Follicular mucinosis in patients with hematologic malignancies other than mycosis fungoides: A clinicopathologic study

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Background: Follicular mucinosis (FM), which is defined by mucin accumulation within follicular epithelium, may occur in mycosis fungoides (MF). FM without MF is occasionally reported in systemic hematologic malignancies and may be diagnostically challenging.

Objective: To describe clinicopathologic characteristics of FM in patients with hematologic malignancies other than MF.

Methods: Clinical data and histopathology features were analyzed in patients with FM and hematologic malignancies diagnosed between 1994 and 2017.

Results: A total of 18 patients with FM and systemic hematologic malignancies without cutaneous T-cell lymphoma (CTCL) were identified; 9 of them were discovered after hematopoietic stem cell transplantation. No patients with non–CTCL-associated FM (n = 46 [37 biopsy specimens]) developed CTCL during a mean follow-up of 4.3 years. Of the cases of CTCL associated with FM (n = 44 [31 biopsy specimens]), MF was the most common subtype (n = 38), although other CTCLs were identified. FM in patients with non-CTCL hematologic malignancies differed clinically from those with MF-associated FM, presenting most frequently with erythematous papules ($P < .0001$), without plaques ($P < .0001$), without alopecia ($P = .001$), and without histopathologically identified epidermal exocytosis ($P = .013$).

Limitations: A retrospective study in a single cancer center.

Conclusions: FM can present in systemic hematologic malignancies, including after hematopoietic stem cell transplantation. Papular lesional morphologic and histopathologic features may help to distinguish these cases from MF. (J Am Acad Dermatol 2019;80:1704-11.)

Key words: $CD30^+$ lymphoproliferative disorders; CTCL; cutaneous T-cell lymphoma; follicular mucinosis; hematopoietic stem cell transplantation; histopathology; MF; mycosis fungoides.

Follicular mucinosis (FM) is defined by the accumulation of mucin within follicular epithelium that can result in follicular damage. Clinically, FM presents as follicular prominence, acneiform eruption, and focal hair loss. FM in association with various systemic conditions, including hematologic malignancies, hematopoietic stem cell transplantation (HSCT), and other malignant and

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benign skin disorders,[1] has been occasionally reported. However, it is typically reported in the context of cutaneous T-cell lymphomas (CTCLs), specifically, folliculotropic mycosis fungoides (MF).[2,3] Whether FM, especially when seen in a generalized eruption, may represent an early variant or a precursor stage of MF is a matter of controversy.[3,4] FM may develop as a primary process that is considered idiopathic. Idiopathic FM is an uncommon benign disorder that is typically reported in children and young adults, with locally distributed follicular-based papules, patches, or plaques. MF-associated FM is more commonly described in older patients with a diffusely distributed eruption.[3,5-8] MF-associated FM and idiopathic FM frequently look similar clinically, and their histopathologic features, immunohistochemical phenotype, and T-cell receptor gene rearrangement status overlap; thus, diagnosis is based on a combination of clinical, histopathologic, immunohistochemical, and molecular data.[3,5,9-12]

CAPSULE SUMMARY

- Follicular mucinosis in association with systemic hematologic disorders other than mycosis fungoides is poorly characterized.
- Clinicopathologic features of follicular mucinosis in the setting of hematopoietic stem cell transplantation and diverse systemic hematologic malignancies differ from those of mycosis fungoides–associated cases, and follicular mucinosis is not necessarily a precursor to cutaneous T-cell lymphoma.

In this study, we sought to examine our experience with FM in patients treated at a cancer center, specifically focusing on the clinicopathologic features of FM in patients with non-MF hematologic malignancies.

