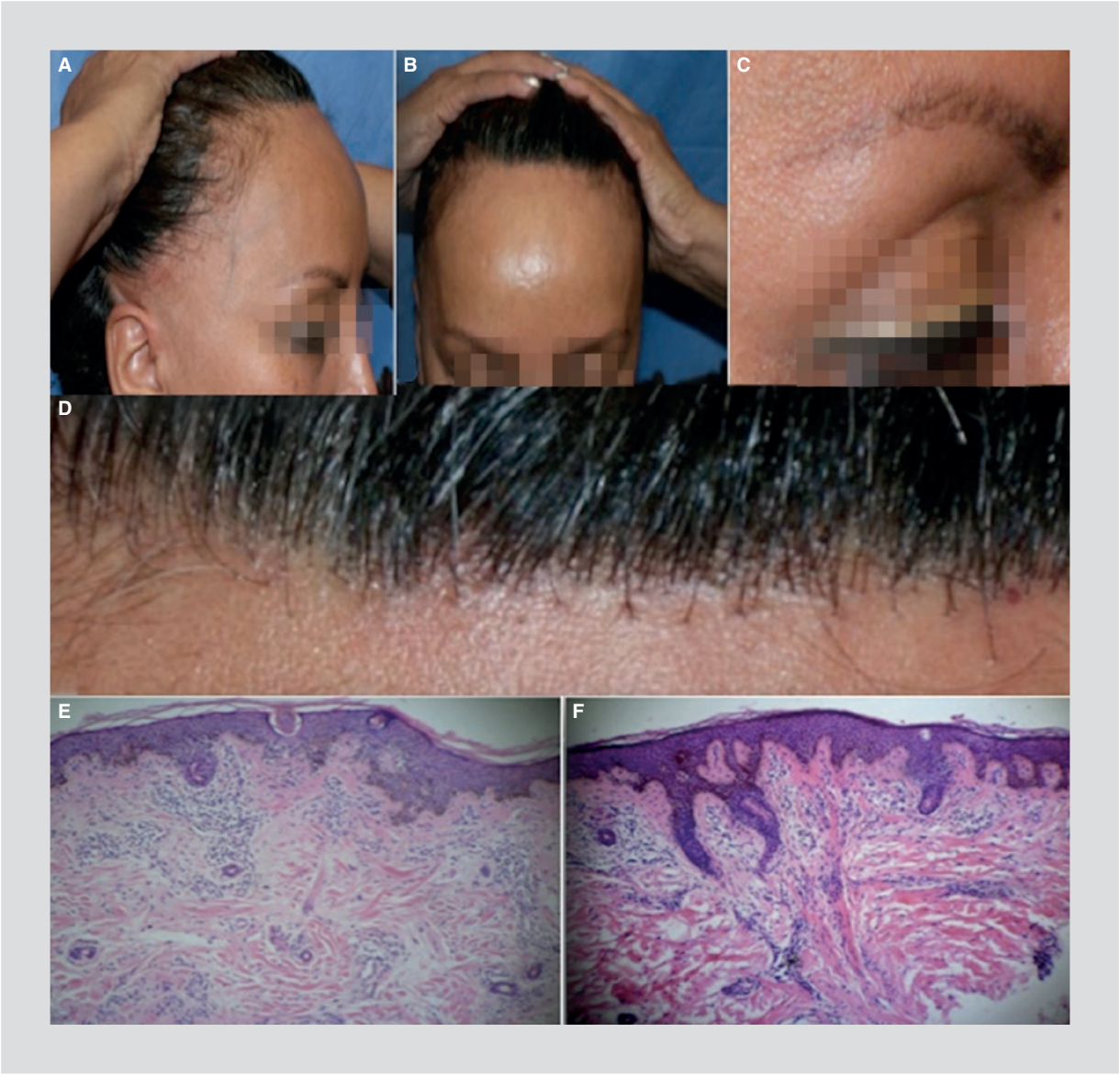

Figure 1. A: *frontotemporal hairline recession.* **B:** *lateral view.* **C:** *diffuse alopecia of the eyebrows. D: Band-like cicatricial alopecia.* **E** *and* **F:** *irregular acanthosis with fibrotic foci throughout the dermal thickness, as well as moderate perivascular lymphocytic infiltrates. Hematoxylin/Eosin.*

subsequent expression of neoantigens, which would generate a destructive T lymphocyte-mediated autoimmune response[12,13], with formation of a cicatricial-type alopecic plaque and irreversible loss of the follicle, given the damage to the bulge area, which contains pluripotent stem cells[14].

