Follicular Mycosis Fungoides, a Distinct Disease Entity With or Without Associated Follicular Mucinosis

A Clinicopathologic and Follow-up Study of 51 Patients

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Objective: To determine the clinicopathologic features and the disease course of patients with follicular mycosis fungoides (MF).

Design: A multicenter, 14-year, retrospective cohort analysis.

Setting: Dutch Cutaneous Lymphoma Group.

Patients: Fifty-one patients with the clinicopathologic features of follicular MF with (n=49) or without (n=2) associated follicular mucinosis. Follow-up data were compared with those of 158 patients with the classic epidermotropic type of MF, including 122 patients with generalized plaque-stage MF (T2 N0 M0) and 36 patients with tumor-stage MF (T3 N0 M0).

Observations: Characteristic clinical features not or rarely observed in classic MF were the preferential localization of the skin lesions in the head and neck region (45 of 51 patients), the presence of follicular papules, alopecia, acneiform lesions, mucinorrhoea, and often severe pruritus. Characteristic histologic findings were the presence of perifollicular neoplastic infiltrates with a variable degree of folliculotropism, but generally no epidermotropism, follicular mucinosis (49 of 51 cases), and often a considerable admixture of eosinophils and plasma cells. Response on initial treatment, risk of disease progression (development of extracutaneous disease and/or death from lymphoma), and disease-specific and overall survival of patients with follicular MF were worse than in classic MF patients. The actuarial disease-specific survival was 68% at 5 years and 26% at 10 years.

Conclusions: Follicular MF shows distinctive clinicopathologic features, is more refractory to treatment, and has a worse prognosis than the classic type of MF; it should be considered a distinct type of cutaneous T-cell lymphoma. Based on these results and those of other studies, we suggest the term follicular MF for cases with or without associated follicular mucinosis.

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Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma, characterized clinically by an indolent clinical course with the subsequent evolution of patches, plaques, and tumors, and histologically by the infiltration of the epidermis by medium-sized to large atypical T cells with cerebriform nuclei.1

See also pages 182 and 244

In the first 10 years after diagnosis, disease progression, including development of extracutaneous disease and disease-related deaths, occurs in only a minority of patients.2 Apart from this so-called classic Alibert-Bazin type of MF, many clinical and histologic subtypes have been reported, including hypopigmented, vesicular, pustular, granulomatous, and other types of MF. Since these variant types of MF have the same clinical course and clinical behavior and require the same therapeutic approach as the classic type of MF, they are generally not considered separate entities. In both the EORTC (European Organization for Research on the Treatment of Cancer)1 classification for primary cutaneous lymphomas and in the WHO (World Health Organization) classification,3 only pagetoid reticulosis and MF-associated follicular mucinosis have been categorized as separate entities. Hereinafter, the latter condition will be referred to as follicular MF, a term also used in the WHO classification for cases with or without associated follicular mucinosis.

Follicular MF has been classified as a separate entity because it has distinctive clinical and histologic features, is more refractory to standard treatment, and has a worse prognosis than classic MF. However, this observation is particularly based on clinical experience of members of the classification committee of the EORTC Cutaneous Lymphoma Group and is not sub-
PATIENTS AND METHODS

Between October 1985 and December 1998, 57 patients with follicular MF were included in the registry of the Dutch Cutaneous Lymphoma Group. Three of the 57 had to be excluded from the present study, 1 because of incomplete follow-up data and 2 because of lack of representative skin biopsy specimens. Another 3 patients were excluded because they had a history of classic epidermotropic MF for 4 to 7 years before they developed skin tumors on the face with the histologic features of MF-associated follicular mucinosis. The final study group consisted of 51 patients. In each patient the diagnosis had been made by an expert panel of dermatologists and pathologists at one of the quarterly meetings of the Dutch Cutaneous Lymphoma Group. The main criteria for diagnosis and for inclusion in the study were the presence of perifollicular-to-diffuse dermal infiltrates with variable numbers of atypical T cells with cerebriform nuclei infiltrating the follicular epithelium and the presence of mucinous degeneration of the follicular epithelium, as confirmed by Alcian blue staining of the first diagnostic biopsy specimens (diagnostic specimens).6,7 Forty-nine patients met both criteria. Two cases with the same cytoarchitectural features in the diagnostic specimen but without associated follicular mucinosis were included as well. The time of evaluation of the first diagnostic specimen was considered the time of diagnosis.

