The spectrum of hair loss in patients with mycosis fungoides and Sézary syndrome

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Background: Alopecia can be a manifestation of mycosis fungoides (MF) and Sézary syndrome (SS), but the prevalence is unknown.

Objective: We sought to describe the clinicopathologic presentation and molecular features of alopecia in patients with MF/SS.

Methods: A retrospective chart review of a prospectively collected MF/SS database was used to identify patients with alopecia. The National Alopecia Areata Registry was used to identify patients with self-reported cutaneous T-cell lymphoma.

Results: Among 1550 patients with MF/SS, 38 patients with patchy, total-scalp, or universal alopecia were identified. Thirteen of 38 (34%) had patchy alopecia clinically identical to alopecia areata. Scalp biopsy specimens were available in 5 of the 13 patients. Specimens from 4 patients had atypical T lymphocytes within the follicular epithelium or epidermis, and that from two patients had a histology of follicular mucinosis. The remaining 25 of 38 (66%) patients with MF/SS included 20 with alopecia within discreet patch/plaque or follicular lesions of MF and 5 with total-body hair loss, which presented only in those with generalized erythroderma and SS.

Limitations: This was a retrospective study done at one cancer center. Biopsy specimens of alopecia were not available for every patient.

Conclusions: Alopecia was observed in 2.5% of patients with MF/SS, with alopecia areata–like patchy loss in 34% and alopecia within MF lesions in 66%. (J Am Acad Dermatol 2011;64:53-63.)

Key words: alopecia areata; alopecia mucinosa; autoimmune hair loss; cutaneous T-cell lymphoma; follicular mucinosis; folliculotropic mycosis fungoides.

Mycosis fungoides (MF), the most common type of cutaneous T-cell lymphoma (CTCL), is characterized histologically by small to medium atypical T lymphocytes with cerebriform nuclei that infiltrate the epidermis (ie, epidermotropism).[1] Folliculotropic MF (F-MF) is a less common variant of MF that is characterized histologically by atypical T lymphocytes that preferentially infiltrate the follicular epithelium. F-MF is thought to have a worse prognosis and more

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aggressive course than conventional MF.[2] Patients with conventional MF usually present with patches or plaques on sun-shielded skin, whereas patients with F-MF usually present with grouped follicular papules, acneiform lesions, and indurated plaques that preferentially affect the head and neck areas.[1] Sézary syndrome (SS) is a leukemic variant of CTCL that is characterized by generalized erythroderma; an absolute Sézary cell count of more than 1000 cells/mm^3; a CD4:CD8 ratio more than 10; loss of any or all of the T-cell antigens CD2, CD3, CD4, CD5; or a T-cell clone in the peripheral blood as demonstrated by molecular or cytogenetic methods.[1]

Histologically, F-MF is defined by the presence of atypical T lymphocytes that preferentially invade hair follicles; the intervening epidermis is usually spared.[1] Deposition of mucin within the follicular epithelium (ie, follicular mucinosis) may or may not be present in F-MF lesions.[1,3] One study concluded that no difference was present in the clinical presentation and behavior of F-MF with or without associated follicular mucinosis.[4] In addition, histologic features of follicular mucinosis can be present in the absence of malignant T cells. The term "alopecia mucinosa" is used to describe clinical lesions associated with this histologic finding.[5]

Although two studies, one on follicular mucinosis[6] and another on F-MF,[2] have reported patients with patchy hair loss, the prevalence of T-cell–mediated alopecia among a cohort of patients with CTCL has not been reported. Likewise, the prevalence of cutaneous lymphoma has not been reported in patients with alopecia areata/universalis. In this study, we queried two large databases and identified a group of patients with MF/SS and patchy, total-scalp, and total-body hair loss and reviewed their clinicopathologic presentation and molecular features.

CAPSULE SUMMARY

- Alopecia was observed in 2.5% of patients with mycosis fungoides/Sézary syndrome, with alopecia areata–like patchy loss in 34% and alopecia within patches, plaques, follicular mycosis fungoides lesions, and generalized erythroderma in 66%.
- Total-body alopecia was limited to patients with Sézary syndrome.
- No patient in the National Alopecia Areata Registry self-reported coexisting forms of cutaneous T-cell lymphoma.

METHODS

Patients

The study protocol was reviewed and approved by the University of Texas MD Anderson Cancer Center Internal Review Board. We conducted a retrospective analysis of a prospectively collected database of 1550 patients with biopsy-proven MF or SS who were evaluated at our cancer center from 1981 to 2009. As a control, we queried the internal review board–approved National Alopecia Areata Registry of 5000 self-registered patients with alopecia areata, alopecia totalis, or alopecia universalis to identify those who self-reported associated CTCL.[7]

Clinical data

Clinical data collected included ages at onset of cutaneous symptoms leading to the diagnosis of MF/SS, ages at onset of alopecia, and ages at diagnosis of MF/SS (Table I). Race, sex, locations of alopecia, and stages of MF at diagnosis were also recorded (Table I). For patients with documented progression of alopecia, only the extent of hair loss before systemic chemotherapy or radiation was recorded. We excluded all patients whose hair loss resulted from systemic chemotherapy or radiation and those with androgenic alopecia.

