The Spectrum of Histopathologic and Immunohistochemical Findings in Folliculotropic Mycosis Fungoides

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Background: Since the original designation of folliculotropic mycosis fungoides (FMF) as a distinct entity, there has been an increasing appreciation of the broad clinical and histopathologic spectrum with which this disease can present. However, there have been few large histologic studies characterizing the various histopathologic patterns.

Objective: In this study, we attempt to describe the histopathologic and immunohistochemical features of 47 biopsy specimens from 34 patients with FMF.

Methods: We searched our lymphoma database for patients with FMF in which detailed histopathologic information and slides as well as clinical information was available for review. Additionally, immunohistochemical studies for CD4, CD8, and CD1a were performed in all cases in which the block was available.

Results: In addition to the prototypical pattern of a folliculotropic lypmphoid infiltrate with or without mucinosis, the histologic features of follicular mycosis fungoides may include a granulomatous reaction, cystic and comedonal changes, an eosinophilic folliculitis pattern and basaloid folliculolymphoid hyperplasia as well as pustular changes, interface dermatitis and an interstitial dermatitislike pattern. Unlike conventional mycosis fungoides, eosinophils and plasma cells are conspicuous within the accompanying reactive infiltrate. We have also noted an exceedingly high number of Langerhans cells within the follicular epithelium. The CD4:CD8 ratio frequently is 10:1 or greater and the follicles show abundant CD1a positive cells.

Conclusions: FMF may present with a broad spectrum of histopathologic changes including interstitial, granulomatous, fibrotic and acneiform reactions that may lack the typical histologic attributes of a cutaneous T-cell lymphoma. Recognition of these myriad of histologic presentations can be of great diagnostic utility.

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Conflicts of interest: none.

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The clinical recognition of a folliculotropic pattern in mycosis fungoides (MF) has been recognized as far back as the early 1960s.[22] However, the use of the term follicular mycosis fungoides was originally used in 1985 by Kim.[13] In the new World Health Organization-European Organization on Research and Treatment of Cancer (WHO-EORTC) classification scheme, folliculotropic mycosis fungoides (FMF) is recognized as a distinct entity.[30] Some studies suggest a more aggressive course and poorer prognosis for this variant of MF.[29] Additionally, these patients respond poorly to many first tier treatments used in conventional MF such as methclorethamine and psoralen with ultraviolet A. Hence, recognition of this entity both clinically and histologically is significant.

FMF can present with a wide variety of clinical presentations including acneiform lesions, comedones, cysts, alopecia, plaques with follicular papules, pseudotumors, and others.[12,15,20,24–26,28] Therefore, it is not surprising that FMF may also present with a variety of histologic patterns. However, there have been only few small series and case reports detailing the histologic features of this patient group.[2,3,5,11,23] Additionally, these studies have mostly focused on follicular mucinosis and prototypical cases. In following over 34 patients with FMF in our multidisciplinary cutaneous lymphoma clinic, we have come to recognize a number of distinct histologic patterns in this group of patients which have been less discussed in the literature. In this study, we characterize these various histologic patterns. We also studied a number of other parameters such as presence of mucin, epidermotropism, eosinophils as well as CD4, CD8, and CD1a expression and discuss our findings.

MATERIALS AND METHODS

We reviewed 53 biopsy specimens from 34 patients followed in our multidisciplinary cutaneous lymphoma clinic with the diagnosis of FMF. The defining criteria for diagnosis as FMF was presence of progressive clinical

lesions with follicular prominence and a dominant histologic pattern of folliculotropism. The hematoxylin and eosin-stained sections were studied and the histopathologic findings were recorded. Additionally, data was recorded regarding, presence or absence of follicular mucinosis, presence or absence of conventional epidermotropism outside of the follicles and number of eosinophils were noted on a semiquantitative scale either as minimal meaning 5 or less eosinophils per histologic section of a standard 4-mm punch biopsy, moderate meaning 5 to 20, and extensive referring to greater than 20 cells per histologic section of a standard 4-mm punch biopsy. We also noted the location of folliculotropism within the follicle such as infundibular versus isthmic versus bulbar. The data was evaluated by 2 dermatopathologists experienced in evaluating cutaneous lymphomas using a semiquantitative scale.

In 28 cases, immunohistochemistry was performed using monoclonal antibodies for CD4 (1:20; Dako, Carpinteria, CA) and CD8 (1:40; Dako, Carpinteria, CA). Whereas in 23 of these cases immunohistochemistry for CD1a (1:20; Dako, Carpinteria, CA) was also available. The immunohistochemistry was performed on paraffin-embedded material using the horse-radish-peroxidase method. A standard heat-induced epitope retrieval method was used with 0.1 M citrate as buffer (pH 6.0). The CD4:CD8 ratio was recorded in all cases. Additionally, the density of CD1a within the follicular epithelium relative to the adjacent epidermis was also studied in all cases. A Colloidal Iron stain was also performed in 40 cases and the presence or absence of mucin was noted.

Using fresh frozen tissue the polymerase chain reaction (PCR) technique was used to evaluate clonality of the T-cell receptor (TCR) gamma gene in 18 cases. The presence or absence of clonality was also noted.