In all cases diagnostic evaluation at the time of diagnosis consisted of a thorough physical examination, complete blood cell count, serum chemistry studies, and skin specimen evaluation. Lymph node biopsies and thoracic and abdominal computed tomographic scans were performed only in patients with enlarged peripheral lymph nodes. Lymph node involvement was assessed using criteria described previously.10 When indicated clinically, additional studies to determine visceral involvement were performed.

In all cases clinical records and follow-up data, which had been collected yearly, were evaluated. The following variables were recorded: age; sex; duration of skin lesions before diagnosis; type of initial therapy; whether there was a complete remission after initial therapy; the date of disease progression if applicable; and the date of last contact (or death if applicable). Because of difficulties in defining skin stage in patients with follicular MF, disease progression was defined by the development of histologically documented nodal involvement in patients with previously skin-limited disease, the development of visceral involvement in patients with prior skin and/or lymph node involvement, and death due to lymphoma. In all cases, one or multiple skin biopsy specimens obtained at the time of diagnosis, and in most cases also obtained during follow-up, were reviewed.

To evaluate differences in clinical behavior between follicular MF and classic MF, 49 patients with follicular MF presenting with disease confined to the skin were compared with 138 patients with classic MF included in an earlier study.2 This latter group included 122 patients with generalized plaque-stage MF (T2 N0 M0) and 36 patients with tumor-stage MF (T3 N0 M0) without evidence of extracutaneous disease and without associated follicular mucinosis at the time of diagnosis.

Actuarial survival curves were calculated from the date of diagnosis to the date of last contact (or the date of death) using the Kaplan-Meier technique. Differences between survival and disease progression curves were analyzed using the log-rank test. Univariate analysis of possible prognostic factors was performed using the log-rank test and Cox proportional hazards regression analysis. Patients lost to follow-up were considered censored at the time of last contact. Analyses were performed using the SPSS statistical software (SPSS Inc, Chicago, Ill).

RESULTS

CLINICAL CHARACTERISTICS

The main clinical features and relevant follow-up data have been summarized in Table 1. Fifty-one patients, including 42 male and 9 female, were included in this study. Four (8%) of 51 patients were younger than 40 years at the time of diagnosis. At the time of diagnosis, 49 patients (96%) had disease confined to the skin, including 4 patients with enlarged but histologically uninvolved lymph nodes, whereas 1 patient had concurrent lymph node involvement and another, concurrent visceral involvement.

At the time of diagnosis, 34 of 51 patients had only patches, plaques, or (grouped) follicular papules, often associated with alopecia; 14 had concurrent nodules or tumors, and 3 had erythroderma (Figure 1). Acneiform lesions, including comedolike lesions and epidermal cysts, were a prominent feature in 4 patients. Mucinorrhea (ie, discharge of mucinous substance from the follicular orifices) was noted in 3 patients. During the course of their disease, 2 patients developed a leonine face (Figure 2). In 45 of 51 patients, the skin lesions were preferentially localized in the head and neck region at the time of diagnosis. A characteristic finding in 25 of these 45 patients was the presence of plaques or tumors on the head or neck, whereas the trunk and extremities showed only patches or slightly infiltrated plaques and/or grouped follicular papules (Figure 1A-B). Infiltrated plaques in the eyebrows with concurrent alopecia were a common finding. Most patients had moderate to severe pruritus.
HISTOLOGIC FEATURES

A total of 74 representative skin biopsy specimens from these 51 patients were reviewed. These included the 51 diagnostic specimens, 8 prediagnostic specimens obtained 4 to 30 months (median, 12 months) prior to diagnosis, and 15 specimens obtained during follow-up at the time of relapse or disease progression. Characteristically, the diagnostic specimens showed perifollicular and perivascular-to-diffuse dermal infiltrates with variable infiltration of the follicular epithelium by medium-sized to large atypical T cells with cerebriform nuclei (Figure 3). Pautrier microabscesses appeared in only a minority of specimens. Infiltration of the interfollicular epidermis by (atypical) T cells, as in classic MF, was rare. Only 5 of 51 specimens showed infiltration of both the epidermis (epidermotropism) and the follicular epithelium (folliculotropism). Prominent infiltration of the eccrine sweat glands was observed in 3 specimens. In all but 2 cases, the skin specimens showed mucinous degeneration of the hair follicles, varying from focal spots of mucin deposition (which had to be searched for in serial sections) to lakes of mucin (Figure 3B).