Histopathologic, immunohistochemical, and molecular data

Histology slides from available biopsy specimens were stained by hematoxylin-eosin and were reviewed by dermatopathologists. From biopsy reports, we recorded the presence or absence of atypical T lymphocytes within the follicular epithelium (ie, folliculotropism) and the presence or absence of blue, granular material (ie, mucin) within the follicular epithelium (ie, follicular mucinosis). The ratios of $CD4^+$ to $CD8^+$ cells obtained from immunohistochemical studies and clonal T-cell receptor gene rearrangements obtained by polymerase chain reaction were also recorded (Table I).

RESULTS

In all, 38 (2.5%) patients with alopecia before systemic chemotherapy or radiation were identified from a database of 1550 patients with MF/SS. The male to female ratio was 2.5:1; the mean and median ages at diagnosis of MF/SS were 50 and 51 years, respectively (range 20-80 years) (Table I). In all, 32 patients had patchy hair loss, 5 patients had universal hair loss, and one patient had total-scalp hair loss. TNM stages of the 38 patients with MF/SS are found in Table II. Histopathologic findings are presented in Table III. No one in the National Alopecia Areata Registry self-reported coexisting CTCL.

The 38 patients with MF/SS were divided into two groups based on the clinical phenotype of their hair

Abbreviations used:

CTCL: cutaneous T-cell lymphoma
F-MF: folliculotropic mycosis fungoides
MF: mycosis fungoides
SS: Sézary syndrome

loss. Group 1 had hair loss clinically identical to alopecia areata. In these patients, overt MF/F-MF lesions were not present within areas of baldness but were present elsewhere on their bodies. Epidermal changes, when present in areas of baldness, were limited to mild erythema or scaling. Group 2 had hair loss accompanied by overt epidermal changes. These epidermal changes included patch/plaque lesions of MF, follicular lesions of F-MF, or generalized erythroderma associated with SS.

Group 1: Alopecia areata–like hair loss

Among 38 patients, 13 (34%) had patchy hair loss clinically identical to alopecia areata. The male to female ratio was 1:6, and the mean and median ages at diagnosis of MF were 49 and 46 years, respectively (range 20-80 years) (Fig 1, *A* to *D*). The 13 patients had biopsy-proven MF lesions elsewhere on their bodies. Five of the 13 (38%) patients had documented alopecia before or within 1 year of the onset of skin symptoms of MF, and 6 (46%) patients had documented alopecia at least 1 year after the onset of skin symptoms of MF. The onset of alopecia was not known in the two remaining patients.

Alopecia areata–like hair loss on the scalp was the most common, affecting 8 of 13 patients (Fig 1, *A* and *B*). Bilaterally symmetric alopecia on the extremities was the second most common, affecting 6 patients—4 had involvement of both the upper and lower extremities, one had involvement of only the lower extremities (Fig 1, *D*), and one had involvement of only the upper extremities. Facial involvement (ie, eyebrows, eyelashes, beard) occurred in 3 patients and truncal involvement occurred in two (Fig 1, *C*).

Eighteen lesional biopsy specimens were examined from 13 patients with alopecia areata–like hair loss. Molecular T-cell receptor studies showed clonal V-gamma, V-beta, or both gene rearrangements in 6 of 10 patients. In 4 patients, clonal T-cell receptor gene rearrangements were not detected. Seventeen of 18 biopsy specimens had elevated CD4:CD8 ratios (range 3:1 to >10:1). One specimen showed an epidermal T-cell infiltrate with a predominance of $CD8^+$ over $CD4^+$ T cells and clonal T-cell receptor V gamma-III and V-beta gene rearrangements. Clinically, this 20-year-old man (patient 10) presented with an enlarging patch of hair loss on the back of his leg, which progressed to the opposite leg and abdomen. The $CD8^+$ phenotype was consistent with juvenile-onset MF.

Scalp biopsy specimens, available in 5 of 13 patients, had the following features. Atypical T lymphocytes infiltrating the epidermis or follicular epithelium were present in specimens from 4 patients. Mucin deposition within the follicular epithelium (ie, follicular mucinosis) was present in specimens from two patients. In patient 3 atypical T lymphocytes were not detected in a specimen from an alopecia areata–like area on the scalp. In the same specimen, a predominance of $CD4^+$ cells was present and clonal V-beta, V-gamma I, and V-gamma III T-cell receptor gene rearrangements were detected by polymerase chain reaction. Patient 3 had patch MF lesions on her thighs, bilateral axilla, and lower aspect of her back, and plaques of comedonal lesions on her face. A lesional facial specimen had folliculotropic atypical T lymphocytes that spared the intervening epidermis and a histology of follicular mucinosis. Patient 5 had alopecia areata–like hair loss on the bilateral arms and MF lesions on the scalp. Specimens from the arms were not available; however, a lesional scalp specimen had folliculotropic atypical T lymphocytes with a CD4:CD8 ratio of 3:1 and a histology of follicular mucinosis (Fig 2).

Two of 5 scalp biopsy specimens showed atypical intrafollicular T lymphocytes without mucin deposits within the follicular epithelium. Patient 4 had alopecia areata–like hair loss of the scalp, eyebrows, and trunk, and hyperpigmented macules with ichthyotic scale on his lower extremities. His scalp specimen had a clonal V-beta gene rearrangement. Patient 7 had alopecia areata–like hair loss of the scalp and eyelashes, and oval gray patches on the back, legs, and thighs (Fig 1, *B*). Immunohistochemical study performed on the scalp specimen showed a CD4:CD8 ratio of more than 10:1. T-cell receptor study was not performed.