RESULTS

After reviewing all 53 specimens from all 34 patients, we identified 5 histologic patterns that we believe to be distinctive patterns, highly characteristic of FMF. Additionally, several histopathologic patterns were identified that seemed to be not infrequent in biopsy specimens from patients with FMF but were of a nonspecific nature. Hence, recurrent histopathologic findings were divided into those which in the proper clinical scenario could be highly suggestive of FMF and those which can be seen in FMF but are nonspecific.

The 5 patterns felt to be highly characteristic of FMF included, basaloid folliculolymphoid hyperplasia with folliculotropism, granulomatous dermatitis closely associated with a destructive process of the follicular unit with evidence of folliculotropism, eosinophilic folliculitislike presentation with folliculotropism, formation of dilated follicular cysts with folliculotropism, and lastly the prototypical follicular mycosis fungoides with intact follicles with folliculotropism with or without follicular mucinosis. Importantly, it should be noted that many of the patients had multiple biopsies showing different patterns and different patterns within a single biopsy specimen.

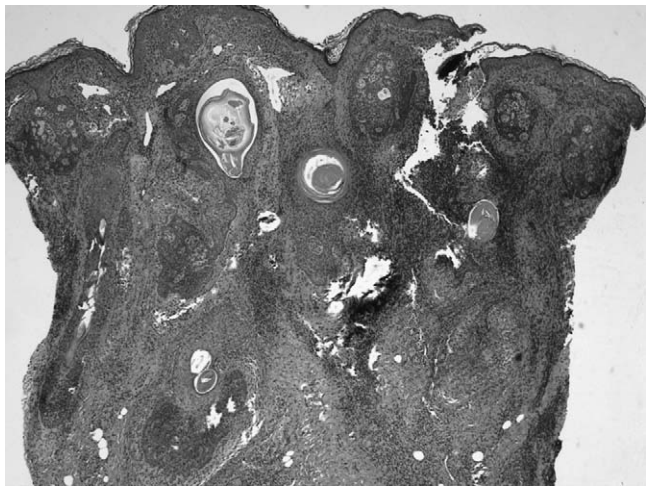

FIGURE 1. Low-power view of basaloid folliculolymphoid hyperplasia. Extensive budding of basaloid islands are seen from the follicular epithelium. There is peripheral palisading of cells and mucinous deposits similar to that seen in basal cell carcinoma. Retraction artifact is minimal.

In this review, we identified basaloid folliculolymphoid hyperplasia in a total of 6 of 34 patients or 18%. In this process, basaloid proliferations of epithelial cells extending from intact hair follicles or complete basaloid transformation of hair follicles is seen (Fig. 1). Mucinous deposits are common. A dermal papillae maybe seen. Retraction artifact is minimal if present at all. There is prominent folliculotropism of atypical lymphocytes into the basaloid islands (Fig. 2).

We identified 8 cases from 8 patients among the 34% total or 24% of cases where granulomatous inflammation with eosinophils and small to medium sized lymphocytes with nuclear irregularity were the predominant findings

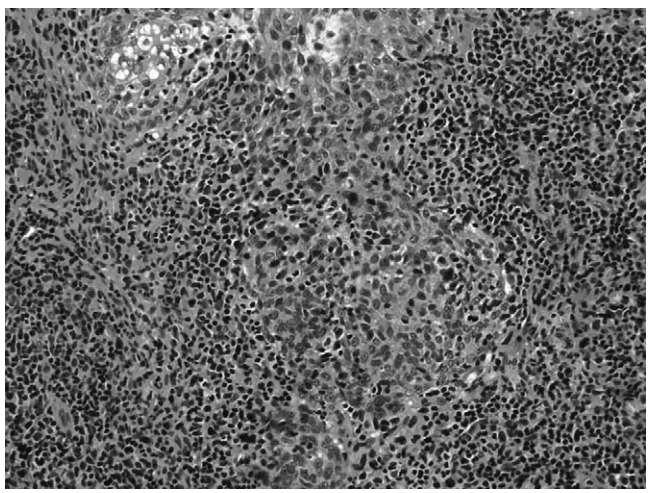

FIGURE 2. High-power view shows folliculotropic lymphocytes lining up along the basilar area of the basaloid islands and infiltrating into the center of the basaloid islands.

(Figs. 3A, B). However, either within a different section of the same biopsy or in a separate biopsy, definitive changes of follicular mycosis fungoides with intact follicles with prominent folliculotropism were identified (Fig. 3C). In some cases, the granulomatous changes were seen directly adjacent to a follicle distended with mucin and lymphocytes or an infundibular cyst with folliculotropism.

We identified 7 patients in our series of 34% or 21% with an eosinophilic folliculitislike histology (Figs. 4A, B). All patients had extensive number of eosinophils (> 20 per section) primarily focused around and within the hair follicles with folliculotropic lymphocytes. Though the lymphocytes were overshadowed by the prominent eosinophils and the specimens sometimes lacked sufficient histologic evidence to reach a definitive diagnosis. Hence, awareness of this pitfall becomes important. As part of our inclusion criteria, all patients had either within the same specimen or a different specimen changes of the prototypical FMF and clinically compatible lesions.