The number of atypical T cells infiltrating the follicular epithelium was generally low and did not correlate with the amount of mucin deposition. The perifollicular infiltrates consisted of variable numbers of medium-sized to large atypical T cells with cerebriform nuclei and blast cells and admixed small lymphocytes, histiocytes, eosinophils (which were numerous in 13 of 51 specimens), and plasma cells, in particular in patients with secondary bacterial infection (Figure 3C). Concurrent patches on the trunk showed essentially the same histologic features, though the number of atypical T cells was often less than in the more infiltrated lesions in the head and neck, which made a definite diagnosis in these specimens more difficult or even impossible.

Immunohistochemical analysis demonstrated a CD3+CD4-CD8+ phenotype of the neoplastic T cells in all cases studied. Small numbers of scattered CD30+ blast cells were regularly observed, as were small clusters of admixed B cells. In the initial diagnostic specimens of 7 of the 51 patients, we found a considerable number of blast cells (>15%; generally a mixture of CD30+ and CD30- blast cells). Six of these 7 patients died of lymphoma 11 to 100 months (median, 40 months) after diagnosis.

In follow-up specimens taken during disease progression, the dermal infiltrates tended to become more diffuse, sometimes showed complete effacement of the follicular structures, and invariably showed increasing numbers of CD30+ and/or CD30- blast cells. In the 8 prediagnostic specimens, the dermal infiltrates were mainly confined to the perifollicular areas. Although some of these specimens already contained small numbers of atypical T cells in the follicular epithelium and in the perifollicular infiltrates, the size and morphologic characteristics of the infiltrating T cells did not warrant a definite diagnosis of follicular MF.

THERAPY AND FOLLOW-UP

Initial therapy consisted of psoralen plus UV-A (PUVA) treatment in 22 patients and total skin electron beam irradiation (TSEBI) in 11 patients (Table 1). Seven patients were initially treated with local radiotherapy in combination with other therapies, including PUVA with or without retinoids, UV-B, topical mechlorethamine, or topical steroids. For the remaining patients treatments included topical steroids (3 patients), topical mechlorethamine (1 patient), UV-B (1 patient), PUVA in combination with retinoids (1 patient), prednisone (1 patient), azathioprine in combination with topical mechlorethamine (1 patient), or polychemotherapy (2 patients). One patient refused treatment.

Only 8 (16%) of 51 patients, each with disease confined to the skin, achieved complete remission on initial treatment. Six of them had been treated with TSEBI, 1 with PUVA, and 1 with a combination of PUVA, retinoids, and local radiotherapy. Two of these 7 patients were still in complete remission after a follow-up of 38 and 192 months, respectively, and may be considered cured.

<table>
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<tr>
<th>Characteristic</th>
<th>Finding</th>
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<tr>
<td>Age at diagnosis, median (range), y</td>
<td>57 (15-84)</td>
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<tr>
<td>Male-female ratio</td>
<td>4.7 (42:9)</td>
</tr>
<tr>
<td>Duration of skin lesions before diagnosis, median (range), mo</td>
<td>48 (4-156)</td>
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*Unless otherwise indicated, data are number (percentage) of patients.

DL indicates histologic features of dermatopathic lymphadenopathy; PUVA, psoralen plus UV-A therapy; TSEBI, total skin electron beam irradiation; and MF, follicular mycosis fungoides.

†Disease progression means development of extracutaneous disease and/or death from lymphoma.

