
Expanding the spectrum of frontal fibrosing alopecia: A unifying concept

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Background: In frontal fibrosing alopecia (FFA), scalp alopecia dominates the clinical picture. However, eyebrow loss and hair loss in other body sites may also occur; this has been documented clinically, but rarely histopathologically. We describe the clinicopathological findings of 13 cases of FFA, with histopathologic data from the scalp, eyebrow, and body hair.

Methods: Thirteen patients with a diagnosis of FFA, seen between 2006 and 2008, were included. Scalp biopsies were performed in all patients for histology and direct immunofluorescence (DIF). Biopsy specimens for histology were taken from the eyebrow in 6 patients and from the upper limb in 5 patients.

Results: All 13 patients were female, 11 of whom were postmenopausal. The median age at onset of alopecia was 57 years. Clinical examination revealed a band of frontal hairline recession in all patients. Eyebrow loss was present clinically in all patients, with loss of body hair in 10 of 13. Histopathologic examination of the scalp, eyebrow, and upper limb skin biopsy specimens showed similar features, including a marked reduction in the number of hair follicles and a perifollicular lymphoid cell infiltrate with perifollicular fibrosis. Direct immunofluorescence was negative in all cases.

Limitations: Not all patients consented to biopsies of the eyebrows or upper limbs.

Conclusion: Eyebrow and peripheral body hair loss is not uncommon in FFA—a finding that is likely underreported. We have demonstrated that alopecia of the upper limbs in FFA is indeed common and, histopathologically, shows features of lichen planopilaris and scarring, similar to findings in the scalp and eyebrows. Consequently, the process of lichen planopilaris with scarring alopecia is generalized rather than localized only to the frontal scalp and eyebrows. (*J Am Acad Dermatol* 2010;63:653-60.)

Key words: cicatricial alopecia; frontal fibrosing alopecia; lichen planopilaris; lichen planus.

BACKGROUND

Frontal fibrosing alopecia (FFA) is a form of cicatricial alopecia with a characteristic clinical presentation. First considered to be uncommon when originally described by Kossard¹ in 1994, a substantial number of subsequent case reports suggests that

Abbreviations used:

DIF: direct immunofluorescence
FFA: frontal fibrosing alopecia
LP: lichen planus
LPP: lichen planopilaris

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Funding sources: None.

Conflicts of interest: None declared.

Presented in part as a poster at the 67th Annual Meeting of the American Academy of Dermatology, March 6-10, 2009, San Francisco, CA.

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0190-9622/\$36.00

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doi:10.1016/j.jaad.2009.09.020

its prevalence may not be as low as previously thought.²⁻³² FFA is increasingly accepted as a variant of lichen planopilaris (LPP), as it shares features with LPP, both clinically and histopathologically.^{3,33} FFA is characterized clinically by a slowly progressive symmetrical band of frontotemporal or frontoparietal hairline recession, usually, but not exclusively, affecting postmenopausal women.^{3,9,17,21,23,28,32} Histopathologically, FFA has features similar to those of LPP, showing a perifollicular lymphoid cell infiltrate and fibrosis, with hair follicle destruction.³

Although scalp alopecia dominates the clinical picture in FFA, concomitant loss of eyebrow hair is also reported frequently.* A less frequent observation is that of an associated hair loss from peripheral body sites, such as the axilla and upper or lower limbs.† This latter phenomenon has been documented clinically, yet has not been investigated histopathologically.

We describe the clinicopathologic findings in 13 cases of FFA seen at the St. John's Institute of Dermatology between the years 2006 and 2008, with histopathologic findings of the scalp, eyebrows, and upper limb hair.

METHODS

This study is a retrospective review of the case records of 13 patients with a clinical and histopathologic diagnosis of FFA seen in the Hair Clinic of the St John's Institute of Dermatology from January 2006 to March 2008. All patients presenting clinically with band-like frontal hairline recession and with histopathologic evidence of LPP were included.