METHODS

Patient selection and clinical data collection

The study was approved by the Memorial Sloan Kettering Cancer Center (MSKCC) Institutional Review Board. A free text search of histopathology reports from the MSKCC Darwin patient database was performed for the following terms: (*skin* OR *cutaneous*) AND (*mucin* OR *mucinosis* OR *mucinosa* OR *mucinosum*). All resultant cases that were diagnosed from January 1994 through July 2017 were evaluated by reviewing their pathology reports and medical records. Patients who did not have a confirmed histopathologic diagnosis of FM by a dermatopathologist at MSKCC or were never seen by a physician at MSKCC were excluded. Clinical data, including diagnoses, demographics, presentation, and follow-up, were collected. Diagnoses of CTCL were confirmed by clinical, histologic, immunohistochemical, and molecular attributes as per the International Society for Cutaneous Lymphomas and the European Organization for Research and Treatment of Cancer guidelines.[2,13,14] History of hematologic malignancy and HSCT before FM detection were noted. We excluded 3 patients and 3 biopsy specimens that showed an incidental finding of FM in a biopsy specimen of a nevus or nonmelanoma skin cancer with no correlation to an eruption or other clinical or histologic findings. The included cases were grouped into a CTCL-associated FM group (MF-associated and other CTCL subgroups) and a non–CTCL-associated FM group (hematologic malignancy–associated and no hematologic malignancy subgroups). The MF-associated and hematologic malignancy–associated FM cases were compared.

Histopathologic analysis

Available skin biopsy specimens showing FM were reviewed by a dermatopathologist (M.P.) who was blinded to the clinical diagnoses. Hematoxylin-eosin–stained slides were evaluated for the following histologic features, as previously described in the literature[9,10]: amount of mucin filling the hair follicles (graded from 1 to 4); presence of dermal mucin; presence of perifollicular lymphoid infiltrate, band-like architecture of the lymphoid infiltrate, and epidermal lymphocytic exocytosis; presence of lymphocytic atypia characterized by enlarged hyperchromatic nuclei with irregular contours; and extent and location of eosinophils (with the grade 0 indicating none, a single plus sign indicating some, and a double plus sign indicating abundant [localization in the hair follicle and/or the dermis]).

Statistical analysis

Qualitative data were expressed as frequencies and percentages, and quantitative data were expressed as means, standard deviations, and ranges. Clinicopathologic features were compared between the 2 groups of patients with MF-associated FM and patients with FM and non-CTCL hematologic malignancy by using a 2-sample *t* test, and chi-square or Fisher exact test. Statistical analyses were performed with IBM SPSS Statistics software (version 24, IBM, Armonk, NY). All tests were 2 sided and *P* values less than .05 were considered statistically significant.

Abbreviations used:

CTCL:	cutaneous T-cell lymphoma
FM:	follicular mucinosis
GVHD:	graft-versus-host disease
HSCT:	hematopoietic stem cell transplantation
LPD:	lymphoproliferative disorder
MF:	mycosis fungoides
MSKCC:	Memorial Sloan Kettering Cancer Center

RESULTS

A total of 90 patients with FM were included in the study: 46 patients (51%) without CTCL and 44 (49%) with CTCL. A total of 68 skin biopsy specimens showing FM from 55 of the 90 patients (61%) were available for pathologic review. Demographics and initial clinical diagnosis for all patients are summarized in Table I. Patients with non–CTCL-associated FM were followed at our institution for periods ranging from 2 months to 21 years after FM was diagnosed (mean 51.7 months), and none developed CTCL during their follow-up.

In all, 18 patients (20%) had a diagnosis of non-CTCL hematologic malignancy at presentation.

Clinical and histologic features of FM in patients with non-CTCL hematologic malignancies are summarized in Tables II and III. The majority of the patients in this group were males (14 of 18 [78%]), and their mean age at diagnosis was 50.8 years. Compared with MF-associated FM patients, a higher percentage of nonwhite patients was noticed in the non-CTCL hematologic malignancy group (45% versus 16%), whereas no differences were found for sex or age between the groups. FM in patients with non-CTCL hematologic malignancies presented most frequently as erythematous papules in 83% (15 of 18), and involving the head and neck in 78% (14 of 18) (as seen in Fig 1). Less frequently, it involved the trunk (in 61% of patients [11 of 18]), presenting only occasionally as plaques, patches, or macules and in none of the cases as tumors or nodules. The clinical presentation differed significantly from that in patients with MF-associated FM, who presented with plaques in 76% of cases (29 of 38 [$P < .0001$]), papules in 13% of cases (5 of 38 [$P < .0001$]), and involvement of the lower extremities in 66% of cases (25 of 38 [$P = .023$]). In addition, whereas none of the patients with non-CTCL hematologic malignancy presented with alopecia, 40% of the patients with MF-associated FM did so (15 of 38 [$P = .001$]).

Histopathologically, the incidence of epidermal exocytosis was lower in FM cases in patients with hematologic malignancies (2 of 16 [13%]) than in FM cases in patients with MF (14 of 28 [50%]) ($P = .013$), whereas all of the other studied histopathologic features did not show significant differences between the groups (Tables II and III).

