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Review Article

Frontal fibrosing alopecia: An overview

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ABSTRACT

Frontal fibrosing alopecia (FFA) is a primary progressive cicatricial alopecia of the frontal, temporal, or frontotemporal scalp. In FFA, hairline recession, scalp pruritus, perifollicular erythema, and eyebrow loss are common at presentation. At present, there are no evidence-based treatment guidelines for FFA; hence, adopted modalities of treatment vary among clinicians. This review is an overview of the disease characteristics and the available therapeutic options in FFA.

Keywords: Frontal fibrosing alopecia, Cicatricial hair loss, Perifollicular erythema, Hairline recession, Treatment

INTRODUCTION

Frontal fibrosing alopecia (FFA) is a cicatricial alopecia characterized by a progressive and symmetrical recession of the frontotemporal hairline, often accompanied by bilateral loss of eyebrows.[1] Steven Kossard described this condition in 1994 for the 1st time.[2] He reported six postmenopausal women who developed a progressive frontal, scarring alopecia that extended to the temporal and parietal hair margins. Perifollicular erythema within the marginal hair line was a conspicuous finding. Histopathology mimicked that of lichen planopilaris. The author used the term "postmenopausal frontal fibrosing alopecia" since the patients lacked the typical lesions of lichen planus and the alopecia was confined to specific areas of scalp. It was suggested that the pathomechanism underlying the postmenopausal, frontal, hairline 'recession may precipitate a reaction pattern, which in turn leads to the follicular destruction observed in "postmenopausal FFA."[2]

Subsequently, similar cases were reported by others.[1,3,4] Recent years have witnessed a dramatic rise in the number of cases reported.[4] Although it still predominantly remains a disease of women of the postmenopausal age (>60 years of age), premenopausal women and men are occasionally affected.[1,3,4] Hence, the term "postmenopausal FFA" is substituted with FFA.[1,3,4]

Epidemiology

Even though the condition is reported in all ethnic groups, more than 85% of cases reported are Caucasians,[4-6] The mean age of the onset of the disease and the mean age at diagnosis, as stated in literature, are 55.6 years and 60.6 years, respectively.[4] The slow progression of the disease and the lack of familiarity with the condition are cited as the reasons for the delay in diagnosis.[4] Valesky *et al*., in a review of case reports and case series, reported that 3.1% of the affected were

male.[4] About 16% of females had onset of disease in the premenopausal age.[4] Atarguine *et al*. reported three girls (14-year-old twin sisters and another 7-year-old girl) with FFA. The twins had onset of disease at the age of 5.[7]

The diseases that are seen in association with FFA as documented in literature are lichen planopilaris, lichen planus, chronic cutaneous lupus erythematosus, thyroid abnormality (mostly hypothyroidism), vitiligo, Sjogren's syndrome, rosacea, and genital lichen sclerosus.[4,8-12] Katoulis *et al*. reported a 72-year-old woman and a 48-year-old man who developed FFA on pre-existing vitiligo of the forehead.[11] There are reports of coexistence of FFA with other non-scarring alopecias such as androgenetic alopecia, alopecia areata, and trichotemnomania (an obsessive compulsive habit where the patient cuts or shaves one's own hair).[13-15] Since the original description of co-occurrence of lichen planus pigmentosus and FFA by Diova, in 24 patients in Durban, similar association was reported by many authors, especially among premenopausal women of dark skin phenotype.[16-18]

Etiology

The exact etiopathogenesis of FFA remains unknown as also the reason for the recent surge in the number of cases.[19] Genetic, hormonal, autoimmune, inflammatory, and environmental factors are considered to play a pathogenic role in this primary lymphocytic cicatricial alopecia.[19]

The reason for the preferential involvement of frontotemporal hairline in FFA is attributed to an increase in number of intermediate follicles and vellus hairs over terminal hairs at this site. It is suggested that FFA specifically targets intermediate follicles and vellus hairs.[20]

The observation of FFA in siblings and family members led to the genetic theory of pathogenesis. Up to 8% of FFA cases are thought to be familial.[21] An autosomal dominant inheritance with incomplete penetrance has been proposed.[22] Daughters of mothers with post-menopausal FFA are reported to be at greater risk for early-onset (premenopausal) FFA.[23] No HLA association has been noted for FFA till date. The HLA-DR1 association noted for classical lichen planus and Graham Little-Piccardi-Lassueur syndrome is not observed in FFA.[24]