Scalp

Two 4-mm punch biopsy specimens were taken from the frontal or frontoparietal hairline of the scalp in 12 of 13 patients and processed in accordance with our St John's protocol,³⁴ a method based on that described by Elston, McCollough, and Angeloni.³⁵ One specimen was sectioned horizontally and the other was bisected, with half of the specimen sent for vertical sectioning and the other half, in Michel's medium, sent for immunofluorescence studies. Direct immunofluorescence (DIF) was performed for immunoglobulins IgG, IgA, IgM, and complement C3. Hematoxylin and eosin slides from the biopsy specimen of one of the 13 patients were received as a referral from an outside hospital, where the specimen had been vertically sectioned.

Eyebrow

Eyebrow biopsies were performed in 6 of 13 patients. These consisted of 3-mm punch biopsies; 4

of 6 were sectioned horizontally and 2 of 6 were sectioned vertically. No DIF was performed.

Upper limb

In 5 of 13 patients, upper limb biopsies were performed in a "blind" fashion, in that they were taken from normal-appearing skin, bearing no visible terminal or vellus hairs. The specimens obtained consisted of three 4-mm punch biopsies (one sectioned vertically and two sectioned horizontally) and three 3-mm punch biopsies (two sectioned vertically and one sectioned horizontally); one patient had two biopsies done of the upper limb. No DIF was performed.

CAPSULE SUMMARY

- Frontal fibrosing alopecia (FFA) is a variant of lichen planopilaris, sharing histopathologic features.
- Although FFA is recognized clinically by a band of frontal and temporal hairline recession, many patients also describe eyebrow loss and body hair loss.
- In this study, histopathologic findings from the scalp, eyebrows, and peripheral body sites all showed similar features, including a reduction in the number of hair follicles and a perifollicular lymphoid cell infiltrate with perifollicular fibrosis.
- We conclude that FFA is a generalized variant of lichen planopilaris that affects multiple body sites.

RESULTS

Clinical findings

Table I summarizes the demographics and clinical data for the 13 patients included in the study. All patients were female and 11 of 13 (85%) known to be postmenopausal. The median (interquartile range [IQR]) age at onset of alopecia was 57 years (48-64), with a median (IQR) duration of 3 years (2-6).

Clinical examination revealed a band of symmetric recession involving the frontotemporal or frontoparietal hairline in all patients (Fig 1, A and Fig 2, A). At the margin of hair loss, perifollicular erythema and scaliness was evident in all patients (Fig 1, A). Partial to total eyebrow loss was clinically reported in all patients, but in contrast with scalp hair loss, no perifollicular erythema, scaliness, or papules were clinically evident (Fig 1, D and Fig 2, D). Body hair loss was documented in 10 of 13 patients (77%). Of these 10 patients, all reported hair loss on the upper limbs, whereas 5 of 13 also had axillary hair loss; of this subset, 4 of 5 patients also had pubic hair loss. Of the 10 patients with hair loss from body sites, the findings were similar to that of eyebrow loss, in that the surrounding skin appeared to be normal, with no visible erythema, scaliness, or papules (Fig 1, G and Fig 2, G). Two of 10 patients (Nos. 6 and 11) experienced peripheral body hair loss before the onset of scalp hair loss. One patient (No. 10) with known vulval and conjunctival lichen planus also experienced eyelash and eyebrow hair loss before

*References 1-3, 6, 7, 9-14, 17, 18, 20-23, 25-29, 31, 32.

†References 3, 7, 9, 14, 20, 21, 23, 25, 27, 28, 31, 32.