Clinical presentation

Typical presentation is that of a head-localized dermatosis that affects the hairline al the frontal-parietal-temporal level, with bilateral and symmetric, progressive and asymptomatic recession, and development of a cicatricial-type alopecic band [3,5,15]. There is only one case affecting the occipital region reported in the literature[10]. Morphology of the dermatosis is that of a cicatricial-looking plaque, with pale surface and atrophic areas, and absence of follicular openings, which can create a contrast with unaffected or ultraviolet radiation-damaged skin[10,11]. The cicatricial appearance can be typical, or in some cases can only be seen as whitish pale spots on the affected area[12]. Dermatosis progression usually reaches up to the vertex area, although it can affect the occipital zone[11]. In 50% of cases there is total or partial eyebrow loss, and up to 37% have axillary involvement. Extension to the trunk

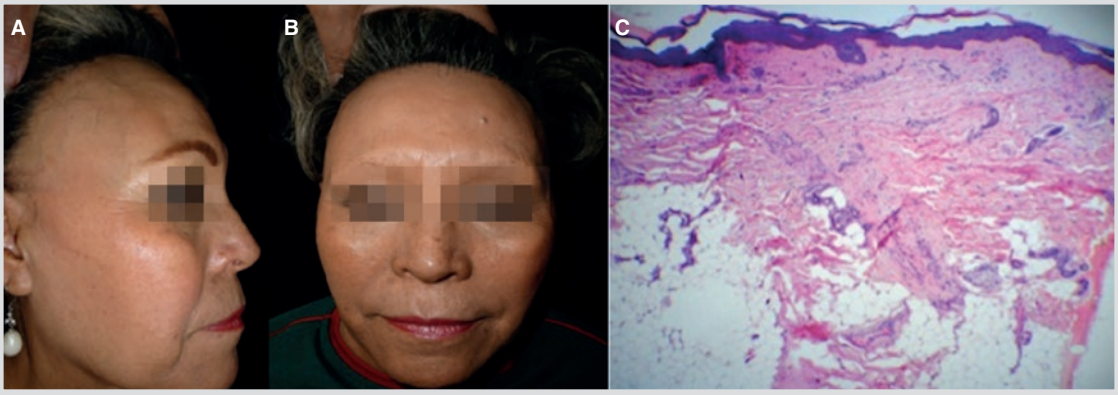

Figure 2. A *and* **B:** *hairline recession with eyebrow loss. C: irregular acanthosis. Abundant fibrosis foci and sparse perivascular lymphocytic infiltrates throughout the dermal thickness. Hematoxylin/Eosin.*