One of 5 scalp specimens had an epidermal infiltrate of atypical T lymphocytes with a predominance of $CD4^+$ over $CD8^+$ cells. Neither follicular involvement by atypical cells nor a histology of follicular mucinosis was present. This patient (patient 11) had alopecia areata–like hair loss of the scalp and diffuse pink patches on his chest, back, and extremities. Interestingly, this patient also had a history of lymphomatoid papulosis that progressed to MF.

Group 2: Patients with alopecia within MF lesions

In all, 25 of 38 (66%) patients had alopecia within overt MF lesions (Fig 1, *E* to *J*). These lesions

Table I. Patients with mycosis fungoides or Sézary syndrome with patchy, total-scalp, or total-body hair loss

	Age, y						MF/SS				
Patient No.	Race/sex	Skin sx onset	Dx of MF	Alopecia onset	Stage at dx	Location of of alopecia	Site of bx	FM	Fol	CD4:CD8 in bx	TCR in bx
Patients with alopecia areata–like hair loss (n = 13)											
1	NA/F	76	76	76	IA	Scalp	Skin	+	+	ND	+Vg2,+Vg3
2	W/M	40	42	40	IB	Beard, trunk, extremities	Skin	–	+	P-CD4	+Vg1
3	AA/F	35	45	35-45	IB	Scalp	Skin	+	+	4:1	ND
							Scalp	+	–	P-CD4	+Vg1,+Vg3,+Vb
4	AA/M	46	48	46-48	IVA	Scalp, trunk, eyebrows	Skin	–	+	4:1	ND
							Scalp	–	+	ND	+Vb
5	W/M	30	31	30	IA	Upper extremities	Skin	+	+	3:1	ND
							Scalp	+	+	3:1	ND
6	W/M	38	46	38	IB	Extremities	Skin	+	+	>5:1	(–)
7	AA/F	54	59	60	IB	Scalp, eyelashes	Skin	–	–	ND	ND
							Scalp	–	+	>10:1	ND
8	W/F	22	55	22-55	IB	Scalp, extremities	Skin	+	+	P-CD4	ND
9	W/M	75	80	80	IIA	Scalp	Skin	–	–	P-CD4	(–)
10	W/M	18	20	18	IA	Lower extremities	Skin	–	–	CD4<CD8	+Vg3,+Vb
11	W/M	54	56	56-63	IA	Scalp	Skin	–	–	4:1	+Vg
							Scalp	–	–	P-CD4	ND
12	W/M	28	34	34	IIA	Extremities	Skin	–	–	5:1	(–)
13	AA/F	31	44	54	IB	Scalp	Skin	–	–	ND	(–)
Patients with alopecia within overt MF lesions (n = 25)											
Patients 14-20 have SS											
14	W/F	49	51	50	IVA	AU	Skin	–	–	ND	+Vb,+Vg
15	W/F	50	54	54	IVA	AU	Skin	–	+	ND	+Vg
							Scalp	–	–	ND	ND
16	W/M	41	46	44	IVB	AU	Skin	–	–	P-CD4	+Vg
							Scalp	–	+	ND	ND
17	W/F	54	55	55	IVB	Scalp	Skin	–	–	ND	+Vb2, +Vg
18	W/M	72	76	75	IVB	AU	Skin	–	–	4:1	+Vb5.1
19	W/M	47	69	47-69	IVA	AU	Skin	–	–	P-CD4	+Vb,+Vg
20	W/M	66	66	66	IVB	Trunk	Skin	–	–	5-10:1	+Vg
21	W/M	?	36	72	IVB	Scalp	Skin	+	+	P-CD4	+Vg
							Scalp	–	–	ND	ND
22	A/F	44	44	44	IA	Eyebrows	Skin	+	+	P-CD4	(–)
23	H/M	32	37	37	IIB	Eyebrows, trunk, extremities	Skin	–	+	5:1	ND
24	W/M	45	45	46	IA	Lower extremities	Skin	+	+	4:1	+Vg1
25	W/M	41	47	49	IA	Eyebrows	Scalp	+	+	4-5:1	+Vg
26	W/F	50	60	61	IIB	Eyebrows, scalp	Skin	+	+	>10:1	+Vb

27	H/M	45	46	45-46	IVA	Upper extremities, trunk	Skin	–	+	P-CD4	(–)
28	W/M	44	45	44	IA	Scalp	Skin	+	–	ND	ND
							Scalp	+	+	P-CD4	+Vg1, +Vg2
29	W/M	50	59	56	IIB	Eyebrows, scalp, trunk	Skin	–	+	P-CD4	+Vg3
30	W/M	37	47	46	IB	Lower extremities	Skin	–	+	P-CD4	+Vg1,+Vg2
31	H/F	28	29	28	IB	Scalp	Skin	–	+	P-CD4	+Vg1
32	H/M	22	30	22-30	IA	Lower extremities	Skin	–	+	ND	ND
33	H/M	57	57	61	IB	Scalp, extremities	Skin	+	+	P-CD4	+Vg3
34	W/M	47	49	53	IA	Lower extremities	Skin	+	+	P-CD4	(–)
35	W/M	64	74	74-80	IIB	Scalp	Skin	–	–	>4:1	+Vb, +Vg1
							Scalp	–	–	>4:1	ND
36	H/M	39	51	51	IB	Scalp	Skin	–	–	4:1	(–)
37	W/M	52	77	52-77	IA	Lower extremities	Skin	–	–	4:1	ND
38	AA/M	74	74	77	IB	AT	Skin	–	–	3-4:1	(–)

