Folliculotropic Mycosis Fungoides

Single-Center Study and Systematic Review

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Objectives: To clarify clinicopathologic features and reconcile discrepancies in previous studies of folliculotropic mycosis fungoides (FMF).

Design: A single-center retrospective clinicopathologic study and a systematic review of FMF.

Setting: Tertiary referral center in the midwestern United States.

Patients: Patients with clinical and histopathologic evidence of FMF seen at the tertiary referral center during a 12 1/2-year period.

Main Outcome Measures: Clinicopathologic features of FMF.

Results: Fifty patients (32 male [64%] and 18 female [36%]) met study criteria for the clinicopathologic review. Pruritic patches, plaques, and folliculocentric lesions (milia, cysts, and alopecia) on the head, neck, and trunk were common clinical findings. The mean time to diagnosis of FMF was 5.0 years. Diagnostic latency did not affect risk of death. One-year and 5-year overall survival rates were 96% and 62%, respectively. Frequent microscopic features were follicular mucinosis (74%) and epidermotropism (54%). Systematic review of 186 additional patients confirmed male predominance (ratio of men to women, 3.2:1.0), prevalent pruritus (73%), frequent follicular mucinosis (69%) and epidermotropism (37%) microscopically, and common head, neck, and trunk involvement. Combined data demonstrated that 6% of patients with FMF had concurrent non–mycosis fungoides hematologic malignant neoplasms and that the 5-year overall survival rate was 62% to 64%.

Conclusion: Folliculotropic mycosis fungoides has distinct clinical and microscopic features and is associated with a poor 5-year overall survival rate.

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FMF between January 1, 1995, and July 31, 2007. We searched for the terms follicular, folliculotropic, pilotropic, adnexotropic, and syringotropic, as well as variations of them. We also searched the Mayo Clinic dermatopathology database for these terms. Our search was conducted in accord with Minnesota statute 144.293; we included only patients who had not denied access to their medical records for research purposes. Clinical inclusion criteria were the following: medical record with clinical descriptions from our institution; persistent cutaneous lesions compatible with FMF; and papules, patches, plaques, nodules, pustules, or erythroderma. Histopathologic inclusion criteria were cutaneous biopsy specimens available for review; histopathologic findings consistent with mycosis fungoides, atypical lymphoid infiltrate surrounding or involving perifollicular epithelium, CD4 predominance of lymphocytic infiltrate (when immunohistochemistry had been performed), epidermotropism (supportive criterion), and follicular mucinosis (supportive criterion). Two patients with typical clinical findings of FMF (alopecic plaques) were included, despite the absence of folliculotropism but the presence of atypical lymphocytes manifesting syringotropism microscopically in 1 patient and the absence of a hair follicle in biopsy specimens available but the presence of papillary dermal and epidermotropic atypical lymphocytes in the other patient.

All available histopathology slides for patients who received a clinical or histopathologic diagnosis of FMF (or a synonym) were reviewed by a board-certified dermatopathologist (R.H.W.) or by an experienced dermatopathology fellow (B.R.W.). Several slides were reviewed by both observers to ensure consistency. The following data were noted: character of inflammatory infiltrate, features of immunohistochemical staining when available, presence or absence of large-cell transformations or dermal tumors, and evidence of folliculotropism, syringotropism, epidermotropism, or follicular mucinosis. Histopathologic findings for multiple biopsy specimens were combined on a per-patient basis to facilitate analysis.

We reviewed the electronic medical record of each patient who had microscopically confirmed FMF. The recorded clinical features included the following when available: sex, age at symptom onset, physical findings, clinical course, time between symptom onset and diagnosis of mycosis fungoides, time between symptom onset and diagnosis of FMF, other clinical characteristics (such as associated symptoms, presence of draining material, and presence of hematologic or oncologic comorbidities), and results of relevant radiologic imaging and molecular-based studies (ie, results of flow cytometric immunotyping and T-cell receptor [TCR] gene rearrangement analysis of the involved skin or peripheral blood).

Standard descriptive statistics were used to summarize the data. For survival analysis, duration of follow-up was calculated from the date of the mycosis fungoides diagnosis to the date of the last follow-up or death. Overall survival was estimated using the Kaplan-Meier method. Adverse clinical outcomes were defined as the development of nodules, erythroderma, microscopically confirmed extracutaneous involvement, or death from disease. Time to the first adverse clinical outcome was calculated from the date of onset of skin lesions; for patients without an adverse clinical outcome, the interval was censored at the date of the last clinical follow-up. Separate univariate Cox proportional hazards regression models were fit to evaluate the association between patient characteristics and time to death or time to first adverse clinical outcome. The hazard ratio (HR) that was estimated from the Cox proportional hazards regression model and the corresponding 95% confidence interval (CI) were used to summarize the associations. All calculated P values were 2-sided, and \( P < .05 \) was considered statistically significant. Analyses were performed using commercially available statistical software (SAS, version 9.1; SAS Institute, Inc, Cary, North Carolina).