Follicular cystic change with central keratinous debris and folliculotropic lymphocytes in the surrounding follicular epithelium was identified in 5 patients or 15%. In most cases multiple large dilated cystic structures lined by atrophic infundibular epithelium with a granular layer could be seen. An accumulation of compact kerarin material without significant mucinous deposits was noted within the lesions. In general cases that display significant mucinous degeneration resulted in destruction of the follicular unit without significant cyst formation. However, in some cases large intrafollicular cystic pools of mucinous material were observed. In all cases there were lymphocytes infiltrating the follicular epithelium (Fig. 5), yet in some cases the lymphoid infiltrate was inconspicuous without marked atypia. Clinically, these cases typically correlated to either large cystic acneiform lesions, comedones, or smaller keratosis pilaris like follicular-based papules. Eosinophils could be observed in 3 of 5 patients. In 4 of 5 cases, the lymphocytes were small to medium sized, whereas in 1 case medium to large lymphocytes were seen permeating the follicular epithelium.

The fifth pattern observed is the most recognized prototypical pattern with intact follicles and folliculotropism with or without follicular mucinosis (Fig. 6). Among 17 diagnostic specimens from 15 patients or 44% of patients, this was the exclusive pattern. However, in the majority of cases including those with the other 4 patterns discussed, this pattern could be at least focally identified.

We have also identified 2 patients with syringolymphoid hyperplasia with syringotropism. Both of these patients showed an element of folliculotropism, however, syringoid hyperplasia and syringotropism was the

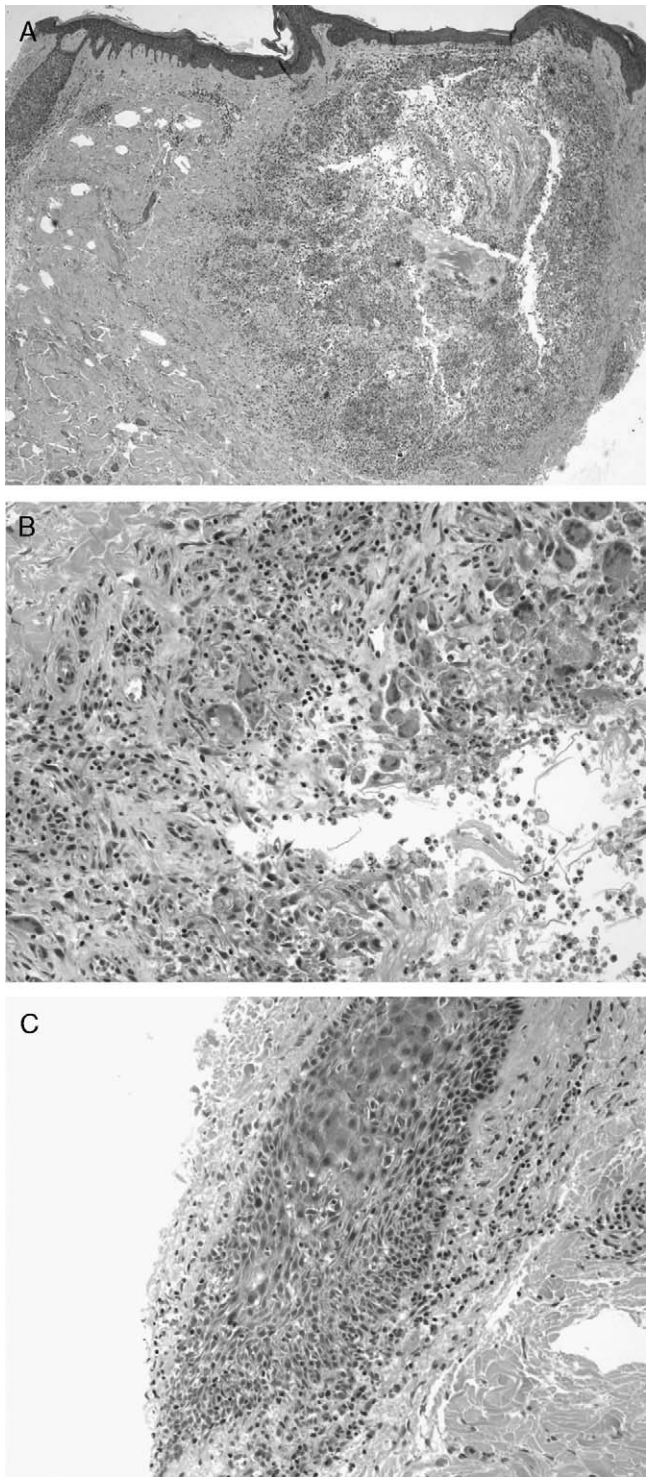

FIGURE 3. A, A low-power view showing focal granulomatous changes with foreign body giant cells and lymphocytes on one end. The opposite side of the biopsy shows a follicular structure which is infiltrated by lymphocytes with nuclear atypia. B, A higher power view of the granulomatous area shows that in addition to the granulomatous changes there are numerous hyperchromatic lymphocytes. There is residual keratin debris and a naked hair shaft in this case. C, Higher power of the follicle from the opposite end of the biopsy shows some follicultropic lymphocytes crowding around the follicular epithelium.