Table I. Patient demographics and clinical data

Patient	Age (y)	Sex	Ethnicity	Postmenopausal at onset of alopecia	Scalp alopecia	Eyebrow alopecia	Upper limb alopecia	Duration of scalp alopecia (y)
1	64	F	C	+	+	+	—	1
2	60	F	C	+	+	+	+	N/K
3	61	F	C	+	+	+	+	3
4	79	F	C	+	+	+	—	2
5	42	F	A	N/K	+	+	—	3
6	58	F	C	+	+	+	+	2
7	62	F	C	+	+	+	+	7
8	74	F	C	+	+	+	+	6
9	64	F	C	+	+	+	+	4
10	52	F	C	+	+	+	+	9
11	54	F	C	+	+	+	+	4
12	75	F	C	+	+	+	+	2
13	40	F	C	N/K	+	+	+	7

+, Present; —, absent; C, Caucasian; A, Afro-Caribbean; N/K, not known.

onset of scalp hair loss; no other patients in this cohort had skin lesions of coexisting lichen planus.

Histopathologic findings

Histopathologic examination of the scalp, eyebrow, and upper limb biopsy specimens showed similar features in all cases. These included a reduced number of hair follicles and perifollicular lymphoid cell infiltrate with perifollicular fibrosis. Direct immunofluorescence was negative.

Scalp. All 13 patients had biopsy specimens taken from the scalp. The mean number of hair follicles was considerably reduced, to 7 (range, 1-22) terminal hair follicles per 4-mm scalp biopsy specimen (normal mean for Caucasians is 30).³⁶ One patient in our group was Afro-Caribbean (No. 5); her scalp biopsy had only one terminal hair follicle per 4-mm scalp biopsy specimen (normal mean for Afro-Caribbeans is 18).³⁶ Fibrous tracts with follicular dropout, consistent with a reduction of hair follicle density, was a prominent feature in 13 of 13 patients (Fig 1, *B* and Fig 2, *B*). Perifollicular lymphoid cell infiltrate and perifollicular fibrosis were evident in all 13 patients (Fig 1, *C*). A vacuolar interface change of the follicular epithelium was seen in 6 of 13 patients (Fig 2, *C*). All these features were consistent with LPP.

Eyebrow. Follicular scars with follicular dropout were seen in 6 of 6 patients (Fig 1, *E* and Fig 2, *E*). A reduction in the number of hair follicles was also evident, with a mean of 5 (range, 1-13) terminal follicles per 3-mm punch biopsy specimen. Terminal hairs were present in all 6 patients and vellus hairs in 5 of 6. All terminal hairs had an active perifollicular lymphocytic infiltrate, perifollicular fibrosis, and focal interface change (Fig 1, *F* and Fig 2, *F*). Such

findings were present throughout the hair cycle, involving both anagen and telogen hair follicles. Five patients had vellus hairs affected in a similar fashion to the terminal hairs; however, the degree of inflammation was variable. All such findings were similar to those observed in the scalp.

Upper limb. Upper limb biopsy specimens were obtained from 5 of the 10 patients who reported peripheral alopecia. Vellus hairs were seen in 2 of 5 patients, while no hair follicles were identified in 3 of 5 patients. A perifollicular lymphocytic infiltrate with interface change and perifollicular fibrosis was seen in one vellus-telogen hair in 1 of 5 patients (Fig 2, *H*). Dermal fibrous tracts associated with residual portions of arrector pili muscle were present in all 5 patients (Fig 1, *H, I, J*).

DISCUSSION

In 1994, Kossard¹ described 6 postmenopausal women with a distinctive progressive scarring alopecia affecting the frontal hairline, often extending to the temporal and parietal regions, which contrasted with the usual multifocal appearance of LPP, yet had histologic features indistinguishable from those of LPP. Kossard termed this "postmenopausal frontal fibrosing alopecia" and further characterized it clinically and histologically in a subsequent study.³ Since 1994, more than a hundred cases have been reported.²⁻³² A summary of the case reports and case series is given in Table II, which demonstrates that although a significant number of FFA cases have previously been documented with eyebrow and body hair loss, only a few eyebrow biopsies were performed.^{3,20} No peripheral body sites have undergone biopsy.