Of the 18 patients with non-CTCL hematologic malignancy, 9 had undergone HSCT before diagnosis of FM and 9 had no history of HSCT (Tables IV and V). In 8 of the patients with hematologic malignancy and no HSCT, the malignancy was active at the time of diagnosis of FM and 1 patient was in remission after being treated with chemotherapy. In 3 patients, FM developed while they were being treated with chemotherapy. In 2 cases the FM eruption preceded diagnosis of the hematologic malignancy: in the first patient, chronic diffuse pruritic erythematous patches were reported 5 years before the diagnosis of B-cell lymphoplasmacytic lymphoma, and in the second patient, an erythematous pruritic eruption on the trunk and extremities coincided with the appearance of lymphadenopathy a few months before receipt of a diagnosis of Hodgkin lymphoma, nodular sclerosing subtype. In the 9 patients who presented with FM and hematologic malignancy after HSCT, onset of FM occurred from less than a month to up to 7 years after HSCT.

In all, 28 patients with FM had no associated CTCL or hematologic malignancy; they had variable presentations. Three patients had a history of solid tumors (prostate cancer, gastrointestinal stromal tumor, and Kaposi sarcoma) and 2 patients had HIV infection. All the other patients were otherwise well, and 2 of them have been reported by us elsewhere.[8]

Within the group of patients with CTCL-associated FM, 6 had types of CTCL other than MF (Table I). Clinicopathologic correlation in a patient with FM and primary cutaneous $CD30^+$ lymphoproliferative disorders (LPD) is shown in Fig 2.

DISCUSSION

A skin biopsy specimen showing mucin accumulation within the follicular epithelium raises a concern for MF versus a less worrying diagnosis of idiopathic FM. These 2 entities and the challenge of distinguishing between them are well described in the literature. There are limited data on FM in the context of systemic and cutaneous disorders other than MF, and these conditions are poorly characterized. Mir-Bonafé et al reported on a series of 13 cases with FM associated with nonlymphoid skin conditions, mainly inflammatory disorders, emphasizing that FM is a reactive histologic pattern that can be seen unrelatedly to CTCL.[1] In our study of FM in a population of patients at a cancer center, FM was unrelated to CTCL in 51% of the cases, with none of these 46 patients developing CTCL after a mean follow-up of 4.3 years. Our findings support the

Table I. Patients' demographics and clinical diagnoses at presentation

Characteristic	CTCL-associated FM (n = 44)	Non–CTCL-associated FM (n = 46)
Mean age at diagnosis ± SD, y (range)	55.0 ± 17.0 (16-87)	44.3 ± 16.4 (11-77)
Sex, n (%)		
Male	26 (59)	26 (57)
Female	18 (41)	20 (43)
Race, n (%)		
White	37 (84)	29 (63)
African American	3 (7)	4 (9)
Asian	0 (0)	4 (9)
Hispanic	3 (7)	6 (13)
N/A	1 (2)	3 (6)
Diagnosis, n (%)		
CTCL	44 (100) Mycosis fungoides: 38 (86) Primary cutaneous $CD30^+$ lymphoproliferative disorders: 4 (10) Primary cutaneous $CD4^+$ small/medium T-cell lymphoproliferative disorder: 1 (2) Peripheral T-cell lymphoma, unspecified: 1 (2)	0 (0)
Hematologic malignancies	3 (7) Burkitt lymphoma: 1 Chronic lymphocytic leukemia: 1 Follicular lymphoma: 1	18 (39) Hodgkin lymphoma: 3 Chronic lymphocytic leukemia: 3 Acute myeloid leukemia: 2 Mantle cell lymphoma: 2 Diffuse large B-cell lymphoma: 2 Myelodysplastic syndrome: 2 Multiple myeloma: 2 Chronic myeloid leukemia: 1 Lymphoplasmacytic lymphoma: 1
HSCT	0 (0)	9 (20) Autologous HSCT: 5 Allogeneic T-cell–depleted HSCT: 2 Double umbilical cord and haploidentical HSCT: 2
HIV	1 (2)	2 (4)

CTCL, Cutaneous T-cell lymphoma; *FM*, follicular mucinosis; *HSCT*, hematopoietic stem cell transplantation; *N/A*, not available; SD, standard deviation.