A, Asian; *AA*, African American; *AT*, alopecia totalis; *AU*, alopecia universalis; *bx*, biopsy; *dx*, diagnosis; *F*, female; *FM*, follicular mucinosis; *Fol*, folliculotropism; *H*, Hispanic; *M*, male; *MF*, mycosis fungoides; *NA*, Native American; *ND*, not done; *P-CD4*, predominance of $CD4^+$ cells; *SS*, Sézary syndrome; *sx*, symptoms; *TCR*, clonal T-cell receptor gene rearrangement; *Vb*, V-beta T-cell receptor gene rearrangement; *Vg*, V-gamma T-cell receptor gene rearrangement; *W*, Caucasian; *(+)*, positive; *(–)*, negative.

Table II. Stages at diagnosis of mycosis fungoides or Sézary syndrome

Stage	Patients with alopecia areata–like hair loss (n = 13)	Patients with alopecia within overt MF lesions (n = 25)
IA	4 (31%)	7 (28%)
IB	6 (46%)	5 (20%)
IIA	2 (15%)	0 (0%)
IIB	0 (0%)	4 (16%)
III	0 (0%)	0 (0%)
IVA	1 (8%)	4 (16%), 3 of 4 had SS
IVB	0 (0%)	5 (20%), 4 of 5 had SS

MF, Mycosis fungoides; *SS*, Sézary syndrome.

Table III. Histopathologic findings of biopsy specimens

Histopathologic findings	Patients with alopecia areata–like hair loss (n = 18 specimens)	Patients with alopecia within overt MF lesions (n = 30 specimens)
Folliculotropism	4 (2 from scalp)	8 (1 from scalp)
Folliculotropism with follicular mucinosis	6 (1 from scalp)	8 (2 from scalp)
Follicular mucinosis	1 (1 from scalp)	1
Epidermotropism without folliculotropism	7	13 (3 from scalp)

MF, Mycosis fungoides.

included localized patch/plaque and follicular lesions, and generalized erythroderma that was present in 7 patients with SS, 5 of whom had total-body alopecia (Fig 1, *J*). Group 2 had a male to female ratio of 3.17:1. The mean and median ages at diagnosis were 53 and 52 years, respectively (range 29-77 years). Five of 25 (20%) patients had documented alopecia before or within 1 year of onset of skin symptoms. Sixteen of 25 (64%) patients had documented alopecia at least 1 year after the onset of skin symptoms. The onset of alopecia was not known in the remaining 4 patients.

The morphology of MF lesions present within alopecia included patches or infiltrated plaques in 9 (36%) patients (Fig 1, *E* and *H*), follicular lesions (eg, follicular accentuation, follicular erythema resembling keratosis pilaris) in 7 (28%) patients (Fig 1, *I*), generalized erythroderma in 7 (28%) patients (Fig 1, *J*), and indurated boggy pink nodules or plaques in two patients (8%) (Fig 1, *F* and *G*). Alopecia within patch or plaque lesions of the scalp was most common, affecting 9 of 25 patients (Fig 1, *E* and *H*). Bilateral extremities were affected in 8 of 25