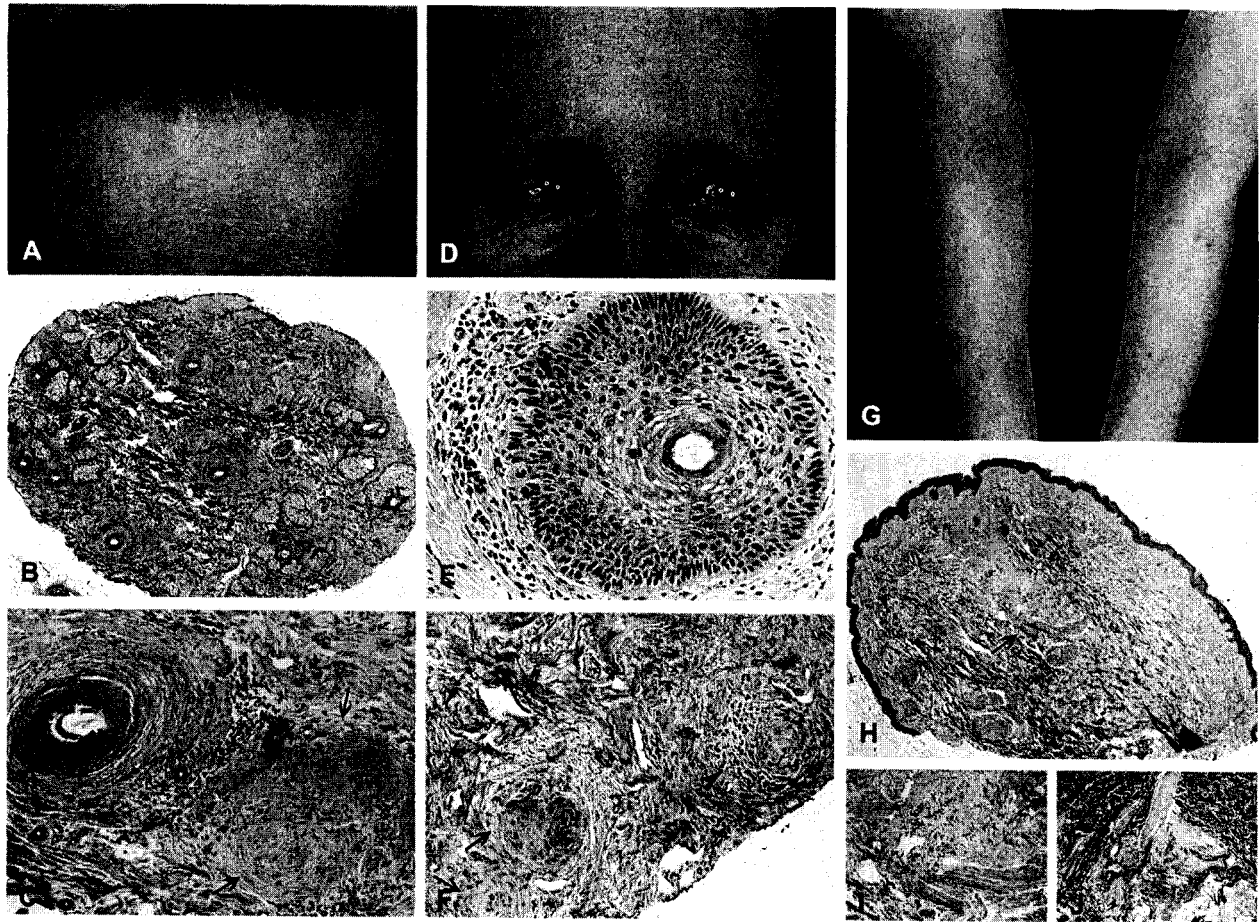


Fig 1. Patient 11. Scalp: Frontal hairline recession with perifollicular erythema (A). A horizontally sectioned biopsy specimen from this area shows reduced hair density with follicular dropout at the level of the isthmus (B). Concentric perifollicular fibrosis with lymphoid cell infiltrate and a follicular scar (*arrows*) is seen at higher power (C). Eyebrows: Noninflammatory, nonscarring alopecia of the eyebrows (D). Dense perifollicular lymphoid cell infiltrate and perifollicular fibrosis (E). Dermal follicular scars (*arrows*); residual lymphoid cell infiltrate is seen on the right side of the field (*dart*) (F). Upper limbs: Noninflammatory, nonscarring alopecia of the upper limbs (G). A biopsy specimen from clinically “normal”-appearing skin reveals absence of hair follicles and residual portions of arrector pili muscles; *arrow* outlines a dermal follicular scar (H), better appreciated at higher power (I), and outlined by elastic van Gieson stain, showing loss of elastic fibers (J). (B, C, E, F, H, I: Hematoxylin-eosin stain; J, elastic van Gieson stain; original magnifications: B and H, $\times 40$; C and J, $\times 200$; E and I, $\times 400$; F, $\times 600$.)

Since the original description, several reports have included premenopausal women,^{3,9,17,21,23,28,32} and it has been proposed that “postmenopausal frontal fibrosing alopecia” is better renamed simply as “frontal fibrosing alopecia,” as the condition is not restricted to postmenopausal women. Nevertheless, a few patients with premature menopause have shown an earlier onset of FFA, indicating a possible hormonal role in its etiology. Two cases of FFA affecting men have been reported.^{10,24}

FFA is thought to be a variant of lichen planus (LP); in fact, the North American Hair Research

Society classification system currently classifies FFA as a lymphocytic primary cicatricial alopecia within the spectrum of LPP.³³ Indeed some patients with FFA have coexistent mucosal or cutaneous lesions of LP.^{5,9,11,32} Furthermore, a few patients with overlapping signs of FFA and Piccardi-Lassueur-Graham-Little syndrome have led some authors to postulate that the two conditions are phenotypically related, again supporting the relationship between LP and FFA.²⁸ In our group of patients, however, only one patient had preexisting LP, that was vulvar and conjunctival, but with no cutaneous lesions.