Table II. Comparison of clinical parameters among patients with non-CTCL hematologic malignancy–associated FM and MF-associated FM

Characteristic	MF-associated FM (n = 38 patients)	Hematologic malignancy-associated FM (n = 18 patients)	*P* value
Mean age at diagnosis ± SD, y	54.0 ± 16.6	50.8 ± 14.9	.494
Sex, n (%)			
Male	21 (55)	14 (78)	.104
Female	17 (45)	4 (22)	
Race, n (%)			
White	31 (82)	9 (50)	**.022**
African American	3 (8)	1 (6)	
Asian	0 (0)	4 (22)	
Hispanic	3 (8)	3 (17)	
N/A	1 (2)	1 (5)	
Type of lesions, n (%)*			
Papules	5 (13)	15 (83)	**<.0001**
Plaques	29 (76)	3 (17)	**<.0001**
Macules	0 (0)	2 (11)	.099
Patches	23 (61)	6 (33)	.057
Nodules/tumors	6 (16)	0 (0)	.162
Folliuclar prominence, n (%)	6 (16)	5 (28)	.305
Alopecia, n (%)	15 (40)	0 (0)	**.001**
Distribution, n (%)*			
Head and neck	31 (82)	14 (78)	.732
Trunk	29 (76)	11 (61)	.239
Upper extremities	16 (42)	7 (39)	.819
Lower extremities	25 (66)	6 (33)	**.023**
Unilesional, n (%)	6 (16)	1 (6)	.409
Pruritus, n (%)	26 (68)	11 (61)	.763

Boldface indicates statistical significance.
CTCL, Cutaneous T-cell lymphoma; *FM*, follicular mucinosis; *MF*, mycosis fungoides.
*A patient can present with more than one lesion type/body area.

Table III. Comparison of histopathologic features among patients with non-CTCL hematologic malignancy–assocaited FM and MF-associated FM

Histopathologic feature	MF-associated FM, n (%) (n = 28 biopsy specimens)	Hematologic malignancy-associated FM, n (%) (n = 16 biopsy specimens)	*P* value
Follicular mucin			
Grade 1	6 (21)	2 (13)	.732
Grade 2	13 (47)	7 (44)	
Grade 3	5 (18)	5 (31)	
Grade 4	4 (14)	2 (13)	
Dermal mucin	1 (4)	1 (6)	>.999
Lymphoid infiltrate			
Perifollicular infiltrate			.141
None	0 (0)	1 (6)	
Some	21 (75)	14 (88)	
Dense	7 (25)	1 (6)	
Epidermal exocytosis	14 (50)	2 (13)	**.013**
Band-like infiltrate	12 (43)	4 (25)	.236
Lymphoid cytologic atypia	22 (79)	11 (69)	.492
Eosinophils			
None	8 (29)	2 (13)	.457
Some	12 (42)	9 (56)	
Abundant	8 (29)	5 (31)	
In dermis	14 (70)	11 (79)	.704
In dermis and hair follicle	6 (30)	3 (21)	

Boldface indicates statistical significance.
CTCL, Cutaneous T-cell lymphoma; *FM*, follicular mucinosis; *MF*, mycosis fungoides.

concept that FM should not be considered as a variant of MF or a precursor stage of CTCL, as was previously suggested.[3,4]

Of the FM cases in our cohort, 20% were seen in patients with a history of systemic hematologic malignancy and no CTCL, with half of them being FM that developed after HSCT. An association of FM and hematologic malignancies (mostly Hodgkin lymphoma,[15-17] acute myeloid leukemia,[18] and chronic lymphocytic leukemia[19,20]) has been reported in small case series and case reports, and FM has been rarely described after HSCT.[21-23] In our study, FM occurred in association with various systemic hematologic malignancies and HSCT. This group of 18 patients with non-CTCL hematologic malignancy consisted mostly of males, who generally presented as an eruption with papular morphologic features, only rarely with plaques, and without alopecia. Histopathologically, dense perifollicular infiltrates, epidermal exocytosis, and band-like infiltrate were uncommon. The patients with FM after HSCT were predominantly nonwhite males, and all presented with a papular eruption, mostly involving the head and neck and the trunk. Erythematous follicular-based papules were discrete (Fig 1, *A*), were not clustered or linearly arranged, and did not have a waxy firm appearance; the surrounding skin was not shiny or indurated, as is frequently seen in papular mucinosis.[24] Furthermore, microscopically, mucin was deposited in the hair follicles (Fig 1, *B* and *C*) and was seen only rarely in the dermis. Three similar cases of FM in male patients after HSCT for hematologic malignancies have been previously reported in the literature: 1 in a 48-year-old after autologous HSCT for multiple myeloma,[22] 1 in a 19-year-old after