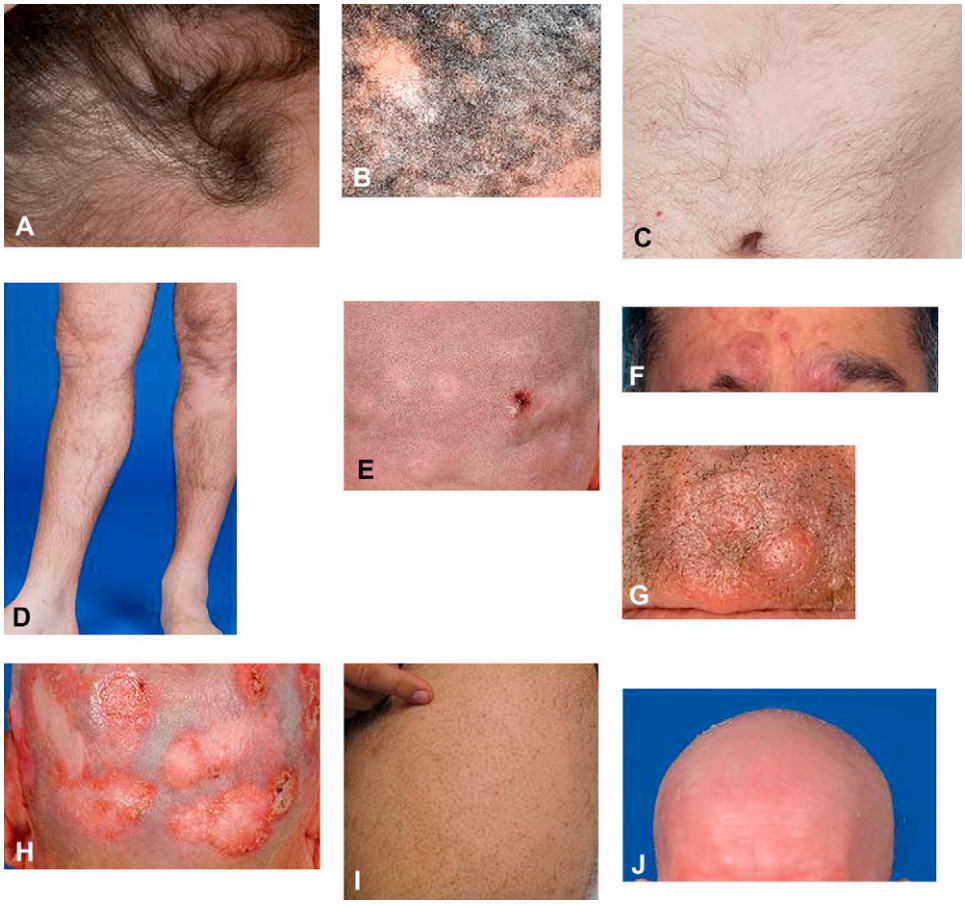

Fig 1. Clinical spectrum of hair loss in patients with mycosis fungoides and Sézary syndrome (SS). **A** to **D**, Patchy hair loss clinically identical to alopecia areata from patients 8, 7, 2, and 6, respectively. **E**, Patchy hair loss on scalp with erythematous patches and plaques present at areas of baldness, patient 28. **F**, Indurated plaques on bilateral brow region accompanied by alopecia, patient 23. **G**, Indurated plaques in beard region with localized alopecia, patient 25. **H**, Patchy alopecia on scalp with ulcerated patches and plaques at areas of baldness, patient 29. **I**, Patchy hair loss on medial thigh with follicular prominence and follicular erythema, patient 32. **J**, Total-body hair loss in patient 14, who had erythroderma and SS.

patients—7 patients had only lower extremity involvement, and one patient had both upper and lower extremity involvement (Fig 1, *I*). Lower extremity lesions within alopecia included follicular erythema and follicular prominence in 6 of 8 patients (patients 27, 30, 32, 33, 34, and 37) (Fig 1, *I*) and patch/plaque lesions in two of 8 patients (patients 23 and 24). Five of 25 patients had facial lesions. Three of the 5 patients had indurated plaques/nodules on their faces—eyebrows were affected in two patients (patients 22 and 23) (Fig 1, *F*), and the bearded area was affected in one patient (patient 25) (Fig 1, *G*). One patient (patient 26) had acneiform lesions on the face, and another (patient 29) had ulcerated plaques on the lateral brows. The trunk was affected in 4 of 25 patients—two had patch/plaque lesions (patients 23 and 29), one (patient 20) had generalized erythroderma and SS, and one (patient 27) had follicular accentuation on the back.

Five of 7 patients identified with SS also had total-body hair loss that occurred before their receiving radiation or systemic chemotherapy (Fig 1, *J*). An unexpected finding was that all 5 patients identified with total-body hair loss had coexisting SS and generalized erythroderma. In all 5, the onset of alopecia occurred concurrently with or after the onset of skin symptoms. When SS was diagnosed, all 5 patients had documented total-body hair loss.

Thirty biopsy specimens from 25 patients in group 2 were reviewed. Immunohistochemical studies were done on 22 of the 30 specimens. All showed CD4:CD8 ratios greater than 3:1, including one specimen that showed a ratio greater than 10:1 (Fig 3). This specimen demonstrated F-MF and was taken

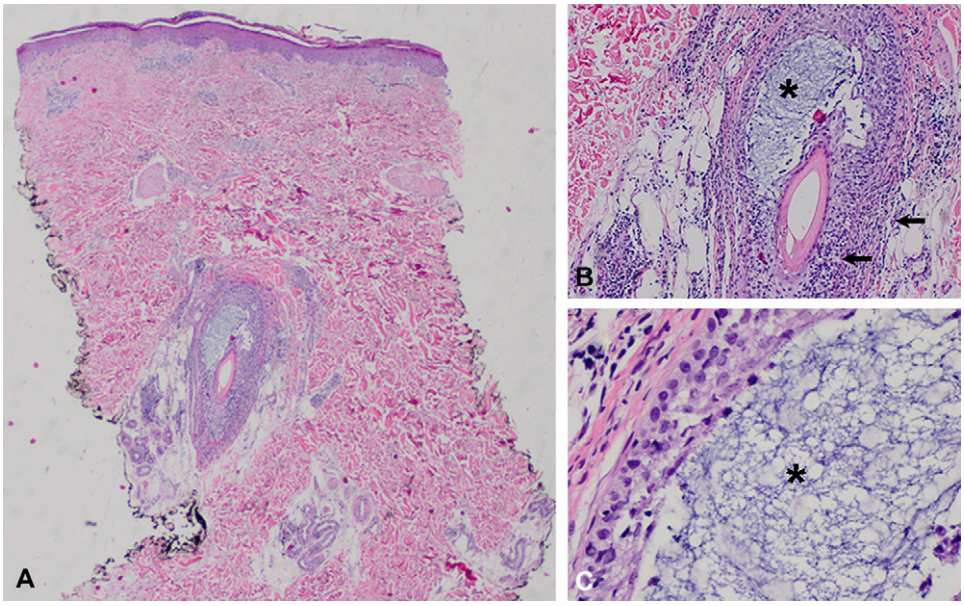

Fig 2. Lesional biopsy specimen collected from left arm of patient 5. **A** and **B**, Follicular mucinosis characterized by basophilic granular material (mucin) within hair follicles (*) accompanied by atypical perifollicular and intrafollicular lymphocytes (*arrows*). **C**, Intrafollicular mucin with characteristic beads-on-a-string appearance (*). (**A** to **C**, Hematoxylin-eosin stain; original magnifications: **A**, ×20; **B**, ×200; **C**, ×400.)

from the right buttock of patient 26. Clonal V-beta, V-gamma, or both T-cell receptor gene rearrangements were detected in 17 of the 22 specimens analyzed.