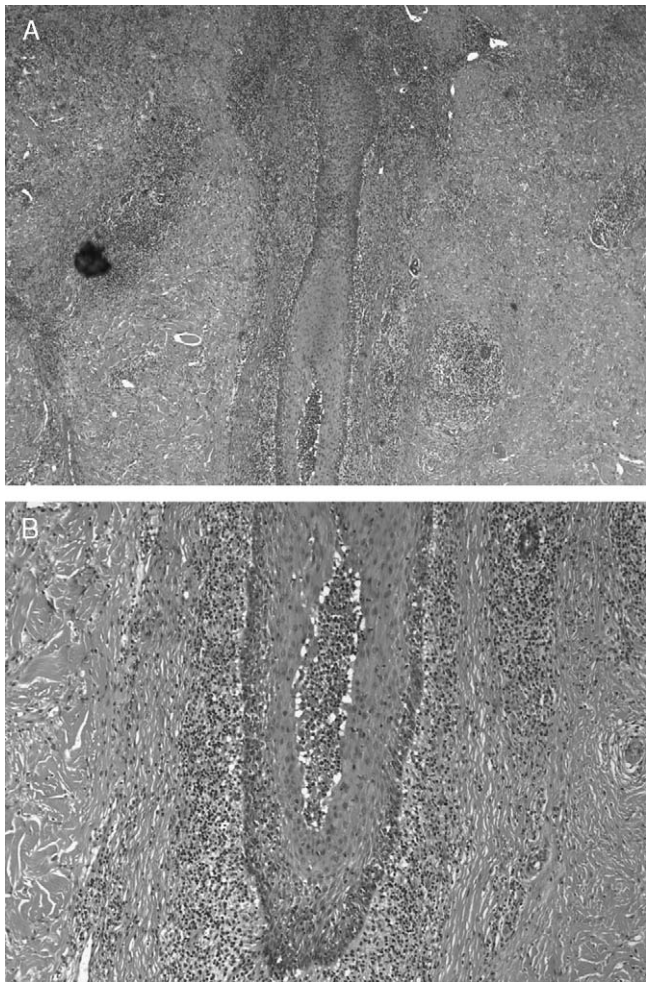

FIGURE 4. A, A low-power view shows a dense perifollicular and perieccrine lymphoid infiltrate with extensive number of eosinophils. At multiple sites surrounding the follicle, folliculotropic lymphocytes are seen entering the follicular epithelium. B, The center of the follicle and the follicular epithelium is loaded with eosinophils. Numerous lymphocytes are also seen.

prominent finding and in 1 case the lesions were acrally distributed. Hence, we felt these cases would be better classified as syringotropic MF and did not include them in this study. However, there are clearly overlapping features.

A variety of nonspecific changes were also identified from patients with FMF in lesions which were clinically suspected of being lymphoma. These included neutrophilic pustular lesions within or adjacent to the follicular epithelium. This was observed in 5 biopsies from 4 patients. Coexisting syringotropism was noted in 5 specimens from 3 patients none of which showed significant syringoid hyperplerasia. Prominent interface dermatitis with apoptotic keratinocytes and basal vacuolopathy either within the follicular epithelium or epidermis was noted in 7 specimens from 4 patients. Large cell transformation was seen in 3 biopsies from 3 patients. In all cases, there was a dense infiltrate of large atypical cells with a Grenz zone and prominent folliculotropism was not identified.

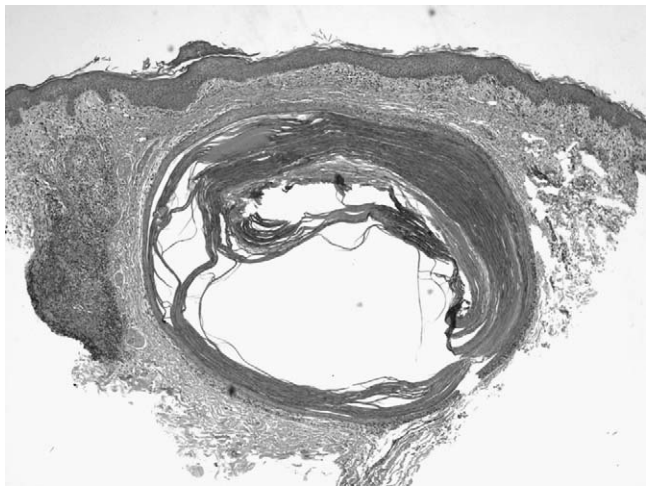

FIGURE 5. At low power an epidermoid cyst with atrophied follicular epithelium is seen. Few folliculotropic lymphocytes can be spotted in the follicular epithelium. On one lateral side, a follicle with some changes of basaloid folliculolymphoid hyperplasia is seen. Numerous lymphocytes are seen infiltrating the follicular and basaloid areas.

Prominent epidermotropism of nonfollicular epithelium was seen in lesions from 5 of the 34 patients, approximately 15%, whereas focal epidermotropism was seen in 9 cases. We also noted in 4 cases of patients who had well-established FMF, 4 biopsies from nonfollicular sites showed a chronic lymphocytic infiltrate with prominent papillary dermal fibroplasia and lymphocytes in lacunae with small to medium size and nuclear irregularity without epidermotropism. This maybe a result of a lesser tendency of lymphocytes in FMF to enter the epidermis. Many biopsies also reveal histologic features associated with pruritus as noted by the presence of superficial excoriations, extravasation of erythrocytes and lamellar fibroplasias, acanthosis, spongiosis, and overall superimposed features of lichen simplex chronicus.