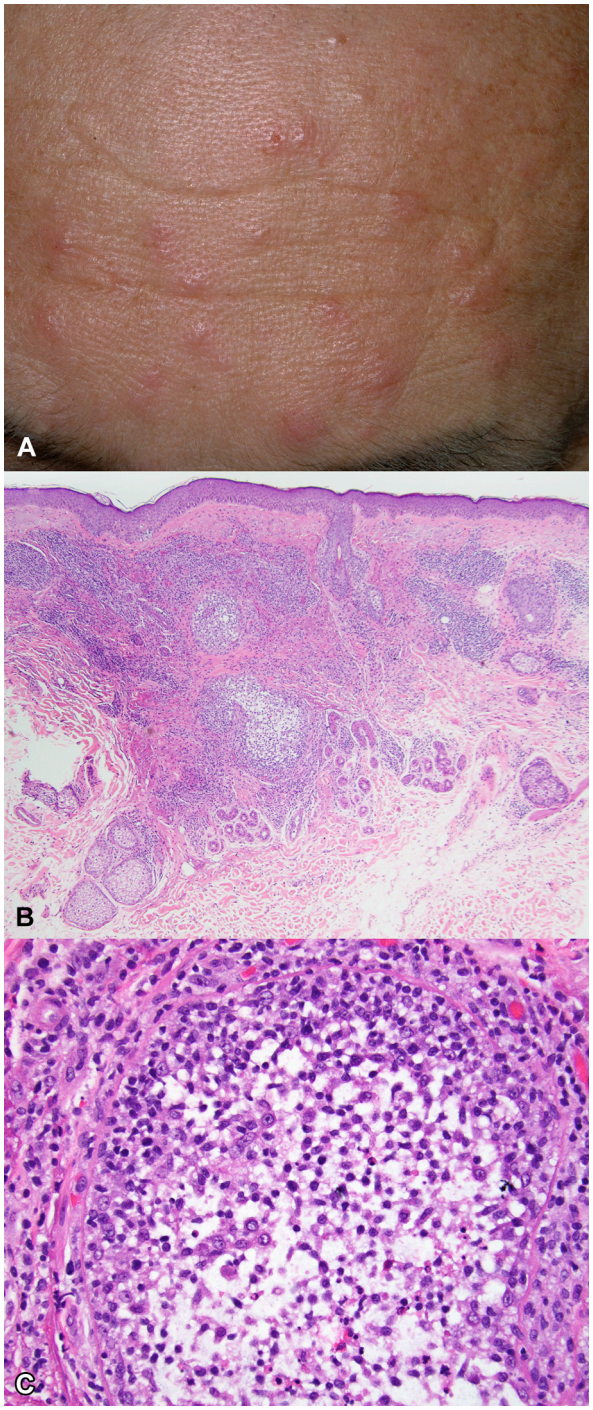

Fig 1. Follicular mucinosis in a 50-year-old patient with history of mantle cell lymphoma after autologous hematopoietic stem cell transplantation. **A,** Clinical features. Erythematous papules on the face. **B** and **C**, Histopathology. Dermal atypical lymphohistiocytic infiltrate with follicular mucinosis. (**B** and **C**, Hematoxylin-eosin stain; original magnifications: **B,** ×10; **C,** ×40.)

allogeneic HSCT for acute lymphoblastic leukemia,[21] and 1 in a 17-year-old after allogeneic HSCT for acute myeloid leukemia.[23] The first 2 patients presented with a papular eruption involving the face or the head, neck, and upper trunk 3 to 5 weeks after the transplant. The third case appeared with patches and follicular prominence on his trunk and extremities 9 months after the transplant. Interestingly, in the 2 former patients, mild acute cutaneous graft-versus-host disease (GVHD) was diagnosed before they presented with FM, whereas in our cohort, only 1 patient had a history of chronic GVHD. Our findings and the previously reported cases suggest that FM is a reactive pattern that can be found in papular eruptions, can appear between a month and up to several years after transplantation regardless of the HSCT type, is transient in most cases, and is not associated with CTCL. Additional cases should be studied to evaluate the possible association of FM after HSCT and GVHD.