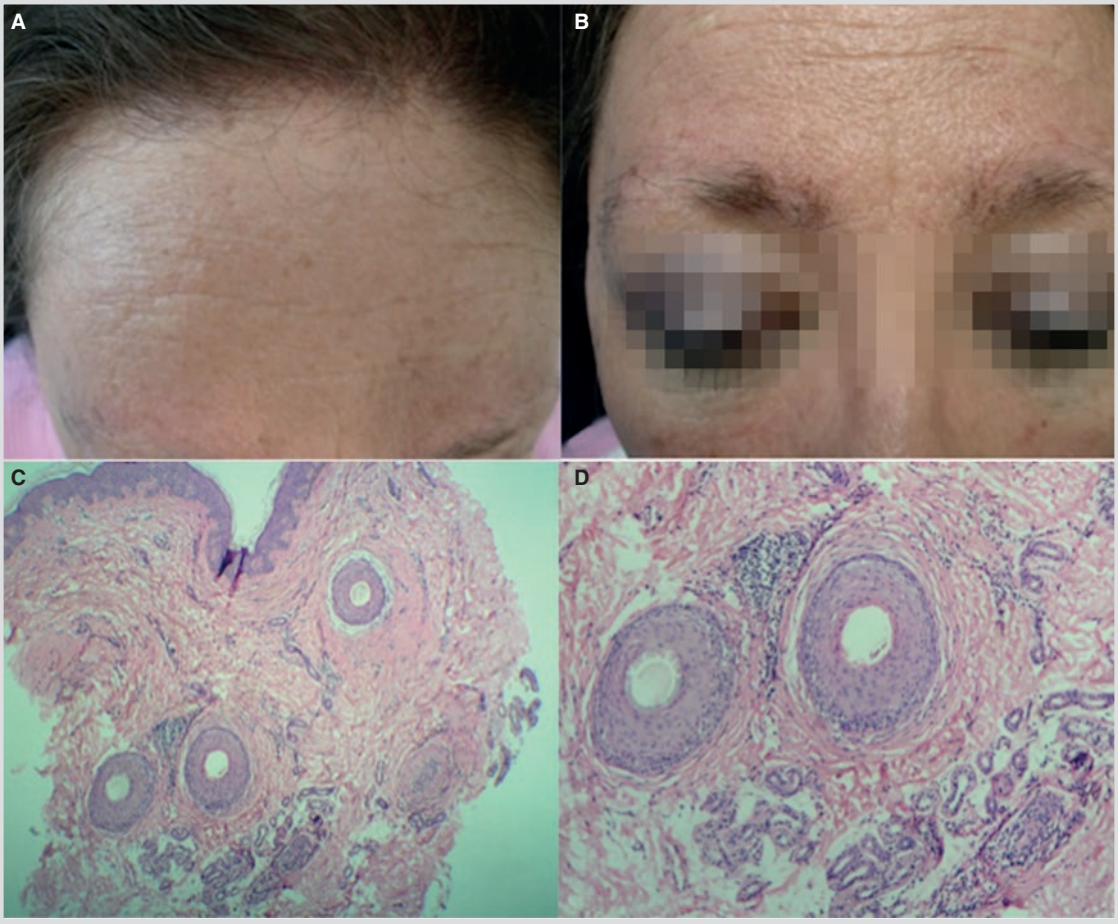

Figure 3. A: *frontal hairline recession.* **B:** *diffuse alopecia of the eyebrows starting at middle third.* **C** *and* **D:** *horizontal section. Laminated horny layer. Abundant fibrosis foci throughout the dermal thickness and sparse perivascular lymphocytic infiltrates. Hematoxylin/Eosin.*