We evaluated the number of eosinophils as few to none (< 5 per section) versus moderate numbers (5 to 20 per section), versus extensive (> 20 eosinophils). Cases with granulomatous or pustular inflammation were not included. In 22 cases there were few to none, 10 cases showed moderate numbers and 8 cases showed extensive number of eosinophils with an eosinophilic folliculitislike presentation. In general in almost all cases where the infundibulum and isthmic portion of the follicle could be evaluated, the folliculotropism involved both areas. There was typically minimal involvement of the bulbar area. The results of staining with colloidal iron showed prominent intrafollicular mucin deposits in 18 of 40 cases or 45% of cases in which a follicle was present in the sections.

Clinical Summary

Among the 34 patients, the average age was 57 and the male to female ratio was 3.86:1. Cases with any of the 4 nonprototypical histologic patterns such as basaloid

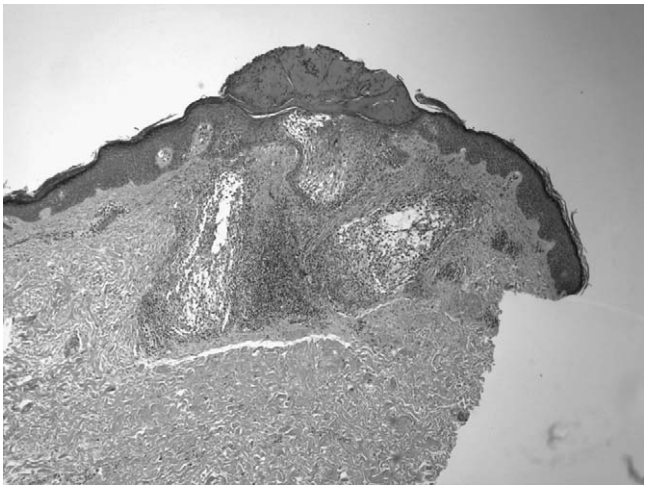

FIGURE 6. Classic type follicular mycosis fungoides with follicular mucinosis.

folliculolymphoid hyperplasia with folliculotropism, eosinophilic folliculitislike, cystic, or granulomatous were especially common in the head and neck areas. Specifically among cases where the clinical distribution was available, 4 of 6, 5 of 7, 4 of 4 and 7 of 8 of the cases from the respective histologic patterns involved the head and neck area. This gives a total of 20 of 25 cases or 80%. In the classic type, 7/14 or 50% of cases had head and neck lesions. Lesions of basaloid folliculolymphoid hyperplasia were most frequently periorbital eyebrow and forehead plaques with alopecia, 4 of 6 cases. Eosinophilic folliculitislike lesions were also frequently on the face and typically were large succulent nodules accompanied by pustular lesions. Cystic lesions were also clinically cystic or comedonal. Although granulomatous lesions were typically follicular-based papules, plaques or cystic lesions.

Among the 34 cases, good clinical descriptions were available in 27 cases. In only 4 cases were lesions of conventional MF such as truncal patches and plaques identified. However, even in these cases the predominant pattern was that of papules and plaques with follicular prominence with or without alopecia. These findings were present at the onset and throughout the clinical course for all 27 patients. This was a direct result of the inclusion criteria for the study.

In general the number of biopsies and years to diagnosis were similar among the various histologic patterns. The exception to this rule was in cases with a granulomatous pattern. In general patients with this histologic pattern required the most biopsies to be diagnosed. The number ranged from 2 to 5 with an average of 3.25 biopsies among the 8 patients with this pattern. The distribution of lesions, number of biopsies to diagnosis, and years to diagnosis are summarized in Table 1.

Immunohistochemistry and Molecular Studies

In 28 cases, the CD4:CD8 ratio of the intrafollicular lymphocytes was evaluated (Table 2). In 23 cases, the ratio was greater than or equal to 10:1. In the remaining 5 cases, the ratio varied from 6:1 to 8:1. The CD4-positive lymphocytes were seen primarily in the infundibular and isthmic epithelium (Figs. 7A, B). In 23 cases the density of CD1a-positive cells was examined. In 19 of the 23 cases a complete epidermis as well as intact follicles were evaluable and the density of CD1a-positive cells was evaluated in the follicular epithelium relative to the nonfollicular epithelium. The Langerhans cells were seen predominantly in the infundibular and isthmic portion of the follicle with lesser amounts in the bulbar area of the follicle. In 16 cases, the ratio was greater than 10:1, including 3 cases which showed prominent conventional epidermotropism (Fig. 8).

In the remaining 3 cases in which the ratio was less than 10:1, all cases consisted of cystic lesions with folliculotropism in the atrophic follicular epithelium. In these 3 cases, only very few CD1a-positive cells were identified in the follicular epithelium and the density was less than that seen in the overlying epidermis. None of these 3 cases had conventional epidermotropism, however, all cases did have folliculotropism of other noncystic follicles either within the same section or another biopsy. The diagnosis of FMF in these 3 cases was clear, as all patients had progressive plaques with cystic and acneiform changes, at least 1 biopsy showing clear changes of conventional folliculotropism with or without mucinosis and all 3 patients had a positive clone detected by PCR for the TCR gamma gene.

Additionally, immunohistochemical staining for CD1a was performed in 5 cases of conventional MF in which a hair follicle was evident. Only rare Langerhans

TABLE 1. Distribution and Time to Diagnosis for Histologic Subtypes

Histologic Subtype	Head and Neck Distribution*	Average No. Biopsies	Average Years to Diagnosis
Basaloid folliculolymphoid hyperplasia	4/6	2	2 y
Eosinophilic folliculitis	5/7	2.86	Data only available for 2 cases which were 8 mo and 8 y
Cystic	4/4	2.6	3.5 y
Granulomatous	7/8	3.5	3.7 y
Prototypical cases	7/14	2.3	3.5 y

*The denominator in all cases is based on the number of cases for which the relevant information was available.