Inflammatory infiltrate (predominantly constituted of CD8+ T lymphocytes) targets the infundibulo-isthmic (bulge) region of hair follicle. Inflammation of the infundibulo-isthmic region prevents regeneration of hair by destroying the hair follicle stem cells. Deficiency of peroxisome proliferator activated receptor (PPAR)-γ is postulated as the cause for inflammation that is directed against the hair follicle stem cells.[19]

The role of hormones in FFA remains rather unclear. Hormonal etiology was hypothesized since a high incidence of FFA was noted in postmenopausal women, in women who underwent hysterectomy/oophorectomy and in women who had an early menopause.[21,25] Coexistence of FFA with androgenic alopecia, protective effect noted for intrauterine device and response observed to anti-androgenic therapy also supported a role for hormones in the etiopathogenesis.[21,25] However, a study on serum androgen levels in 43 premenopausal women with FFA reported no consistent alterations, suggesting that hormone levels were not directly implicated in the pathogenesis of FFA.[26] Dehydroepiandrosterone (DHEA) and DHEA-sulfate are essential for normal activity of PPAR-γ. Postmenopausal decline of these hormones is considered as the cause for the PPAR-γ deficiency noted in FFA.[27]

It is proposed that loss of follicular immune privilege (as observed in patients with alopecia areata) also contributes to the inflammation against the self-antigen (hair follicle stem cell) in FFA.[19] Whether the increased scalp sweating experienced by some of the patients is a cause for inflammation or a result of it, needs further analysis.[19] Doche *et al*. reported a decrease in substance P and an increase in calcitonin gene-related peptide in the scalp of patients with FFA and cited this as the reason for the decrease noted in the density of epidermal nerve fibers.[28] Substance P, through the upregulation of major histocompatibility complex I and beta-2-microglobulin, may cause hair follicle collapse.[29]

The late onset of the disease points to a role for environmental factors as well and it is suggested that exposure to the same environmental triggers could be the reason for its occurrence in family members.[19] Questionnaire-based studies carried out in female and male patients indicated a role for sunscreens or their concurrent use with hair dye as a triggering factor.[30,31] Callander *et al*. reported a better outcome with the avoidance of sunscreen use on the forehead, while an exacerbating role was noted for UV filters in hair care products.[32] It is suggested that the retention of certain ingredients of facial or hair care product within the hair follicle (since the affected patients show low sebum production) could be the precipitating factor for FFA, rather than a specific ingredient acting as the offender on its own.[30] Introduction of UV filters in facial products in the late 1980s and the rise observed in FFA in recent decades, suggest a potential role for UV filters in disease causation.[19]

A cross-sectional study of 72 women diagnosed with FFA found that chronic tobacco exposure may play a protective role in FFA, probably by reducing the prolactin level.[33] FFA has been reported following cosmetic procedures such as face lift surgery and hair transplantation.[34]

CLINICAL FEATURES

Many authors consider FFA as a variant of lichen planopilaris that shows a patterned distribution. They suggest that since FFA is associated with involvement of other body sites and face, it cannot be considered as a process localized to frontotemporal region.[1] On the other hand, the frequency of coexisting lichen planus or history of lichen planus in FFA (2%–17%) is lower than the same observed in LPP (28%–50%).[3,6] Whether FFA and LPP are different manifestations of the same disease process or two different entities with similar histopathology remains unclear.[35]

Band-like recession of frontotemporal hairline [Figure 1] is the hallmark of FFA.[19] Sometimes, patients may complain of pruritus or burning sensation or trichodynia.[19] Depressive symptoms related to hair loss may be seen in some patients.[36] A very common feature is the complete or lateral loss of eyebrows. Sometimes, FFA of eyebrows could be the sole manifestation when it may go undiagnosed for long. Less frequently occipital, retroauricular, or sideburns FFA is reported.[19]

Occasionally, FFA can affect eyelashes, the hairs of pubic region, axilla, trunk, or limbs.[19]

Three clinical patterns of hair loss are described for FFA.[20] They include linear pattern, diffuse pattern, and pseudo-fringe sign pattern. Fringe sign is described in traction alopecia as the retention of some hair along the hairline ahead of the area of alopecia.[37] Similar clinical presentation (frontal and/or temporal unaffected primitive hairline) when observed in FFA is termed as pseudo-fringe sign pattern.[38] In patients who do not show pseudo-fringe sign, the frontal hair line is assessed and those who show a band of uniform hairline recession without any loss of hair density behind the hairline are diagnosed to have linear pattern FFA. Patients manifesting diffuse or zigzag band-like alopecia of frontal hairline with at least 50% decrease in frontal hair density with consistent trichoscopy features are classified to have diffuse pattern alopecia.[19,20] In a study of 242 females with FFA, pseudo-fringe sign pattern FFA showed better prognosis and less eye brow involvement. Diffuse pattern was associated with the worst prognosis with respect to disease progression.[20]