Lesional scalp biopsies were done in 6 of 25 patients in group 2. All 6 specimens showed atypical lymphocytes infiltrating the epidermis or follicular epithelium. Three of 6 specimens showed atypical T lymphocytes infiltrating the epidermis without follicular involvement. Immunohistochemical study, done in one of the 3 specimens, had a CD4:CD8 ratio greater than 4:1. Two of 6 specimens showed atypical T lymphocytes infiltrating the follicular epithelium and a histology of follicular mucinosis. Both specimens had increased CD4:CD8 ratios and clonal V-gamma gene rearrangements. The one remaining scalp biopsy specimen had atypical T lymphocytes infiltrating the follicular epithelium without a histology of follicular mucinosis. Supporting studies were not done on this specimen.

DISCUSSION

To our knowledge, this is the first study reporting the prevalence and the spectrum of hair loss occurring in MF/SS and the prevalence of MF/SS in those with alopecia areata, a benign T-cell–mediated autoimmune disease. Hair loss was identified in only 2.5% or 38 of 1550 patients with MF/SS. In contrast, the prevalence of self-reported MF/SS was 0% in an alopecia areata database of 5000 individuals. Although the prevalence of alopecia in MF/SS was lower than expected, we found a broad spectrum of hair loss, which fell into two groups. The minority had patchy hair loss clinically identical to alopecia areata, whereas the majority had patchy hair loss within localized MF lesions or universal hair loss accompanied by generalized erythroderma and SS. Unexpectedly, total-body hair loss resembling alopecia universalis was observed only in patients with generalized erythroderma and SS, the leukemic variant of CTCL. Also unexpectedly, not all alopecia in patients with MF was associated with F-MF.[2] In addition, F-MF may or may not be associated with hair loss and/or a histology of follicular mucinosis, and current terminology has become problematic. Regardless of the clinical phenotype of hair loss, the presence of atypical T lymphocytes in the epidermis or follicular epithelium indicates that MF contributed to alopecia in these patients. We further showed that alopecia areata and MF are distinct entities, given that no one from the National Alopecia Areata Registry of 5000 patients reported CTCL. However, the pathogenesis of T-cell–mediated hair loss in both diseases may be similar.

Hair loss clinically identical to alopecia areata was found in 13 of 38 (34%) patients with MF/SS. Alopecia areata is an organ-specific autoimmune disease characterized by benign perifollicular and

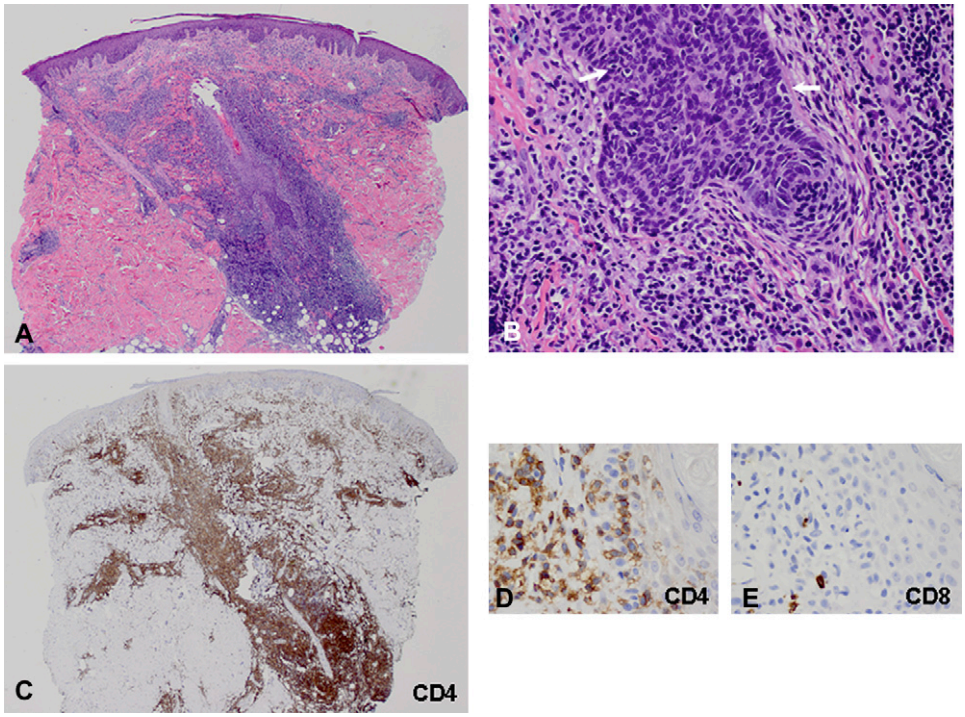

Fig 3. Biopsy specimen collected from right buttock in patient 26. **A**, Folliculotropic mycosis fungoides with dense atypical perifollicular and intrafollicular lymphocytic infiltrate. **B**, Atypical lymphocytic infiltrate with folliculotropism (*arrows*). **C** to **E**, Majority of lymphocytes are $CD4^+$ T cells with CD4:CD8 ratio greater than 10:1. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×20; **B**, ×100. **C** and **D**, Immunohistochemical stain for CD4; original magnifications: **C**, ×20; **D**, ×400. **E**, Immunohistochemical stain for CD8; original magnification: ×400.)