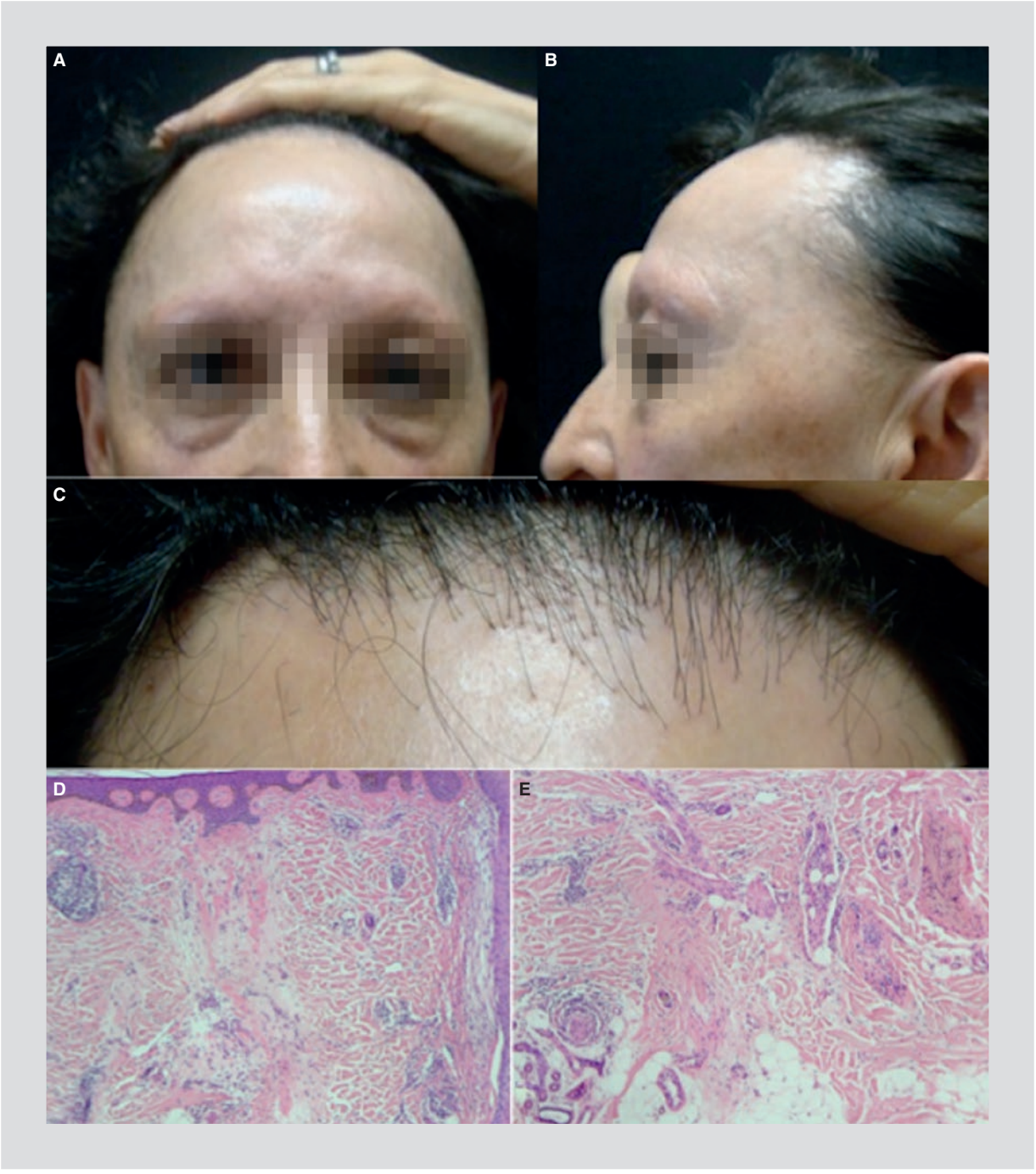

Figure 4. A: *fontoparietal band-like hairline recession.* **B:** *absence of eyebrows.* **C:** *discrete perifollicular erythema and isolated hairs.* **D** *and* **E:** *laminated horny layer, moderate irregular acanthosis. Superficial and reticular dermis with focal lymphocytic infiltrates surrounding vessels and adnexae. Zones of collagen fibrosis. Hematoxylin/Eosin.*

and/or upper limbs is less common[6]. There are clinical data indicating activity of the underlying lesion: both the presence of perifollicular erythema and follicular horny plugs formation are the most informing. Tosti et al. described the lonely hair sign, which refers to the isolated presence of terminal hair at the original hairline; it is found in up to 53% of cases[16].

On physical examination, the glabellar-frontal distance, which in normal women is on average 6 cm, has to be measured; in these cases, it increases between 6.5 and 12.5 cm (average: 8.5 cm). The condition tends to arrest in an average of 12 months, although the stage when stabilization occurs cannot be predicted[6,11].

Diagnosis

Diagnosis of the condition is essentially clinical. There are several methods that help to confirm the diagnosis, but histopathology is the most accurate, although it is not indispensable[15]. At the plaque-activity stage, there is interface dermatitis and dyspigmentation, with a lichenoid pattern-lymphocytic infiltrate characteristically affecting the isthmus and infundibular zones, respecting the lower third of the follicle[12]. Additionally, perivascular lymphocytic infiltrate, infundibular hypergranulosis, vacuolar degeneration of the basal layer and outer root sheath with keratinocyte necrosis, absence of follicles and replacement by moderate or abundant fibrous tracts are observed[3,5,11,12,17].

To rule out other known causes of alopecia, a hormone profile can be obtained, with levels of luteinizing and follicle-stimulating hormones, prolactin, androstenediol glucuronide, estradiol, free testosterone and D-4 androstenedione, as well as a thyroid profile, which have been found to be normal in all reported cases of patients with this dermatosis. So far, only 4 patients have tested positive to anti-DNA antibodies (range: 1:40-1:160)[3].

Dermatoscopic results have only been assessed by Inui et al. in a study of 4 cases, where the following was reported: follicular openings loss, perifollicular erythema (care should be taken when positioning the dermascope, since excessive pressure can make for this sign to be overlooked), whitish fine scaling and absence of yellowish dots (this is one difference with alopecia areata). Immunohistochemistry reveals a T cell infiltrate at the level of the isthmus and infundibulus[9].

Differential diagnosis/associations

Given the clinical, histopathological and immunohistochemical features of this dermatosis, generally indistinguishable from lichen planopilaris (LPP), FFA is currently considered a localized variety of it. However, there are subtle differences between them both, since LPP has multiple cicatricial areas of variable topography (especially the vertex and parietals), which can coalesce. An association of FFA with lichen planus pigmentosus in up to 50% of cases has been reported in the literature[18]. An LPP variant, the Graham-Little-Picardi-Lassueur or Graham-Little-Feldman syndrome, describes concomitance of cicatricial alopecia on the scalp with follicular lichen planus and non-cicatricial-type alopecia affecting the eyebrows, axillae or pubis[3,14].

Other differential diagnoses, in addition to those already mentioned, include alopecia areata and androgenetic alopecia, with whom FFA can even coexist. The former is a non-cicatricial type alopecia that can also show eyebrow loss, although generally not bilaterally. The ophiastic variety can be very difficult to differentiate, since both dermatoses affect the frontal-parietal-temporal-occipital region, but this one affects the occipital area more often, unlike FFA. In women, androgenetic alopecia generally does not involve the frontal hairline, is of the non-cicatricial type and shows follicle miniaturization, with non-specific perivascular inflammation. Other less likely differential diagnoses include lupus erythematosus and traction alopecia, which can be clinically differentiated, as well as by the patient´s history[3,5,6]. Other associated conditions are the Sjören syndrome, vitiligo and thyroid disease, although these associations are not conclusive[5-11].