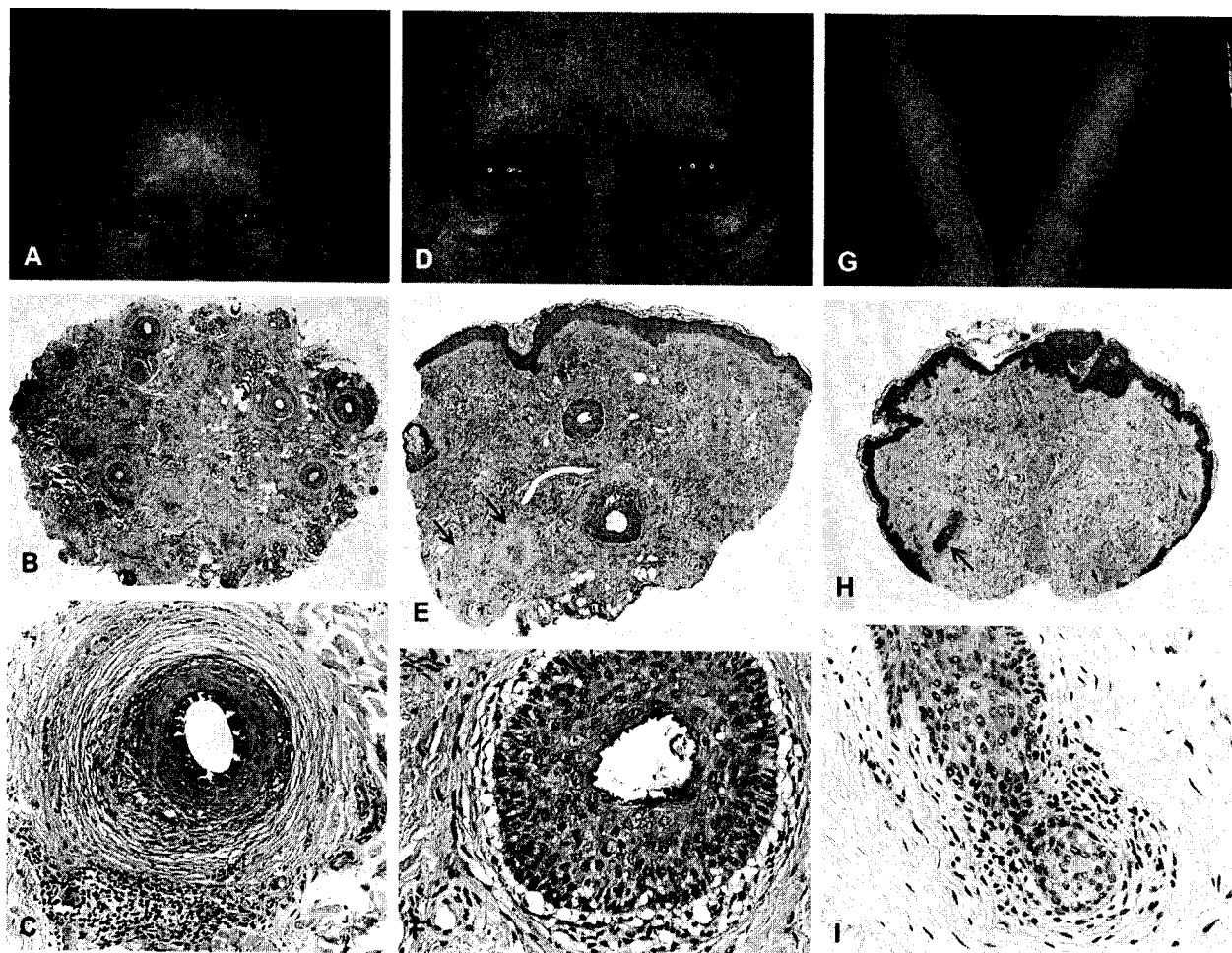


Fig 2. Patient 2. Scalp: Advanced band-like recession of the frontoparietal hairline (A). A horizontally sectioned biopsy specimen shows reduced hair density with follicular dropout, perifollicular fibrosis, and dense perifollicular lichenoid cell infiltrate (B); higher power showing the vacuolar interface change and prominent concentric perifollicular fibrosis (C). Eyebrows: Noninflammatory, nonscarring alopecia of the eyebrows (D). Only two hair follicles are present, plus numerous follicular scars (arrows) (E). High-power view of a hair follicle shows vacuolar interface change with perifollicular lymphoid cell infiltrate (F). Upper limbs: Alopecia of upper limbs (G). A biopsy specimen from clinically "normal"-appearing skin reveals only one residual vellus hair follicle in telogen phase (arrow) (H); at higher power, this hair follicle shows vacuolar interface change, perifollicular lichenoid cell infiltrate, and mild perifollicular fibrosis (I). (B, C, E, F, H, I: Hematoxylin-eosin stain; original magnifications: B, E, H, $\times 40$; C, F, I, $\times 400$.)

The histopathologic findings from the scalp hair of all our patients were consistent with LPP and similar to previous studies of FFA, demonstrating cicatricial alopecia, with reduction in the number of hair follicles, perifollicular fibrosis, a perifollicular lymphoid cell infiltrate, and interface dermatitis. Considerable individual and ethnic variation in hair density exists; approximately 30 terminal and 5 vellus hair follicles are expected in a "normal" Caucasian 4-mm punch biopsy scalp specimen, whereas approximately 18 terminal and 3 vellus hair follicles are found in a "normal" Afro-Caribbean

4-mm punch biopsy scalp specimen.³⁶ In our study, a mean of 7 terminal hair follicles were seen per 4-mm punch biopsy, indicating a considerable reduction in hair density.