intrafollicular T-cell infiltrates, cytokine production, and dyskeratosis that affect anagen-stage hair follicles (Table IV).[8-10] Alopecia areata presents as patchy hair loss with no or minimal epidermal change. When present, epidermal changes are limited to mild erythema and scaling. Alopecia areata can progress to alopecia totalis (total-scalp hair loss) or alopecia universalis (total-body hair loss). The alopecia results from breakage of the anagen hair shaft from inflammation, causing abnormal differentiation and keratinization.[8,9] A perifollicular and peribulbar infiltrate of activated $CD4^+$ cells is thought to facilitate the cytotoxic functions of activated $CD8^+$ cells in the intrafollicular infiltrate.[8] The diagnosis of alopecia areata requires both hair loss in patches and histology showing benign peribulbar and/or intrabulbar T-cell infiltrates.

In contrast, alopecia occurring within overt clinical lesions of MF was more common and was found in 66% or 25 of 38 patients with MF/SS. Fourteen of the 25 patients were further classified as having F-MF. Because of the confusion in the terminology in the literature, we also assessed the frequency of "follicular mucinosis," a histologic term used to describe the deposition of basophilic, finely granular and stringy material anywhere in pilosebaceous units in hematoxylin-eosin–stained tissue sections.[5] Mucin is composed of hyaluronic acid and sulfated acid mucopolysaccharides, but its origin remains unclear.[5,11,12] One theory is that mucin arises from increased production by follicular keratinocytes,[12] whereas another theory postulates that it could result from increased release of acid mucopolysaccharides from their bound proteins.[11] Two clinical types of follicular mucinosis have been proposed but do not always hold true. One type is idiopathic benign follicular mucinosis, which is not associated with cutaneous lymphoma. The other type is follicular mucinosis caused by atypical intrafollicular and/or perifollicular T lymphocytes, which can be clonal in nature. This latter type results in F-MF.[13] Benign follicular mucinosis, when associated with alopecia, is called "alopecia mucinosa." Alopecia mucinosa typically presents as hair loss within patches or indurated plaques of perifollicular papules.[6,13] Controversy exists on whether idiopathic follicular mucinosis is benign, given that patients with alopecia mucinosa have progressed to MF.[14] Some argued

Table IV. Definitions

Alopecia areata	An organ-specific autoimmune disease presenting as patchy, total-scalp, or total-body hair loss with no or minimal epidermal change (ie, mild erythema or scales). Histologically, it is characterized by benign perifollicular and/or intrafollicular T-cell infiltrates with cytokine production affecting anagen-stage hair follicles.
Alopecia mucinosa	A clinical term used to describe a patch of localized hair loss with a histology of mucin deposition anywhere in the pilosebaceous units and an absence of malignant T cells.
Follicular mucinosis	A histologic term used to describe the deposition of basophilic, finely granular material (ie, mucin) within the follicular epithelium.
Folliculotropic mycosis fungoides	A variant of mycosis fungoides characterized by preferential infiltration of the follicular epithelium by atypical T lymphocytes with cerebriform nuclei, with or without follicular mucinosis or infiltration of the intervening epidermis.

that the apparent progression resulted from a delay in the diagnosis of F-MF, which these patients had from the start.[15] It can be difficult to make a diagnosis of early MF because of a paucity of atypical T lymphocytes in the presence of a benign inflammatory infiltrate,[1,13] and no guidelines specific to F-MF are available at this time. As an example, a scalp biopsy specimen from patient 3 had a histology of follicular mucinosis and an absence of atypical lymphocytes, but additional lesional specimens had atypical intrafollicular T lymphocytes. Therefore, multiple biopsy specimens may be necessary to diagnose MF and F-MF.[16]

Alopecia is a known clinical finding in patients with MF, yet no study has reported the demographics of a cohort of patients with alopecia and MF/SS. Our cohort of 38 patients was predominantly male (male:female, 2.5:1) and had a median age at diagnosis of MF of 51 years. Their demographics were comparable with patients with MF/SS at large (male:female, 1:6-2.0:1; median age at diagnosis, 55-60 years).[1] Most of the patients we identified presented in early stage MF, which reflects the disease's increased incidence and indolent nature.[1]

From 38 patients, we identified 13 patients whose hair loss was clinically identical to alopecia areata. This group showed a predominance of men (male/female, 1:6) and was younger than patients with MF at large (median age at diagnosis, 46 years). About half developed alopecia and skin symptoms within 1 year of each other, whereas the other half developed alopecia more than 1 year after the onset of skin symptoms of MF. This finding suggests that alopecia may be an early sign of MF and that biopsy may help to make the correct diagnosis.

In patients whose hair loss was clinically identical to alopecia areata, scalp was the most common location of hair loss, followed by symmetric areas on the bilateral lower extremities, face (ie, eyebrows, eyelashes, beard), and trunk. Although their alopecia was not associated with overt epidermal changes, biopsy specimens, when available, demonstrated MF. Specimens had atypical T lymphocytes infiltrating the epidermis or hair follicles, elevated CD4:CD8 ratios, and clonal T-cell receptor gene rearrangements. These findings support the hypothesis that alopecia may result from follicular involvement with either benign T-cell infiltrates (ie, alopecia areata) or malignant, activated, or clonal lymphocytes (ie, MF). Hence, clinical suspicion is warranted when evaluating patients with alopecia areata–like hair loss.