TABLE 2. Summary Data for All Patients

Patient No.	Age	Sex	Histologic Patterns	Intrafollicular CD4:CD8 Ratio*	CD1a Follicular to Nonfollicular Ratio*	Molecular Results	Eosinophils
1	59	M	GR, EF	NA	> 10:1	Positive	Extensive
2	57	F	GR, EF	> 10:1	NA	NA	Extensive
3	55	M	GR, EF	> 10:1	> 10:1	Positive	Extensive
4	76	M	GR	> 10:1	> 10:1	Positive	Few
5	71	M	GR, BFH	8:1	> 10:1	NA	NA
6	45	M	GR, C	> 10:1	Rare follicular cystic CD1a cells	Positive	Moderate
7	28	M	GR, BFH	7:1	> 10:1	Positive	Few
8	57	F	GR	6:1	NA	NA	NA
9	61	M	C	> 10:1	Rare follicular cystic CD1a cells	Positive	Moderate
10	65	M	C, BFH	> 10:1	> 10:1	Positive	Few
11	32	M	C	> 10:1	> 10:1	Positive	Few
12	75	M	C	> 10:1	Rare follicular cystic CD1a cells	Positive	Moderate
13	53	M	EF	NA	NA	NA	Extensive
14	73	M	EF	> 10:1	NA	NA	Extensive
15	53	M	EF	> 10:1	> 10:1	Positive	Extensive
16	60	M	EF	> 10:1	> 10:1	NA	Extensive
17	64	M	BFH	> 10:1	> 10:1	Positive	Moderate
18	39	M	BFH	> 10:1	NA	Positive	Few
19	50	M	BFH	6:1	> 10:1	Positive	Moderate
20	48	F	PR	> 10:1	NA	NA	Moderate
21	54	M	PR	6:1	> 10:1	NA	Few
22	75	M	PR	> 10:1	> 10:1	NA	Few
23	68	M	PR	> 10:1	NA	Negative	Few
24	53	M	PR	NA	NA	NA	Few
25	48	F	PR	NA	NA	Positive	Few
26	30	M	PR	> 10:1	> 10:1	NA	Moderate
27	61	F	PR	> 10:1	NA	NA	Moderate
28	64	M	PR	> 10:1	NA	NA	Few
29	59	M	PR	NA	NA	Positive	Few
30	70	M	PR	NA	NA	Negative	Few
31	69	M	PR	> 10:1	NA	NA	Moderate
32	55	F	PR	> 10:1	> 10:1	NA	Moderate
33	58	F	PR	> 10:1	NA	Positive	Few
34	58	M	PR	> 10:1	> 10:1	NA	Few

*Ratios in granulomatous cases refer to other areas with intact follicles.

BFH indicates basaloid folliculo-lymphoid hyperplasia; C, cystic; EF, eosinophilic folliculitislike; GR, granulomatous; NA, not available; PR, prototypical without any of other 4 patterns.

cells were identified in the follicular epithelium of conventional MF.

Overall, in 16 of 18 patients a positive clone was detected using PCR for the TCR gamma gene on fresh frozen tissue on the first attempt. In 1 of the 2 patients with a negative result, 3 attempts were made to detect clonality all of which were negative. However, this patient later developed large cell transformation with tumor lesions making the diagnosis unequivocal.

DISCUSSION

The range of clinical-pathologic presentation in FMF is extensive and we are only recently appreciating the broad spectrum of changes with which this disease entity can present. In fact many of the patients in our series, may have previously been erroneously diagnosed as having scarring alopecia, severe nodulocystic acne, eosinophilic folliculitis, or granulomatous dermatitis or granulomatous MF. However, on the basis of the clinical correlation and follow up, extensive sampling, immunohistochemical analysis, and clonality studies, we determined the final diagnosis of FMF in all cases included in this study.

Epithelial hyperplasia can occur over several variants of cutaneous lymphomas.[18] Basaloid induction of epithelial cells is a well-recognized phenomenon of the epidermis overlying dermatofibromas. However, we believe that basaloid induction of the follicular epithelium in conjunction with an atypical lymphoid infiltrate is unique to FMF. The resemblance of hair follicles to basal cell carcinoma was originally noted by Pinkus[21] in his initial description of follicular mucinosis. Basaloid folliculolymphoid hyperplasia is a process originally described by Kossard et al[16] in a patient with MF. We have subsequently expanded on this concept in a recent paper demonstrating this pattern in 3 patients with FMF.[8]

In this study, we identified this pattern in 6 of 34 of our patients. All cases exhibited folliculotropism of lymphocytes into the basaloid areas. Importantly, these