DIF was negative in all cases. Previous reports have shown that some, but not all, cases of LPP may demonstrate patchy fibrinogen deposition and globular deposits of IgM or IgA, along the epidermal or infundibular basement membrane zones.³⁷ These may represent colloid bodies, which tend not to be reported in our institution. In addition, sample bias may have played a role, as "burnt-out" areas of LPP

Table II. Reported cases of frontal fibrosing alopecia

Author(s) (year of publication)	No. of patients	Premenopausal	Cutaneous LP	Eyebrow loss	Body hair loss
Kossard ¹ (1994)	6	0	0	3/6	N/A
Feldmann et al ² (1996)	2	0	N/A	2/2	0
Kossard et al ³ (1997)	16	1/16	0	13/16	2/16 (axilla, upper and lower limbs)
Lee et al ⁴ (1997)	1	0	0	N/A	N/A
Trüeb and Torricelli ⁵ (1998)	1	0	0*	0	0
Camacho-Martinez et al ⁶ (1999)	6	0	0	4/6	0
Grunewald et al ⁷ (1999)	1	0	0	1/1	1/1
Guijarro et al ⁸ (2001)	1	0	N/A	N/A	N/A
Faulkner et al ⁹ (2002)	1	1/1	1/1	1/1	1/1 (upper and lower limbs)
Stockmeier et al ¹⁰ (2002)	1	Male patient	0	1/1	0
Claude et al ¹¹ (2002)	3	0	1/3	3/3	0
Heyer et al ¹² (2002)	1	0	0	1/1	0
Naz et al ¹³ (2003)	4	0	0	2/4	N/A
Dawn et al ¹⁴ (2003)	2	0	0	2/2	1/2 (axilla)
Fiorucci et al ¹⁵ (2003)	2	0	0	0	N/A
Török et al ¹⁶ (2003)	1	0	0	0	0
Vaisse et al ¹⁷ (2003)	20	1/20	N/A	12/20	0
Mirmirani et al ¹⁸ (2003)	1	0	0	1/1	0
Herrmann et al ¹⁹ (2004)	2	0	0	N/A	N/A
Tosti et al ²⁰ (2005)	14	0	0	9/14	2/14 (axilla and pubis)
Moreno-Ramirez et al ²¹ (2005)	16	3/16	0	8/16	6/16 (axilla)
Clark-Loeser and Latkowski ²² (2005)	1	0	N/A	1/1	N/A
Jumez et al ²³ (2005)	6	2/6	0	6/6	2/6 (axilla and pubis)
Kossard and Shiell ²⁴ (2005)	1	Male patient	0	0	N/A
Poblet et al ²⁵ (2006)	8	0	0	6/8	1/8 (axilla)
Defo et al ²⁶ (2006)	1	0	0	1/1	0
Schröder et al ²⁷ (2006)	2	0	0	1/2	1/2 (lower limbs)
Abbas et al ²⁸ (2007)	1	1/1	1/1	1/1	1/1 (axilla)
Inui et al ²⁹ (2008)	4	0	0	4/4	N/A
Sato et al ³⁰ (2008)	1	0	0	0	0
Katoulis et al ³¹ (2009)	1	0	0	1/1	1/1 (axilla)
Tan and Messenger ³² (2009)	18	3/18	5/18	15/18	4/18 (upper or lower limbs)

N/A, Not mentioned.

*Patient had oral lichen planus.

typically show negative immunofluorescence findings.

In 1997, Kossard, Lee, and Wilkinson³ noted total or partial eyebrow loss in 13 of 16 women (81%) with FFA. Since then, eyebrow loss has been a prominent feature in reported cohorts of FFA patients with frequencies of 50%,²¹ 60%,¹⁷ 64%,²⁰ and 83%³² in the larger series. In our study, all of the patients had total or partial eyebrow loss, showing a higher incidence than previously reported. Eyebrow biopsies have been done infrequently; of all the cases reported, only 6 eyebrow biopsies have been performed. Kossard, Lee, and Wilkinson³ biopsied the eyebrow of one patient, showing follicular destruction, while Tosti et al²⁰ biopsied 5 of 9 patients with eyebrow loss, in whom 2 of 5 patients showed perifollicular fibrosis.