The larger group of patients (64%) had localized alopecia within overt MF lesions or total-body alopecia with associated generalized erythroderma and SS. This group demographically resembled patients with MF at large. The median age at diagnosis of MF was 52 years, and the male to female ratio was 3.17. Alopecia in this group tended to develop more than 1 year after the onset of skin symptoms, when compared with those with alopecia areata–like hair loss (64% vs 46%, respectively).

The morphology of MF lesions within alopecia varied based on the area of the body affected. Patch and plaque lesions within alopecia were commonly found on the scalp. Follicular lesions identical to keratosis pilaris were commonly found on the bilateral lower extremities. Indurated plaques with milia and acneiform lesions were commonly found on the face. Follicular lesions and patch/plaque lesions were both found on the trunk. Interestingly, total-body hair loss was present only in patients with generalized erythroderma and SS. This finding suggests that the most severe form of CTCL (ie, SS) is associated with most severe phenotype of hair loss (ie, alopecia universalis).

Regardless of the clinical phenotype of hair loss, the presence of atypical T lymphocytes within areas of alopecia suggested that MF contributed to hair loss. When follicular mucinosis is present on histology, the water-retaining property of mucopolysaccharides is thought to be responsible for intercellular swelling,

Table V. Differential diagnosis of hair loss of the eyebrows, eyelashes, beard, trunk, extremities, or scalp

Primary dermatoses
Atopic dermatitis
Seborrheic dermatitis
Endocrinologic
Hypothyroidism
Autoimmune
Alopecia areata
Frontal fibrosing alopecia (scalp, eyebrows)
Graham Little syndrome
Discoid lupus erythematosus
Neonatal lupus erythematosus
Localized scleroderma (“en coup de sabre”)
Parry-Romberg syndrome
Infectious
Leprosy (Hansen disease)
Secondary syphilis
Neoplastic
Tumor removal
Systemic mastocytosis
Cutaneous T-cell lymphoma (mycosis fungoides)
Trauma
Alopecia artefacta
Tattoo removal
Trichotillomania
Exogenous agents
Chemotherapy
Radiation
Niacin
Thallium
Retinol (vitamin A)
Genodermatoses/congenital
Keratosis follicularis spinulosa decalvans (scalp, eyebrows, eyelashes)
Keratosis pilaris atrophicans faciei (ulerythema ophryogenes) (starts in eyebrows, spreads to face)
Ichthyosis follicularis with atrichia and photophobia (eyebrows)
Ectodermal dysplasia
Fraser syndrome
Meige syndrome
Congenital erythrodermas (Omenn syndrome, Netherton syndrome, severe combined immunodeficiency disorder)

which may damage the follicular epithelium.[12] The mechanism(s) by which atypical T lymphocytes contribute to hair loss remain(s) unclear; however, inflammatory damage to the follicular keratinocytes caused directly by T cells, natural killer cells, and/or the cytokines they produce has been speculated.[17] Clinical trials have demonstrated that bexarotene, an retinoid x receptors selective retinoid, is effective in treating MF.[18-20] In addition, we have observed that bexarotene gel successfully caused remission of hair loss associated with alopecia mucinosa, F-MF,[21] and alopecia areata.[22] Bexarotene may work in part by inducing T-cell apoptosis.[23]

Antigen presentation may also be important for generating activated T cells. Interestingly, MF and alopecia areata are associated with similar HLA-DR and DQB alleles, which could restrict antigen presentation.[24,25] Thus, T cells in both alopecia areata and MF may be triggered by common peptide antigens derived from self or other agents. Oligoclonality of T cells within alopecia areata lesions has also been observed.[26] Furthermore, T cells can transfer alopecia areata in a xenograft model.[8]

It remains to be determined whether hair loss in an independent prognostic indicator in CTCL. In one study[2] comparing the overall survival of patients with F-MF and conventional MF, the 5- and 10-year overall survivals were comparable between the two groups for disease stage less than or equal to IIA. However, the 15-year overall survival was 91% for conventional MF and 41% for F-MF. For disease stage greater than or equal to IIB, the overall survivals for F-MF and conventional MF were comparable. From the F-MF group of 43 patients, 65% had alopecia.[2] It is unclear whether alopecia is a prognostic indicator in MF, independent from its association with F-MF.

Although MF is a cause of alopecia, other causes of hair loss of the eyebrows, eyelashes, beard, trunk, extremities, and scalp should also be considered when evaluating patients presenting with alopecia (Table V).[27]

In summary, we found that patchy, total-scalp, or total-body hair loss was rare in patients with MF/SS, present in 2.5% of these individuals. The clinical spectrum of hair loss included patchy hair loss identical to alopecia areata, localized hair loss within overt MF lesions, and total-body hair loss present only in patients with generalized erythroderma and SS. Alopecia areata–like hair loss may accompany the onset of MF, and alopecia universalis may accompany the onset of SS. Therefore, clinical suspicion is warranted. The benign alopecia areata and malignant F-MF may share a common pathogenesis mediated by folliculotropic T lymphocytes, whether or not they are clonal or malignant. Further studies are needed to define hair follicle antigens in alopecia areata and F-MF and to develop more effective therapies.

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