The exact mechanism underlying the deposition of mucin selectively within the follicular unit is

Table IV. Clinical features of FM in patients with non-CTCL hematologic malignancy after HSCT and with no HSCT

Characteristic	FM in patients with hematologic malignancy after HSCT (n = 9 patients)	FM in hematologic malignancy patients and no HSCT (n = 9 patients)
Mean age at diagnosis ± SD, y	48.3 ± 16.3	53.3 ± 4.6
Sex (male:female), n (%)	7:2 (78:22)	7:2 (78:22)
Race, n (%)		
White	3/9 (33)	6/9 (67)
African American	1/9 (11)	0/9 (0)
Asian	4/9 (44)	0/9 (0)
Hispanic	1/9 (11)	2/9 (22)
N/A	0/9 (0)	1/9 (11)
Type of lesions, n (%)*		
Papules	9/9 (100)	6/9 (67)
Plaques	0/9 (0)	3/9 (33)
Macules	1/9 (11)	1/9 (11)
Patches	1/9 (11)	5/9 (56)
Nodules/tumors	0/9 (0)	0/9 (0)
Folliuclar prominence, n (%)	4/9 (44)	1/9 (11)
Alopecia, n (%)	0/9 (0)	0/9 (0)
Distribution, n (%)*		
Head and neck	8/9 (89)	6/9 (67)
Trunk	6/9 (67)	5/9 (56)
Upper extremities	5/9 (56)	2/9 (22)
Lower extremities	3/9 (33)	3/9 (33)
Unilesional, n (%)	0/9 (0)	1/9 (11)
Pruritus, n (%)	5/9 (56)	6/9 (67)

CTCL, Cutaneous T-cell lymphoma; *FM*, follicular mucinosis; *HSCT*, hematopoietic stem cell transplantation; *N/A*, not available; SD, standard deviation.
*A patient can present with more than one lesion type/body area.

Table V. Histologic features of FM in patients with non-CTCL hematologic malignancy after HSCT and with no HSCT

Histopathologic feature	FM in patients with hematologic malignancy after HSCT, n (%) (n = 7 biopsy specimens)	FM in hematologic malignancy patients and no HSCT, n (%) (n = 9 biopsy specimens)
Follicular mucin		
Grade 1	1/7 (14)	1/9 (11)
Grade 2	2/7 (29)	5/9 (56)
Grade 3	4/7 (57)	1/9 (11)
Grade 4	0/7 (0)	2/9 (22)
Dermal mucin	1/7 (14)	0/9 (0)
Lymphoid infiltrate		
Perifollicular infiltrate	7/7 (100)	8/9 (89)
Epidermal exocytosis	0/7 (0)	2/9 (22)
Band-like infiltrate	2/7 (29)	2/9 (22)
Lymphoid cytologic atypia	6/7 (86)	5/9 (56)
Eosinophils		
None	1/7 (14)	1/9 (11)
Some	2/7 (29)	7/9 (77)
Abundant	4/7 (57)	1/9 (11)

CTCL, Cutaneous T-cell lymphoma; *FM*, follicular mucinosis; *HSCT*, hematopoietic stem cell transplantation.

unknown. Follicular keratinocytes have been postulated to be the source of mucin, and an etiologic role has been proposed for cell-mediated immune mechanisms and possible stimulation by cytokines released from perifollicular T lymphocytes.[9] This might be supported by a possible association in our study between FM and alteration of cell-mediated immune mechanisms in patients after HSCT or underlying hematologic malignancy.

Recognition of the possible occurrence of non-CTCL FM in patients with hematologic malignancies and after HSCT is important to spare these patients from unnecessary diagnostic and therapeutic strategies. A history of lymphoma and other hematologic disorders is occasionally reported in patients with MF. In a recent study, 6 of 203 patients with folliculotropic MF had a history of hematologic malignancies,[25] and in our study, 3 of the 44 patients with MF-associated FM had a history of hematologic neoplasms. Our findings suggest that certain clinical characteristics and histologic features may support the diagnosis of non-CTCL FM in patients with hematologic malignancies.