Even though, clinically, the eyebrow hair loss appears to be noninflammatory and nonscarring, our eyebrow histopathologic findings confirm the changes observed by Kossard, Lee, and Wilkinson³ and Tosti et al²⁰ with permanent hair follicle loss documented by fibrous tracts in the dermis as well as signs of active inflammation of the remaining hair follicles. These changes are similar to those of the scalp (perifollicular lymphoid cell infiltrate, follicular interface changes, and perifollicular fibrosis), in keeping with LPP. The inflammatory cell infiltrate targeted terminal, intermediate, and vellus hair follicles and any stage of the hair cycle, from anagen to telogen. In this regard, Tosti et al²⁰ observed a selective involvement of the intermediate and vellus-like hair follicles. Although no data are available on the number of hair follicles normally present in a

3-mm punch biopsy specimen taken from the eyebrow, the presence of fibrous tracts at the isthmus and supraisthmus area is indicative of permanent hair loss.

Peripheral body hair loss was noted in 10 (77%) of our patients with FFA. Hair loss on the upper limbs was seen in all 10, while 5 also had axillary hair loss. Of these 5 patients, pubic hair loss was seen in 4. This is a relatively high proportion of individuals with peripheral body hair loss, compared with frequencies of 0%,¹⁷ 12%,³ 14%,²⁰ 22%,³² and 37%²¹ in several series with similar numbers of patients. As with eyebrow hair loss, the clinical appearance of upper limb hair loss is that of a noninflammatory, nonscarring alopecia. However, in all of our 5 patients with biopsies, the presence of follicular scars in the dermis was demonstrated histopathologically, a feature of permanent hair loss, with one patient showing a telogen hair follicle with perifollicular lymphoid cell infiltrate, interface changes, and perifollicular fibrosis.

Although these histopathologic changes were subtle, our findings nevertheless show that the hair follicle loss in this region of the body is part of the same fibrotic process involving the scalp and the eyebrows, despite the fact that the clinical appearance of limb hair loss in our cohort of patients was noninflammatory and nonscarring.

In conclusion, clinically we have showed that eyebrow and peripheral body hair loss is common in patients with FFA—a finding most likely underreported. We have also demonstrated histopathologically that hair loss from the eyebrow and upper limbs share similar features, suggesting that the process of permanent hair follicle loss is in fact generalized rather than localized only to the frontal scalp and eyebrow.

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AMERICAN BOARD OF DERMATOLOGY EXAMINATION DATES

The In-Training Examination for dermatology residents will be administered online at dermatology residency training centers in the United States and Canada on March 24, 2011, and on March 28, 2011 for overseas programs. The deadline for receipt of applications is January 15, 2011.

The MOC-D/Recertification Examination will be administered as a proctored paper-and-pencil examination in Prometric testing centers on February 9, 10, 11, 14, 15, and 16, 2011 (deadline for receipt of applications is September 13, 2010) and August 8, 9, 10, 11, 15, and 16, 2011 (deadline for receipt of applications is March 14, 2011).

The Certifying Examination will be held at the testing center of the American Board of Pathology in Tampa, Florida on July 18-21, 2011 and July 25-28, 2011. The deadline for receipt of applications is March 1, 2011.

The examination for subspecialty certification in Dermatopathology will be administered at the testing center of the American Board of Pathology in Tampa, Florida on September 12, 2011. The deadline for receipt of applications is May 15, 2011. (Dermatologists must submit applications to the American Board of Dermatology office and pathologists to the American Board of Pathology office.)

The examination for subspecialty certification in Pediatric Dermatology will be administered again in 2012 (date to be determined). The deadline for receipt of applications is April 1, 2012.

For further information about these examinations, contact the ABD office (address and phone numbers below) or check the ABD website at www.abderm.org.

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