For our systematic review, the clinical, histopathologic, molecular, and prognostic data from our study were compared with those from previous retrospective clinical and histopathologic studies and case series of FMF, which we identified using PubMed searches and bibliographic cross-referencing. Search terms included folliculotropic mycosis fungoides, pilotropic mycosis fungoides, follicular mycosis fungoides, and adnexotropic mycosis fungoides. Studies describing 3 or more patients with FMF were included. Whenever possible, data were combined by weighted mean.

### RESULTS

Fifty patients met study inclusion criteria (Figure 1). Characteristics of 50 study patients (32 male and 18 female) are summarized in the first column of eTable 1 (http://www.archdermatol.com). The mean interval between onset of symptoms and diagnosis of mycosis fungoides was 3.9 years. The mean age at diagnosis of mycosis fungoides (57.7 years) was similar to the mean age at diagnosis of FMF (58.8 years). For 31 patients, folliculotropic lesions were recognized at or before the time of microscopic diagnosis of mycosis fungoides. The mean age at diagnosis of mycosis fungoides was significantly older for women than for men (63.1 years vs 54.6 years; \( P = .04 \), 2-sample t test). Five patients (4 male and 1 female) were younger than 40 years at the time of diagnosis of mycosis fungoides.

Of 41 patients whose medical record included staging data at the time of diagnosis, most patients (30 [73%]) had skin involvement only, without erythroderma. Four patients (10%) had generalized erythroderma. Six patients (15%) had clinical lymphadenopathy but negative microscopic findings from a lymph node biopsy, and only 1 patient (2%) had microscopically confirmed nodal involvement. One patient was found to have visceral involvement at the time of staging.

Clinical features at the time of initial presentation are listed in Table 1, and representative clinical images are shown in Figure 2. Of 47 patients whose symptoms were recorded, 44 (94%) had symptoms that were associated with their skin disease, including pruritus (35 patients [74%]) and pain (13 patients [28%]). Mucinorrhea (ie,
Table 1. Clinical Characteristics of Patients With Folliculotropic Mycosis Fungoides in the Present Study and in Previous Retrospective Studies and Case Series

<table>
<thead>
<tr>
<th>Variable</th>
<th>Present Study (n=50)</th>
<th>van Doorn et al.¹ 2002 (n=51)</th>
<th>Gerami et al.² 2008 (n=63)</th>
<th>Gerami and Guitart,³ 2007 (n=34)</th>
<th>Cerroni et al.⁴ 2002 (n=28)</th>
<th>Hodak et al.⁵ 1999 (n=9)</th>
<th>Vergier et al.⁶ 1996 (n=9)</th>
<th>Flaig et al.⁷ 2001 (n=9)</th>
<th>Pereyro et al.⁸ 1997 (n=3)</th>
<th>Combined Data, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomical Area</td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>29 (58)</td>
<td>45 (88)</td>
<td>37 (58)</td>
<td>20/25 (80) b</td>
<td>14 (50)</td>
<td>2 (22)</td>
<td>NA</td>
<td>NA</td>
<td>3 (100)</td>
<td>72</td>
</tr>
<tr>
<td>Trunk</td>
<td>30 (60)</td>
<td>NA</td>
<td>41 (95)</td>
<td>NA</td>
<td>23 (82)</td>
<td>8 (89)</td>
<td>NA</td>
<td>NA</td>
<td>3 (100)</td>
<td>79</td>
</tr>
<tr>
<td>Extremities</td>
<td>38 (76)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>9 (32)</td>
<td>6 (67)</td>
<td>NA</td>
<td>NA</td>
<td>3 (100)</td>
<td>62</td>
</tr>
<tr>
<td>Genitalia and buttocks</td>
<td>10 (20)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1 (11)</td>
<td>1 (11)</td>
<td>NA</td>
<td>NA</td>
<td>1 (100)</td>
<td>5</td>
</tr>
<tr>
<td>Morphologic Features of Lesions</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patches, plaques, or papules</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodules</td>
<td>9 (18)</td>
<td>14 (27)</td>
<td>26 (60)</td>
<td>NA</td>
<td>0</td>
<td>1 (11)</td>
<td>NA</td>
<td>NA</td>
<td>1 (33)</td>
<td>27</td>
</tr>
<tr>
<td>Erythroderma</td>
<td>4 (8)</td>
<td>3 (6)</td>
<td>3 (7)</td>
<td>NA</td>
<td>2 (7)</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>7</td>
</tr>
<tr>
<td>Alopecia</td>
<td>19 (38)</td>
<td>NA</td>
<td>28 (65)</td>
<td>NA</td>
<td>NA</td>
<td>7 (78)</td>
<td>3 (33)</td>
<td>NA</td>
<td>NA</td>
<td>51</td>
</tr>
<tr>
<td>Folliculocentric lesions such as milia, cysts, and acneiform lesions</td>
<td>25 (50)</td>
<td>4 (8)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>9 (100)</td>
<td>9 (100)</td>
<td>NA</td>
<td>3 (100)</td>
<td>41</td>
</tr>
<tr>
<td>Mucinorrhea d</td>
<td>6/47 (13)</td>
<td>3 (6)</td>
<td>A few cases</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>9</td>
</tr>
<tr>
<td>Pruritus</td>
<td>35/47 (74)</td>
<td>Most patients</td>
<td>30 (70)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3 (100)</td>
<td>73</td>
</tr>
<tr>
<td>Comorbid Malignant Neoplasms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hematologic</td>
<td>3 (6)</td>
<td>NA</td>
<td>2 (5)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>5.5</td>
</tr>
<tr>
<td>Solid organ</td>
<td>5 (10)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2 (22)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>11.8</td>
</tr>
</tbody>
</table>