FM is a common histologic finding in folliculotropic MF, and it has been reported in 78% of the cases included in a recent study.[25] FM can also be found in biopsy specimens of cutaneous lymphomas other than MF (either CTCLs or cutaneous B-cell lymphomas).[26,27] The finding of FM in primary cutaneous CD30$^+$ LPD is unusual; 6 cases that were initially misdiagnosed as folliculotropic MF have

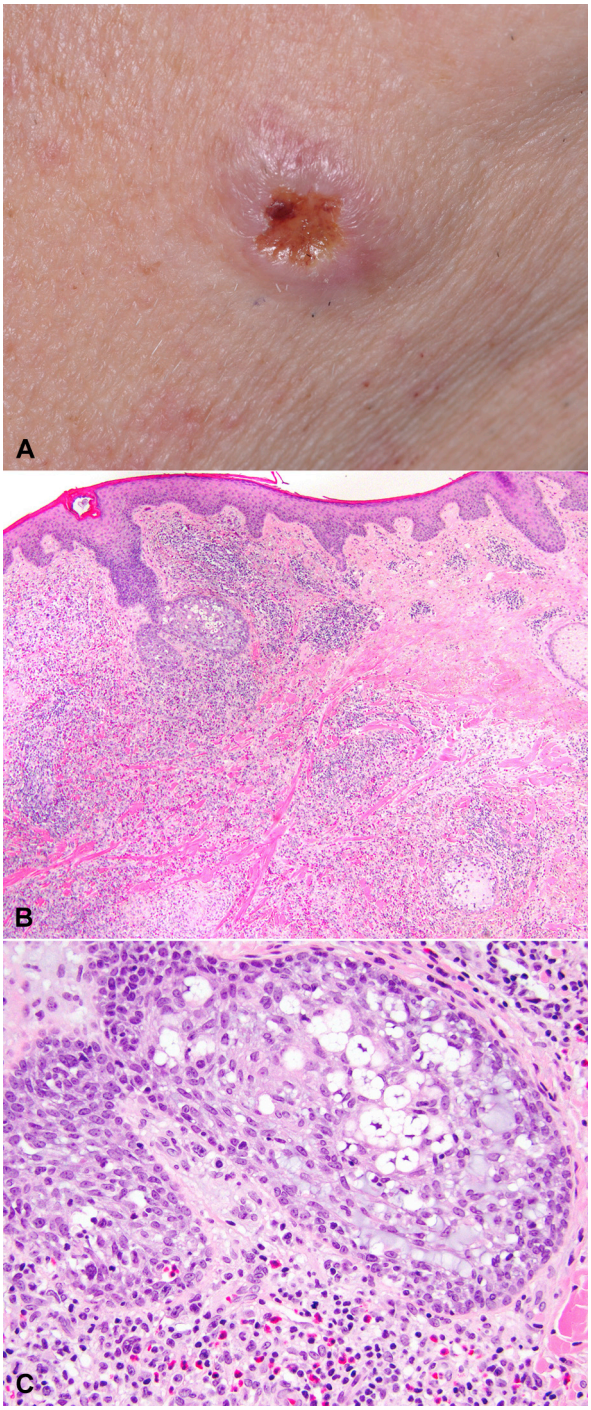

Fig 2. Primary cutaneous CD30$^+$ lymphoproliferative disorder with follicular mucinosis in a 71-year-old patient. **A,** Clinical features. Erythematous ulcerated papule on the neck. **B** and **C**, Histopathology. Dense dermal and subcutaneous atypical lymphoid infiltrate with eosinophils and follicular mucin. (**B** and **C**, Hematoxylin-eosin stain; original magnifications: **B,** ×10; **C,** ×40.)

been reported in the literature so far.[28] FM has also been reported in the setting of cutaneous lesions of adult T-cell leukemia lymphoma.[29] In our study, we report 4 additional cases of $CD30^+$ LPD with FM as well as $CD4^+$ small and medium CTCL and cutaneous peripheral T-cell lymphoma, unspecified, suggesting that the presence of FM in CTCL types other than MF may not be a rare condition, as was previously thought.

Limitations of our study include its retrospective design and its being performed in a single cancer center.

In conclusion, FM can be seen in association with hematologic malignancies and HSCT, and the clinical presentation and histologic features in such cases may help to distinguish it from CTCL-associated FM.

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