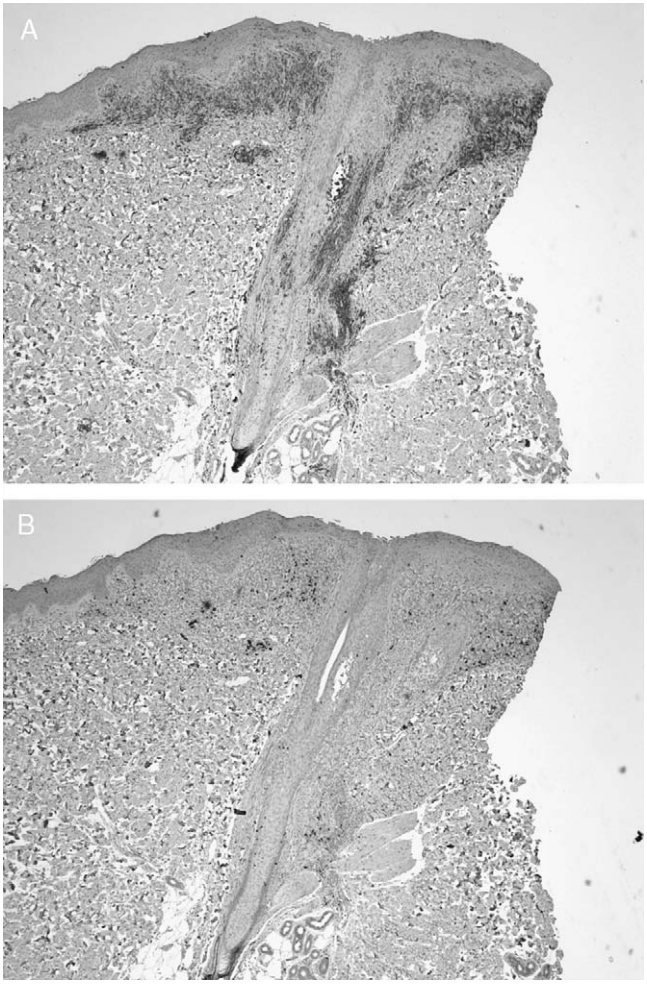

FIGURE 7. A, Immunohistochemical labeling with CD4. B, Immunohistochemical labeling with CD8.

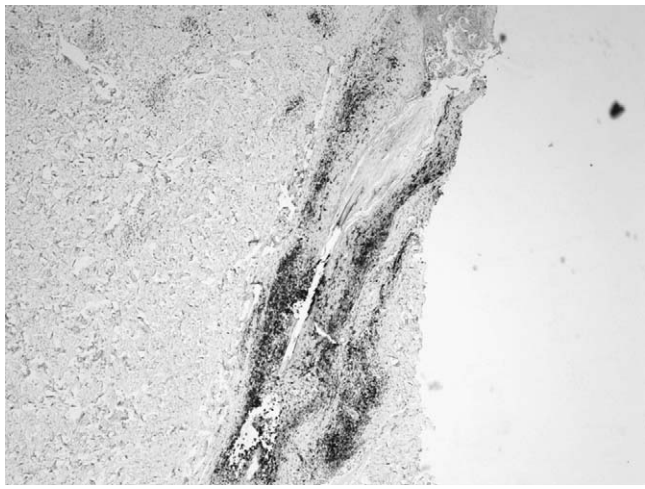

FIGURE 8. Immunohistochemical labeling with CD1a shows dense infiltration of the follicular epithelium with Langerhans cells.

changes can exist on a wide spectrum from areas with focal budding basaloid islands from hair follicles to widespread basaloid proliferations involving the entire dermis mimicking a basal cell carcinoma or trichoepithelioma. We are unaware of any other lymphoma or inflammatory disorder which can present with this pattern. Therefore, recognition of this pattern can be very helpful diagnostically.

Folliculotropic lymphocytes in epidermoid cysts is an important pattern which can be easily overlooked for a number of reasons. None of the cases had prominent mucin. Other case reports of this pattern also mention lack of mucin.[10,27] Also, epidermotropism of the surrounding nonfollicular epithelium was absent in all cases. This is also not surprising as the largest series on FMF to date, which includes 50 patients, reported epidermotropism of the nonfollicular epithelium in only 5 cases or 10% of the total.[29] These lesions are the histologic counterpart to the patients which clinically present with acneiform, cystic, and comedonal changes as well as keratosis pilaris like areas.[7,27] Hence, it is important to include FMF in the differential diagnosis for such lesions particularly elderly males with large plaque lesions with acneiform pattern in the head and neck distribution. A positive clone using PCR for the TCR gamma gene was obtained in all these cases. A unique and fascinating finding in our study is the lack of prominent Langerhans cells in the follicular epithelium in this specific subset, although folliculotropic lymphocytes were still present. Anecdotally, it is our impression that the larger or more cystic the follicular infundibulum becomes the more the Langerhans cells are depleted. However, further studies are needed to verify this and elucidate the mechanism.

Granulomatous inflammation as a result of a ruptured follicle is a well-recognized phenomenon. FMF often results in destruction of the follicular epithelium. Hence, it should be of no surprise that a ruptured follicle secondary to mucinous infiltration, cystic changes, or infiltration from atypical lymphocytes could result in a suppurative or granulomatous pattern. This superimposed pathology may compromise the final diagnosis. Interesting among the 5 histologic patterns, this one required on average the greatest number of biopsies to make the diagnosis. Additionally, often the follicular epithelium is not identified and only mixed interstitial inflammatory changes in the adjacent reticular dermis with numerous plasma cells, eosinophils, and histiocytes maybe seen, obfuscating the original neoplastic T cells in the specimen.