Treatment

Since in FFA there is fibrosis follicle destruction and the cause is yet unknown, lack of treatment response is the rule[6].

Steroids

The use of steroids at the early inflammatory stage (first 12 months of evolution) can prevent disease progression. They are employed by systemic or intralesional route, alone or in combination with anti-androgens[5,6]. The most widely used is triamcinolone acetonide (20 mg/ml by intralesional route, applying 1 mg/cm^2 on the frontotemporal region and diluting it at 10% for the eyebrow zone), or prednisone systemic cycles at doses of 1 mg/kg[5]. In 2005, Moreno-Ramírez studied the use of triamcinolone acetonide. A 1 mg/cm^2 dose was applied every 3 months in a dilution of 20 mg/ml on the scalp and 2 mg/ml on the eyebrows. Rapid stabilization of the hairline recession process was observed in 44.4% of treated patients (n = 9)[19]. The recommended topical corticoids belong to the high-potency group, such as clobetasol propionate[6,17].

Antiandrogens

The most widely used is finasteride, at doses of 1-2 mg/day, alone or associated with 1 ml of minoxidil 5% for indefinite time. Vañó-Galván et al. used finasteride in 102 FFA-diagnosed patients, out of whom 47% showed clinical improvement, and 53%, stabilization. Dutaseride, a type 1 and 2 5α-reductase, has also been used. In 2009, it was used at a dose of 0.5 mg day per day for one year in 13 postmenopausal women with FFA; in 33%, the disease was arrested and in 11.1% there was hair growth[19].

In another study with 18 patients, a weekly dose of 0.5 mg was used, with improvement found in 44% of cases and stabilization in 56%, indicating that the treatment with oral or intralesional antiandrogens might be useful[4].

Antimalarial agents

Due to their immunosuppressant and anti-inflammatory effect, the use of hydroxychloroquine has been proposed at doses of 200 mg every 12 h for at least 6 months.

Pioglitazone

Pioglitazone belongs to the thiazolodinediones group, agonists of the peroxisome proliferator-activated receptor gamma, which in the follicle act as lipid metabolism and peroxisomal biogenesis regulators, as well as in the control of the inflammatory response and, therefore, they are likely to help to maintain the pilosebaceous unit homeostasis. Doses of 15 mg every 24 h for 8 months have been used.

Hair transplantation

There is little experience with this method, and data are not encouraging, since hair loss is observed one year after transplantation with relapse of the disease[19].

Other treatments with poor outcomes so far include the use of topical retinoids and oral isotretinoin[5,6,17]. Recently, the use of calcineurin has been proposed in the active phase of the disease, such as topical tacrolimus, with variable results.[20] Owing to its use in lichen planus, the study of cyclosporine as treatment for FFA has been proposed.

Commentary

The presented cases are consistent, both on their clinical presentation and the accompanying characteristics, with cases described in the literature. All involve postmenopausal women with cicatricial alopecia, hairline recession and eyebrows partial or total loss. Dermatosis axillary extension is present in cases 3 and 4. Perifollicular erythematosus papulae can be observed in cases 1 and 4, indicating disease activity, with the benefit of high-potency steroids administration at this phase of the disease.

Another important data is the glabellar-frontal distance, which, if measured at first and subsequent visits, may guide on dermatosis progression. Laboratory tests of all 4 patients were found to be within normal parameters; none of the four described cases had lichen planus, oral mucosa lesions or nail involvement. Interestingly, in spite of cicatricial alopecia being a condition where follicles are absent, Jacquet's sign was negative in all cases, which may be secondary to the existing fibrosis.

With regard to histopathology reports, the literature refers that in cases with activity, interface dermatitis and lymphocytic infiltrate arranged in foci are observed. This finding is observed in cases 1 and 4. In cases 2 and 3 only collagen fibers replacement by fibrosis is observed, which reflects the final stage of the disease.

As previously mentioned, there is no treatment whatsoever for late or fibrous stage FFA. In these cases, doctor-patient relationship is very important, so that the latter trusts the detailed explanation of the condition that, as physicians, we have to grant, together with clarification of doubts in order to avoid for false expectations on the disease to be created. The use of topical or intralesional steroids is only recommended at the activity phase; and in the cases where the follicle is still present, calcineurin inhibitors, antiandrogens and minoxidil are useful.

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