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The follow-up period varied between 8 and 239 months (median, 48 months; mean, 58 months). Development of lymph node or visceral involvement was documented in 14 and 7 patients, respectively. Disease progression defined as the development of extracutaneous disease or death from lymphoma occurred in 20 (39%) of 51 patients, and occurred 11 to 168 months (median, 45 months) after diagnosis. The calculated risk of disease progression during the first 5 years after diagnosis was 37%; at 10 years, 66%. At the conclusion of the study, 26 patients had died, 20 from lymphoma. The 5- and 10-year disease-specific survival rate was 68% and 26%, respectively. The respective overall survival rates at 5 and 10 years were 64% and 14%. Univariate analysis demonstrated no association between disease-specific survival and age at diagnosis, sex, duration of skin lesions before diagnosis, or response to initial treatment.

FOLLICULAR MF VS CLASSIC MF

To evaluate differences in clinical behavior and prognosis between follicular MF and classic MF, we compared...
relevant clinical features of the 49 patients with follicular MF who had disease confined to the skin with the features of 122 patients with generalized plaque-stage MF and 36 patients with tumor-stage MF without evidence of extracutaneous disease and without associated follicular mucinosis (Table 2). Patients with follicular MF showed a significantly higher male-female ratio and less frequently achieved complete remission on initial treatment. The calculated risk of disease progression, as defined in this study, within the first 5 years after diagnosis was 36% for follicular MF vs 12% for classic plaque-stage MF and 24% for tumor-stage MF. Disease-specific and overall survival in patients with follicular MF were significantly lower than in patients with generalized plaque-stage MF, and were roughly similar to patients with tumor-stage MF without associated follicular mucinosis (Figure 4).

**COMMENT**

The results of the present study clearly demonstrate that follicular MF has distinctive clinicopathologic features and should be considered a distinct disease entity. Characteristic histologic features include the primary perifollicular localization of the dermal infiltrates, with variable infiltration of the follicular epithelium by medium-sized to large atypical T cells with cerebriform nuclei. In most cases the epidermis is spared (folliculotropism instead of epidermotropism). Mucinous degeneration of the follicular epithelium occurs in most cases, and a considerable admixture with eosinophils and plasma cells is frequently present.

Clinical characteristics include the preferential localization of the skin lesions in the head and neck area (45 of 51 patients), the presence of papules (often grouped), alopecia, frequent secondary bacterial infection, and, less commonly, the presence of acneiform lesions and mucinorrhea. Unlike in classic MF, pruritus is often severe and may represent a good parameter of disease activity: in several patients, a relapse after initial therapy was preceded by the reappearance of pruritus. In addition, patients with follicular MF proved generally more refractory to standard classic MF therapies, showed more frequent disease progression, and had a less favorable prognosis (Table 2).

This more unfavorable prognosis suggests a true biological difference in clinical behavior between patients with follicular MF and patients with the classic epidermotropic type of MF, which is consistent with the conclusion of a recent study. The similar duration of skin lesions before diagnosis in patients with follicular MF and patients with classic-type MF indicates that the difference in survival does not simply result from a selection of patients with
more advanced disease in the present study (Table 2). Comparison of the disease-specific and overall survival data indicate that patients with follicular MF have a similar (at 5 years) or worse (at 10 years) survival than patients with tumor-stage MF (Table 2). Nevertheless, under the classic MF classification systems, most of our patients with follicular MF would have been classified as stage IA (T1 N0 M0) or IB (T2 N0 M0), and only 14 of them had nodules or tumors at the time of diagnosis. This supports our contention that these clinical staging systems for MF are not very useful in patients with follicular MF. For instance, patients presenting with a solitary patch or plaque on the face do not have stage IA or T1 N0 M0–stage disease. Because of the perifollicular localization of the dermal infiltrates, such patients should always be considered to have tumor-stage disease, regardless of the clinical appearance of the skin lesion, and should be treated accordingly.

MF-ASSOCIATED FOLLICULAR MUCINOSIS VS FOLLICULAR MF

In recent years, the term follicular MF or cutaneous T-cell lymphoma (also folliculocentric MF or pilotropic MF) has been introduced for a rare clinical variant of MF characterized by follicular papules, follicular keratoses, comedolike lesions, and epidermal cysts. Histologically, perifollicular infiltrates are present showing marked folliculotropism, but there is generally no epidermotropism or follicular mucinosis. Evaluation of published reports of “follicular MF” demonstrates considerable clinical heterogeneity and suggests that this term has been used for the diagnoses of at least 3 different groups of patients.