In all 8 of our patients who presented with a granulomatous pattern we observed clinical features suggestive of FMF. This includes areas of alopecia, follicular papules, and cystic or comedonal changes. Additionally, in all 8 cases either within the same specimen in a separate section or within a separate biopsy we were able to see areas with characteristic changes of FMF. Some follicles were distended by mucin whereas

others showed cystic dilation with infiltration by atypical lymphocytes.

Although these cases maybe considered as granulomatous MF by others, when taking into account the clinical presentation and the presence of clear folliculotropism in other sections from the same patient, we believe these cases are best classified as FMF. Hence, it is our experience and opinion that most cases referred to as granulomatous MF, excluding granulomatous slack skin, likely represent FMF with follicular rupture or destruction. Likewise, many others have identified folliculotropism and granulomatous changes simultaneously in patients with MF.[4,11] Again, we emphasize the fact that although we include this pattern as a specific finding for FMF, this has to be taken in the proper context and the diagnosis should be approached as in other cases of MF incorporating clinical, histologic, and molecular data.

In our series, 7 patients presented with lesions histologically showing changes of eosinophilic folliculitis. However, besides the dense eosinophilic infiltrates, folliculotropic lymphocytes were also noted. Although we realize that eosinophilic folliculitis is a pattern that can be seen in a number of dermatoses, including the HIV-related condition, Ofuji disease, parasitic disease, arthropod bites, and others, we believe that it maybe the presenting feature of FMF as well. However, as MF can also result in profound immunosuppresion, we recognize that in some occasions the eosinophilic folliculitis noted in cutaneous T-cell lymphoma may be a reaction pattern associated with immune suppression. In cases of eosinophilic folliculitis, sections should be examined for folliculotropism of lymphocytes as well. Clonality studies were available in 2 of 6 cases and were positive in both cases. Hence, although we realize that eosinophilic folliculitis is a nonspecific finding,[31] we believe in the right context such as HIV-negative, non-asian adults with patches and plaques with follicular prominence in the head and neck area it is suggestive of FMF and a thorough search for folliculotropic lymphocytes should be performed. Others have previously noted a relationship between eosinophilic folliculitis and follicular mucinosis.[14,17]

In 15 of our 34 patients, the histologic findings were exclusively those of prototypical changes with intact follicles with or without mucin with prominent folliculotropism. Also, epidermotropism of nonfollicular epithelium was only observed in 5 of 34 cases and mucin was prominent in only 18 of 40 biopsy specimens. This emphasizes the importance of recognizing the other patterns which appeared in 19 of our patients. Neutrophilic pustulation and interface dermatitis are frequent nonspecific changes which may occur in FMF. Although these findings cannot be used to establish a diagnosis, their presence should not exclude a diagnosis of FMF if there is adequate clinical suspicion.

We also observed in some biopsies which lacked follicular units that lesions of FMF may reveal an atypical interstitial lymphoid infiltrate within the reticular dermis reminiscent of the so-called interstitial variant of MF. On the basis of our observation, we raise the possibility that some of the reported interstitial or granulomatous variants of MF are indeed patients with FMF biopsied in areas lacking follicular units due to sampling error or previous destruction of the follicles by the malignant process.

A number of studies have been performed to evaluate the ratio of intraepidermal CD4 to CD8T lymphocytes in MF versus inflammatory disorders. Although the average ratio in MF is typically 3 to 5, it is generally less in inflammatory disorders.[6,19] Significantly, we found in our cases that the intrafollicular ratio was 10:1 or greater in 23 of 28 cases (82%). We hypothesize 2 possible explanations for this. The first being that Langerhans cells frequently are CD4-positive and we found extensive number of Langerhans cells in the follicular epithelium in our cases which is likely skewing the ratio. Additionally, it is possible that cases of FMF maybe more difficult to diagnose and the diagnosis may have been reached at later stages as compared with other forms of MF.

Langerhans cells are usually found at the center point of a epidermotropic lymphocytes in Pautrier absess.[9] Studies have shown that increasing number of epidermotropic lymphocytes correspond to increasing number of epidermal Langerhans cells.[1] In our study, we found that the number of CD1a positive cells in the follicular epidermis was extensive and the ratio of follicular Langerhans cells relative to epidermal Langerhans cells was greater than 10:1 in 16 of 19 cases. The exception was 3 cases with cystic lesions. The reason for depletion of CD1a cells in cystic lesions is unknown and will require further study. It is likely that increased number of CD1a cells in the follicle seen in most cases of FMF may also be seen in inflammatory conditions focused around the follicles such as lichen planopilaris or discoid lupus. Further studies will be needed to evaluate this observation. However, we have never seen this pattern in conventional cases of MF and our 5 control cases of convention MF confirmed this with only rare Langerhans cells being found. In confirmed cases of MF, immunohistochemical staining for CD1a maybe useful in demonstrating a tendency for a folliculotropic pattern.

In summary, we have shown that FMF may present with a spectrum of histologic changes. In any case, a reliable diagnosis requires clinically compatible lesions and histology showing predominant pattern of folliculotropism. However, recognition of some of the other patterns including basaloid folliculolymphoid hyperplasia, cystic changes, eosinophilic folliculiculitis, and granulomatous changes may help early recognition of this condition. Further familiarity with other possible histologic changes such as neutrophilic pustulation, an interstitial dermatitis, and interface changes should also help in the diagnostic work-up of patients with FMF.

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