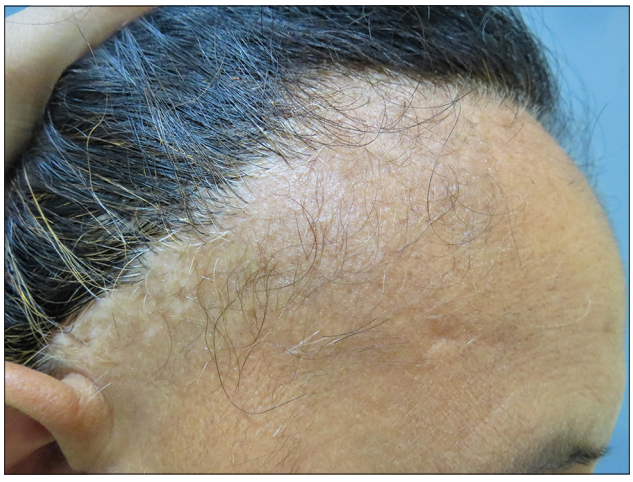

Figure 1: Receded hairline with left out lonely hairs of frontal fibrosing alopecia in a woman. Scarred white areas can be appreciated above the ear denoting the long duration of the disease (image courtesy – Dr. Muhammed Razmi T, MD (PGIMER), DNB, MNAMS, Consultant Dermatologist, IQRAA International Hospital and Research Centre, Kozhikode, Kerala, India).

Tosti *et al.* reported the presence of isolated terminal hairs in the middle of the forehead, at the site of the original hairline (lonely hair) in 30/39 (76.9%) patients with FFA and suggested this as a diagnostic clue.[39] The lonely hairs (3–7 cm long) may or may not be associated with perifollicular erythema or scaling and may be localized in the central or lateral aspect of the forehead.[39] Later, it was suggested that the lonely hair may not be specific to FFA and could be seen in scarring alopecia due to chronic cutaneous lupus erythematosus, follicular keratosis spinulosa decalvans, central centrifugal alopecia, alopecia mucinosa, and lichen planopilaris.[40] All these conditions show lymphocytic infiltrate in histopathology.[40]

Loss of vellus hair along with lonely hair sign is considered as more characteristic of FFA.[19] The involved skin shows slight atrophy and loss of follicular ostia. The skin appears smooth and less pigmented in comparison to the chronically sun exposed skin of the forehead. Affected hair follicles as well as the nearby hair-bearing skin may show signs of inflammation such as perifollicular erythema and/or follicular hyperkeratosis.[19]

Facial erythema, facial papules mainly affecting the forehead, the cheeks and the chin, hypo/hyperpigmented macules, glabellar red dots, increased venous vasculature on the temples, and prominence or depression of frontal veins are the other features noted.[20,35] Wide spread involvement of scalp that spares only a band of hair on the top of the scalp is termed as "clown alopecia."[35]

Fibrosing alopecia in a pattern distribution, initially described by Zinkernagel *et al.* in 15 men and four women, manifests features of both lichen planopilaris and androgenetic alopecia.[41] It is postulated that androgenetic alopecia-induced damage to hair follicles could be the reason for the exaggerated inflammatory response which eventually results in FFA.[41,42] Clinical examination can reveal the features of FFA in a pattern distribution. Evidence of follicular inflammation and at times, fibrosis on trichoscopy evaluation may point to FFA. A dermoscopy-guided biopsy can confirm the diagnosis.[41,42]

DIAGNOSIS

Clinical examination and trichoscopy are the reliable means to diagnose FFA. Tolkachjov *et al.* proposed diagnostic criteria for FFA.[19,43-46] A diagnosis of FFA is made, if a patient has either two major criteria or one major and two minor criteria.[43]

The major criteria are

1. Cicatricial alopecia of the frontal, temporal, or frontotemporal scalp on examination, in the absence of follicular keratotic papules on the body
2. Diffuse and bilateral cicatricial alopecia of eyebrows.

Minor criteria include

1. Perifollicular erythema, perifollicular hyperkeratosis, or solitary hairs on physical or trichoscopic examination in a field of frontal/frontotemporal cicatricial alopecia
2. Histopathologic features of cicatricial alopecia in the pattern of FFA or lichen planopilaris
3. Involvement of additional FFA sites: Occipital area, facial hair, sideburns, or body hair manifesting as hair loss, perifollicular erythema, or perifollicular hyperkeratosis
4. Non-inflammatory facial papules
5. Preceding or concurrent pruritus or pain, at areas of involvement.