Abbreviation: NA, data were unavailable or were unavailable in a format amenable to direct comparison.

a Whether some of the patients in the study by Gerami et al² also were reported in the study by Gerami and Guitart³ is unknown. Whether some of the patients in the study by Cerroni et al⁶ also were reported in the study by Flaig et al⁷ is unknown.

b Limited anatomic distribution of disease data available for 25 patients.

c Limited disease morphologic data available for 27 patients.

d When mucinorrhea was not addressed, it was assumed to be absent.
fluid expression from follicular ostia) was present in 6 patients (13%), of whom 5 had histopathologic evidence of follicular mucinosis. At presentation, 4 patients had erythroderma. During the follow-up period, 1 patient demonstrated the development of erythroderma and the presence of Sézary cells, which were identified on peripheral smear.

Among 50 patients in the study, the most common dermatologic diagnoses attributed to the eruptions (diagnoses later determined to be FMF) included the following: dermatitis (25 patients [50%]), follicular mucinosis (11 patients [22%]), dermatophyte infection (8 patients [16%]), psoriasis (6 patients [12%]), and folliculitis (4 patients [8%]). Several patients had more than 1 previous dermatologic diagnosis. One patient had a forehead nodule diagnosed previously as unspecified peripheral T-cell lymphoma.

Histopathologic features are summarized in eTable 2, and representative photomicrographs are shown in Figure 3. Prominent syringotropism of atypical lymphocytes without folliculotropism was noted in 1 biopsy specimen, and prominent syringotropism was present in another biopsy specimen in which no hair follicle could be found in numerous sections. Both patients had clinical evidence of follicular involvement (associated alopecia) and were included in the analysis. Immunohistochemical data were available for biopsy specimens from 42 patients (84%), with staining of neoplastic lymphoid cells in all specimens indicating a CD3+/CD4+/CD8− immunophenotype. The presence of tissue eosinophilia had low sensitivity (19%) but much higher specificity (70%) for predicting pruritus.

Flow cytometric immunotyping was performed on peripheral blood of 31 patients (62%), resulting in the identification of an unequivocal circulating clone in the specimens from 7 patients (23% of those tested). For 3 patients, the circulating clone was attributed to a lymphoproliferative malignant neoplasm other than mycosis fungoides. To detect TCR gene rearrangement clones, polymerase chain reaction or flow cytometry studies were performed on the peripheral blood of 17 patients (34%). A clonal population of T cells was identified in the peripheral blood of 8 patients (47% of those tested), one of whom had another lymphoproliferative malignant neoplasm. Polymerase chain reaction or flow cytometry studies were performed on the lesional skin of 21 patients, revealing a clone in the specimens from 15 patients (71%). Of 9 patients whose peripheral blood and lesional skin were tested for TCR gene rearrangement, 6 had a clone detected in both tissues. Of 4 patients in whom the peripheral blood clone was compared with that of the skin, 2 had identical clones. Of patients who had both skin and peripheral blood specimens tested for TCR gene rearrangement clones, all were found to have positive clones in lesional skin tissue.