The largest group comprises patients with clinically and histologically classic MF prior to or, less often, concurrent with the development of the follicular lesions. In the present study, 3 patients with 4- to 7-year histories of classic epidermotropic MF developing skin tumors with the histologic features of follicular MF were excluded because such cases show the clinical behavior of classic MF developing tumor-stage disease.

The second group includes patients presenting with acneiform lesions as the predominant or only manifestation of the disease. However, a similar clinical presentation may also occur in patients with associated follicular mucinosis and was a predominant feature in 4 of 51 patients in the present study. One of our patients was
DIFFERENTIAL DIAGNOSIS

Although distinctive clinical and histologic features should facilitate an early and correct diagnosis, it is our experience over the last 15 years that the diagnosis of follicular MF is often overlooked. Because of the preferential involvement of the head and neck area, the absence of patches and plaques on the trunk or buttocks, and the absence of epidermotropic atypical T cells, the diagnosis of MF or cutaneous T-cell lymphoma is often not considered. The following incorrect diagnoses have been made more than once prior to referral: seborrheic dermatitis in patients presenting with erythematous lesions on the scalp and eyebrows; atopic dermatitis, because of the severe pruritus; and facial granuloma with eosinophilia in patients presenting with a solitary plaque on the face and an eosinophil-rich infiltrate. Finally, it should be noted that even when follicular MF is suspected, it may require several biopsies to make a definite diagnosis. It is important that biopsy specimens be taken from the most infiltrated skin lesions, generally in the face or neck, and not only from patches with or without follicular papules on the trunk.

THERAPY

The results of the present study confirm our clinical impression and the scattered data in literature that patients with follicular MF are generally less responsive to standard therapies used in patients with classic MF. Our retrospective study does not allow a meaningful comparison of the effects of the different treatment methods because patients were treated at different institutions, and treatment selection may have been affected by disease severity.
Because of the perifollicular localization of the dermal infiltrates, patients with follicular MF should always be considered to have tumor-stage disease, regardless of the clinical appearance of the skin lesions. Therefore, in patients presenting with a single plaque or tumor or a few clustered skin lesions, but without patches or follicular papules at other sites, radiotherapy is the first choice for treatment. In selected cases with superficial lesions presenting at multiple sites, PUVA treatment might be attempted first. However, in most cases this approach will not result in complete remission. In the present series, complete remission was achieved with PUVA therapy in only 1 of 22 patients. In patients with more infiltrated skin lesions, in particular those who do not respond to PUVA therapy alone, TSEBI is the preferred method of treatment. However, only 6 of 11 patients treated with TSEBI reached complete remission, and 3 of the 6 complete responders had a relapse within 6 months.

The relative unresponsiveness of follicular MF to TSEBI has been reported. In some patients relapsing skin disease may be controlled effectively by a maintenance treatment with topical nitrogen mustard. If TSEBI is not available, PUVA in combination with interferon alpha or retinoids and local radiotherapy for thick tumors may be an alternative. The same approach can be used for relapsing disease following TSEBI. In our experience, multiantigen chemotherapy does not generally result in complete remission in patients with skin-limited disease and should therefore be reserved for patients developing extracutaneous disease.

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REFERENCES


News and Notes

The Regional Conference on Dermatological Laser and Facial Cosmetic Surgery 2002 will be held from September 13 through September 15, 2002, at the new wing of the Hong Kong Convention and Exhibition Center. The conference is jointly organized by the University of Hong Kong, the Hong Kong Society of Dermatology and Venereology, and the Hong Kong Society of Plastic & Reconstructive Surgeons.

Renowned authorities to speak at the conference include Dr Yung-hung Lai (Chang Gung Memorial Hospital, Taiwan), Dr Dieter Manstein (Harvard Medical School, United States), Prof Rolf Nordstrom (Nordstrom Hospital for Plastic and Reconstructive Surgery, Finland), Dr Nivat Polnikorn (Ramathibodi Hospital, Thailand), and Dr Woffles Wu (Woffles Wu Aesthetic Surgery and Laser Center, Singapore).

For more information on the conference, please contact the secretariat at phone (852) 25278898; fax: (852) 28667330, or e-mail: cosfmshk@netvigator.com.

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