The clinical pattern of alopecia helps to differentiate FFA from lichen planopilaris. Traction alopecia may resemble FFA. The clinical background, with a history of use of tight hairstyles and the absence of typical trichoscopic signs of FFA, favour the diagnosis of traction alopecia. Moreover, traction alopecia is not associated with eyebrow hair loss. The absence of lichenoid follicular inflammation and fibrosis, and preservation of sebaceous glands in histologic sections are the other features that distinguish traction alopecia from FFA.[47]

Trichoscopy is useful in differentiating FFA [Figure 2] from other common conditions producing alopecia [Table 1].[19,35,43-46]

HISTOPATHOLOGY

Histopathologically, it is difficult to distinguish between FFA and lichen planopilaris, but histopathology may be useful to confirm the clinical diagnosis of FFA and to differentiate it from cicatricial alopecia due to causes other than lichen planopilaris. Trichoscopy may help to choose the ideal biopsy site.

A lichenoid lymphohistiocytic inflammatory infiltrate around the outer root sheaths of hair follicles involving the infundibular and isthmus regions characterizes the early stage of FFA. Mild perifollicular lamellar fibrosis may be evident. Late stages show severe perifollicular fibrosis and reduced density of follicles. Eventually scar tissue replaces the pilosebaceous units.

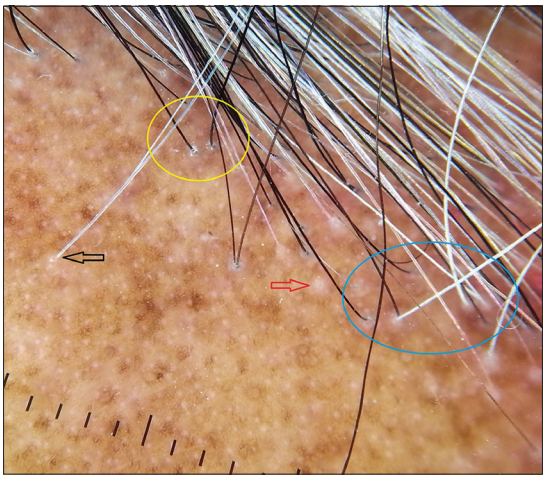

Figure 2: Trichoscopy of frontal fibrosing alopecia showing perifollicular scaling (yellow circle), perifollicular white halo (blue circle), the empty hair follicle (red arrow), and lonely hair (black arrow). (Dermlite DL-4, 3Gen, CA, USA, polarized contact mode, ×10) (Image courtesy – Dr. Muhammed Razmi T, MD (PGIMER), DNB, MNAMS, Consultant Dermatologist, IQRAA International Hospital and Research Centre, Kozhikode, Kerala, India).

The different lesions of FFA (facial erythema, facial papules, and hypo/hyperpigmented macules) show the lichenoid inflammation. The inflammation characteristically spares the inter-follicular epidermis in the frontal hairline of scalp, but this sparing is not observed in specimens from other lesions of FFA.[19]

Pedrosa *et al.* reported a novel histopathology finding in the biopsy specimens from the non-inflammatory yellow facial papules. The characteristic histopathology showed hypertrophic sebaceous glands. Vellus hair follicle and lichenoid inflammation were conspicuously absent.[48] The authors suggested that the observed histopathology could be of an intermediate stage between the initial lichenoid inflammation and the final stage of skin atrophy.[48]

Recently, usefulness of optical coherence tomography has been explored in assessing the progression of the disease.[49]

A study by Tziotzios *et al.* identified circulating microribonucleic acids as highly predictive of the disease status in FFA and further research may give more information on the utility of this method.[50]

Different authors have proposed different scoring systems to grade the severity of FFA. They include FFA severity index (FFASI), FFA severity score (FFASS), and trichoscopic visual scale.[51-53] FFASI is criticized for being too complex for practical purpose.[54] FFASS (evaluates hairline recession, eyebrows, severity, and extent of peri-follicular inflammation,

Table 1: Trichoscopy findings in frontal fibrosing alopecia, lichen planopilaris, androgenetic alopecia, alopecia areata, and traction alopecia.