General follow-up data were available for 47 patients (94%), and treatment data were available for 43 patients (86%). Among 15 patients known to be deceased, the
mean follow-up period from mycosis fungoides diagnosis to death was 3.3 years (range, 0.2-20.4 years). Among 32 patients alive at last follow-up, the median duration from diagnosis of mycosis fungoides to last follow-up was 2.9 years (range, 0 to 14.7 years). The overall survival rates at 1, 2, and 5 years after diagnosis were 96%, 90%, and 62%, respectively. The survival rate was not calculated because fewer than 10 patients still at risk; PUVA, psoralen–UV-A.

**TREATMENT AND FOLLOW-UP**

Initial treatment data are given in Table 2. The mean number of individual treatments per patient was 4.2 (range, 1-10; median, 4.0). Fifteen patients (30% of all 50 patients) were hospitalized for management of their cutaneous disease at some point in the follow-up period. At the time of their last clinical assessment, 21 of 43 patients (49%) for whom treatment follow-up data were available had improved partially or completely. Five of 43 patients (12%) had complete or near-complete resolution of skin lesions at least once in the follow-up period; 1 patient had disease remission throughout the follow-up period. These 5 patients were treated using topical corticosteroids with l-lysine hydrochloride, psoralen–UV-A photochemotherapy as monotherapy, or psoralen–UV-A photochemotherapy with local radiotherapy, topical corticosteroids, or both. Of 43 patients, 7 (16%) had stable disease, and 15 (35%) had progressive disease.

**PROGNOSTIC ASSOCIATIONS**

Among 50 patients identified for the study, 15 (30%) had an adverse clinical outcome. The median time from onset of skin lesions to adverse clinical outcome was 3.4 years (range, 0.4-16.2 years; mean, 5.1 years). Development of an adverse outcome was not associated with male sex (HR, 1.02; 95% CI, 0.36-2.88; P = .97) or with older age at onset (HR per 10-year increase in age, 0.89; 0.58-1.36; P = .58). Adverse clinical outcomes did not seem to be associated with histopathologic findings of follicular mucinosis (HR, 0.55; 95% CI, 0.18-1.68; P = .28), neutrophilic inflammation (0.29; 0.07-1.29; P = .10), eosinophilic inflammation (0.39; 0.14-1.11; P = .08), or granulomatous inflammation (0.17; 0.02-1.30; P = .09). No association was noted between adverse clinical out-
comes and the presence of Sézary cells on peripheral smear (2.17; 0.63-7.52; P = .22).

SYSTEMATIC REVIEW

We identified 8 previously published studies1-8 that each reported the clinical features of FMF in 3 or more patients; FMF has been described in 236 patients overall, including our study. Authors of 2 of the histopathologic studies3,8 also published clinical analyses2,6 that were included in our systematic review; therefore, the same patient data may have been referenced twice in the systematic review analysis. Patient characteristics and diagnostic data are summarized in eTable 1, clinical data in Table 1, histopathologic data in eTable 2, and therapeutic and prognostic data in Table 2.

Also termed pilocentric or follicular mycosis fungoides, FMF is a mycosis fungoides variant characterized by hair follicle epithelium infiltration by neoplastic lymphoid cells.9 It is more common in men than in women.1,8 Compared with that in men, the mean age at disease onset in women was significantly older, coinciding with postmenopausal years. Estrogen could serve as a protective factor (or testosterone as a predisposing factor) in patients otherwise prone to FMF.

Mycosis fungoides has numerous clinical manifestations,1,2,4,10,11 and the folliculotropic variant is no exception. Although head and neck involvement is frequent in FMF, these areas generally are spared in classic mycosis fungoides.4 The clinical index of suspicion for mycosis fungoides may be reduced, leading to a delay in diagnosis.1,4

Several patients with FMF in our series had comorbid hematologic malignant neoplasms. Although composite cutaneous lymphomas have been documented in patients with mycosis fungoides and B-cell chronic lymphocytic leukemia,12 we observed no neoplastic B cells in cutaneous biopsy specimens from our cohort.

The implications of having circulating Sézary cells without erythroderma (observed among 9 patients in our study) are undetermined.13 One group uses the term mycosis fungoides with leukemic involvement to describe mycosis fungoides with circulating Sézary cells in patients not otherwise meeting diagnostic criteria for Sézary syndrome.13 In our study, 1 patient had FMF that progressed to Sézary syndrome.

Just as the clinical features of FMF are varied, so are the histopathologic findings (eTable 2). Distinguishing between the clinical entity of follicular mucinosis (alopecia mucinosa) and FMF can be challenging histologically.5,14-17 Some authors have proposed that mycosis fungoides, follicular mucinosis, and FMF represent conditions along a continuous spectrum.18 Accurate diagnosis is important because follicular mucinosis unassociated with mycosis fungoides, especially in young patients, tends to have a persistent but benign disease course,15 in contrast to FMF.1,2 In our opinion, development of intrafollicular mucin deposits is a nonspecific secondary phenomenon that may occur when neoplastic or nonneoplastic lymphoid cells infiltrate the follicular epithelium. Clinical variables and close observation over time may be required to establish the diagnosis with certainty. Presence of a prominent eosinophilic infiltrate identified in our patients and in others1,3,6,8 was reasonably specific for associated pruritus.

Although clonal T-cell populations were detected in the biopsy specimens of most patients in our study and in others,17-19 detection of a T-cell clone is not specific for cutaneous malignant neoplasms. However, in the appropriate clinical context, the presence of a clone with TCR gene rearrangement may serve as an independent predictor of disease progression.20,21 Blood T-cell clones also are nonspecific and should not be interpreted to mean that the patient has systemic involvement.9 Identical T-cell clones were detected in the blood and skin of 2 patients in our study, which implies systemic disease involvement and may be a marker of poor prognosis.21 Data in our study were insufficient to evaluate this possibility.

Although limited by their retrospective nature and the inability to standardize or directly compare treatments, other studies1,2 and ours found that FMF is less responsive to treatment than classic mycosis fungoides. Some investigators1,22 propose that the deep extension of lymphocytes into the hair follicles limits the response to superficial therapies such as UV-B phototherapy and topical corticosteroids. Other investigators1 have hypothesized that the lymphocyte biologic characteristics that determine pilocentricism also contribute to therapy resistance.

We particularly aimed to calculate 5-year overall survival rates given apparent discrepancies among survival data of previous large retrospective studies.1,2 The present study and the study by van Doorn et al determined 5-year overall survival by measuring the time from diagnosis of mycosis fungoides to death, and these rates were similar (62% and 64%, respectively). Gerami et al used the duration between the time of lesion onset to death. After accounting for a mean time to diagnosis of 4.5 years, the survival rate reported by Gerami et al is similar (67%). Cause-specific mortality rates and time to disease progression could not be calculated because of few cause-specific deaths and our inability to gather accurate data on the timing of disease progression.

Our data may have overestimated the severity of FMF because of the tertiary referral nature of our practice and
the likely possibility that early cases of FMF may not have been recognized. Given the potentially subtle clinical and histopathologic findings in FMF, patients with early stages of the disease may have been unrecognized.

The pathogenesis of FMF is not well understood. Heightened expression of intercellular adhesion molecule 1 in perifollicular keratinocytes in FMF, which may be induced by the neoplastic T lymphocytes, may lead to obstruction of the follicle orifice by neoplastic T cells.4,5,23,24

Skin infection is known to exacerbate mycosis fungoides.25 In the presence of Staphylococcus aureus superantigens, nonmalignant T lymphocytes stimulate the proliferation of malignant T lymphocytes by molecular cross-talk.26 Indeed, several patients in our series with evidence of impetiginization had temporary improvement of their FMF after a course of systemic antibiotics. The finding that bacterial toxins worsen mycosis fungoides most likely has implications for FMF, as the follicular ostia are reservoirs of bacteria and pruritus (a stimulus for scratching) and subsequent impetiginization is a common clinical feature of FMF.

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Author Contributions: Dr Weenig had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Lehman, Cook-Norris, Weenig, Gibson, Weaver, and Pittelkow. Acquisition of data: Lehman, Cook-Norris, Weed, Weenig, and Pittelkow. Analysis and interpretation of data: Lehman, Weenig, Gibson, Weaver, and Pittelkow. Drafting of the manuscript: Lehman, Cook-Norris, Weed, Weenig, and Pittelkow. Critical revision of the manuscript for important intellectual content: Lehman, Cook-Norris, Weenig, Gibson, Weaver, and Pittelkow. Statistical analysis: Weaver. Administrative, technical, or material support: Weenig, Gibson, and Pittelkow. Study supervision: Lehman, Weed, Weenig, Gibson, and Pittelkow.

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REFERENCES


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