Frontal fibrosing alopecia	Lichen planopilaris	Androgenetic alopecia	Alopecia areata	Traction alopecia
Diagnostic finding – Absence of vellus hair, reduced or absent follicular openings **Signs of active inflammation:** Follicular hyperkeratosis visualized as peripilar casts and perifollicular erythema around terminal hairs **Other reported features:** Pili torti, broken hairs, black dots, red and gray dots in eyebrows, white dots (corresponding to the follicular fibrosis seen in dark-skinned individuals)	Blue, gray dots in a target pattern, tubular casts with minimum or absent interfollicular scales, absence of follicular opening, peripilar scaling and erythema, preserved pinpoint white dots (in dark scalp)	Increased proportion of thin and vellus hairs, peripilar signs, and hair diameter diversity > 20%, perifollicular discoloration (hyperpigmentation), variable number of yellow dots	Presence of follicular ostia, yellow dots, black dots, exclamation mark hair, short vellus hairs, broken hairs, tapered hairs **Less common features:** Upright regrowing hairs, pigtail (circle) hairs, Pohl-Pinkus constrictions No pathognomonic feature. Diagnosis based on coexistence of several findings	White dots, broken and miniaturized hairs

pruritus, and pain) is easier to apply, but has the limitation of not considering trichoscopy findings. Moreover, all patients evaluated using FFASS were Caucasian females.[52] Trichoscopic visual scale correlates severity (thickness) of peripilar casts with severity of lymphocytic infiltration at pathology.[53]

TREATMENT

FFA has a slowly progressive disease course that makes an early diagnosis difficult. It has been suggested that a spontaneous remission can occur in many, but Lorrizo and Tosti stressed the importance of early diagnosis and treatment in arresting the disease progression.[19,20] There are no standard guidelines for the treatment of FFA as of now.[19] Accurate assessment of treatment response is difficult, since the disease shows variable course and also has a tendency for spontaneous stabilization.[19] It is suggested that the treatment should be extended to the whole scalp since inflammation is also detected around the infundibulo-isthmic region of hair follicles of clinically unaffected scalp.[55]

The treatment modalities attempted in FFA include topical, intralesional, and systemic medication as well as surgical measures.[19,36]

In the early inflammatory stage, especially when pruritus is present, topical corticosteroids are often prescribed. Another option is topical tacrolimus (0.3–1%) or pimecrolimus (1%), especially since, topical corticosteroids may cause worsening of the skin atrophy associated with FFA.[19] Topical minoxidil is considered useful in FFA, due to its antifibrotic properties.[19] It is recommended that intralesional corticosteroids may be given at a strength of 2.5 mg/ml since the risk of skin atrophy is more at 10 mg/ ml concentration.[19]

The commonly used systemic treatments include 5-α-reductase inhibitors such as finasteride (2.5–5 mg/day) and dutasteride (0.5 mg/day), hydroxychloroquine (maximum dose 5 mg/kg/day), isotretinoin (0.3 mg/kg/day), acitretin (20 mg/day), and cyclosporine (3 mg/kg/day gradually tapered over 5–7 months).[19,36,56,57] 5-α-reductase inhibitors are not recommended in females of child-bearing potential due to its teratogenic effects and in women with personal or family history of breast cancer.[19,36] It is reported that non-inflammatory yellow facial papules may respond to isotretinoin 10 mg on alternate day (the patients also received 2.5–5 mg/day of finasteride or 25–50 mg/day of spironolactone, topical pimecrolimus cream, and vitamin supplements).[48]

Oral tetracyclines (doxycycline 100 mg twice a day or tetracycline 500 mg twice a day), PPAR-γ agonist "pioglitazone" (15 mg/day), naltrexone (3 mg/day), tofacitinib (5 mg twice daily), platelet-rich plasma therapy, excimer laser (once every 2 weeks for average 11 sessions), carbon dioxide laser (once in 2 weeks for 15 sessions), light-emitting diode (once a week for 10 weeks), and hair restoration surgery are the other treatment modalities attempted. Surgery is considered only 1–2 years after achieving disease stabilization.[19,36,56,57]

Oral prednisolone 40 mg/day for 1 week that is tapered by 5 mg/week over 8 weeks is recommended for rapidly progressive FFA, before the patient is put on maintenance treatment with other drugs.[36]

Combination treatment is often preferred considering the treatment resistant nature of the disease. A combination of 5-α-reductase inhibitors or hydroxychloroquine with topical minoxidil and intralesional steroids is often used.[57]

CONCLUSION

FFA is a primary cicatricial alopecia and is showing a dramatic rise in incidence. Since it progresses slowly,

mostly FFA is not diagnosed till late. A better awareness regarding the condition can help the clinician to make an early diagnosis and prompt treatment that may arrest the progression of the disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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