CLINICAL REPORT

# Clinical and Histopathological Features of Folliculotropic Mycosis Fungoides: a Norwegian Patient Series

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Folliculotropic mycosis fungoides is a variant of cutaneous T-cell lymphoma with distinct clinicopathological features. We describe here the clinical presentation, pathology findings and treatment outcome in 15 Norwegian patients. All patients were diagnosed between 1997 and 2010 at Oslo University Hospital. A spectrum of skin lesions, both typical and atypical, such as leonine facies, acneiform lesions, psoriasiform plaques, purulent ulcerations and cystic milia-like lesions for mycosis fungoides, were seen. Histological examination revealed characteristic infiltration of hair follicles with neoplastic T cells associated with partial destruction of the former. A CD4+ immunophenotype of the neoplastic T cells with loss of one or more T-cell markers was demonstrated. In general, the patients were given more aggressive therapeutic regimens than those with conventional mycosis fungoides, and showed a trend towards more rapid disease progression. In conclusion, this case series confirms the distinct clinical and histological features of folliculotropic mycosis fungoides. *Key words: mycosis fungoides; cutaneous T-cell lymphoma; folliculotropic mycosis fungoides.*

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Mycosis fungoides (MF) is a T-cell lymphoproliferative disease characterized by small- to medium-sized malignant T cells that typically infiltrate the epidermis (1, 2). According to the World Health Organization (WHO) classification, the diagnosis MF, including its variants, should be made only when successive appearance of patches, plaques and tumours is observed (3). Variants include folliculotropic MF (FMF), pagetoid reticulosis and granulomatous slack skin disease (3).

FMF is characterized by pronounced infiltration of malignant T cells in the follicular epithelium, and occasionally shows epidermotropism (3–10). Eccrine sweat gland infiltration is occasionally the predominant finding. Such cases have also been described as syringotropic MF (11). FMF preferentially involves the head and neck area (3–10). A range of clinical features can be observed, such as follicular or indurated papules, acneiform lesions, alopecia, plaques, ulcerations and tumours (4–11). It has been shown that patients with FMF often present with a more advanced disease stage, although skin staging can be difficult to assess, and are often unresponsive to standard treatments (8, 9). The latter may be due to the deep localization of the T-cell infiltrate in the hair follicles (3, 9, 12). Several studies have indicated that the prognosis of FMF is poorer than that of conventional MF (2, 3, 7, 12).

In this study we reviewed the clinical and histopathological features of all FMF patients in the Cutaneous Lymphoma Registry and pathology files at Oslo University Hospital in Oslo, Norway. We also studied the outcome of FMF and compared it with that of conventional MF.

## MATERIALS AND METHODS

### Patients

All patients with FMF in the Cutaneous Lymphoma Registry of the Department of Dermatology at Oslo University Hospital, comprising all patients diagnosed in the period 1997 to 2010, were studied. Data on additional FMF patients diagnosed during the same period were retrieved from the files of the Department of Pathology at Oslo University Hospital ($n = 15$). Clinical and histopathological data were reviewed.

The control group comprised all the patients with conventional MF in our clinical database who were followed-up for at least one year, and of whom diagnostic biopsies were available for review ($n = 30$).

### Histopathology review

Histopathology review included review of haematoxylin and eosin-stained as well as Alcian blue-stained tissue slides. In addition, immunoperoxidase-stained sections for CD2, CD3, CD4, CD5, CD7, CD8, CD20 and CD30 were available in all cases. Molecular clonality testing was performed in all cases. The tests were performed according to Greiner et al. (13) for patients diagnosed before 2003 and according to Van Dongen et al. (14) for patients diagnosed after 2003. Histological diagnoses were made according to the WHO classification (3). In all patients, one or multiple skin biopsies were obtained at the time of diagnosis. Additional follow-up biopsies, which were available in most patients, were also reviewed. A diagnosis of FMF was made when predominantly intrafollicular or perifollicular infiltrates of atypical T cells with cerebriform nuclei were seen.

### Clinical data and staging

All patients were staged according to WHO classification for cutaneous lymphomas (3). At the time of presentation, patients were

physically examined, and a blood cell count, serum chemistry and skin biopsy were performed. Computed tomography (CT) of thoracic and abdominal regions was performed in all patients with stage IIB or more, either at the time of diagnosis or at later follow-up. Additional CT scans of the cervical or pelvic region were performed in a few patients on clinical indication. A lymph node biopsy was taken in patients with lymphadenopathy. Quantitation of lymphoma cells in the blood by flow cytometry is a more recent requirement for the staging of MF and Sézary syndrome (15), and was therefore performed in only 2 patients. Clinical staging was performed according to the tumour, node, metastasis, blood classification for cutaneous lymphoma (3, 16).

Disease progression was defined by one of the following events: progression from plaque to tumour stage or to erythroderma; histologically confirmed nodal involvement in patients with disease that was previously limited to the skin; the development of visceral involvement in patients with only prior skin or lymph node involvement; and dissemination to the blood or death due to lymphoma.

### Survival analysis

Survival of patients with FMF or conventional MF was studied according to Kaplan–Meier analysis (17). The difference in survival between FMF and conventional MF was analysed using a log-rank test. Progression-free survival was analysed from stage at time of diagnosis to stage at last follow-up or to death. Analyses were performed using SPSS statistical software (SPSS Inc., Chicago, IL, USA).

### Ethics

The study was approved by the Institutional Review Board of Oslo University Hospital and by the Regional Ethics Committee.

## RESULTS

### Clinical findings

Data on 15 patients with a diagnosis of FMF were retrieved. Eleven patients were retrieved from the Cutaneous Lymphoma Registry and 4 from the Department of Pathology files. Of these, 10 patients were male. Clinical data were available in 13 patients. Median age was 65 years (age range 26–90 years). Median follow-up time was 5 years (range 1–13 years).

The control group comprised 30 patients with conventional MF. Of these, 17 were men. Median age was 64 years (age range 38–90 years). Median follow-up time was 3 years (range 1–30 years).

Patients with FMF constituted 15% of all cutaneous T-cell lymphoma (CTCL) patients ($n=72$) and 21% of all MF patients ($n=51$) in the registry. The majority of patients had lesions in the head-neck region (85%), on the trunk (69%) and/or on the extremities (54%). One patient had lesions on the genitalia and buttocks. The majority of patients reported pruritus.

Three clinical patterns were discerned: patients with typical MF lesions, consisting of erythematous, ulcerating plaques or tumours ($n=7$), patients with typical MF lesions as well as atypical lesions ($n=4$) and those with exclusively atypical lesions ($n=2$). The following atypical lesions were observed: alopecia ($n=4$), diffuse erythema ($n=2$), lichenified dermatitis ($n=2$), leonine facies ($n=1$, Fig. 1), acneiform-like lesions ($n=1$), psoriasiform plaques ($n=1$), crusted-purulent ulceration of the head ($n=1$) and cystic, basal cell carcinoma-like lesions in the face ($n=1$).

Two patients had oral involvement with lymphoma infiltration of the tongue. One patient had a medical history of bladder cancer. All clinical data are summarized in Table I.

### Histopathology findings

The skin biopsies of all FMF patients ($n=15$) showed perifollicular or intrafollicular infiltration with atypical T cells. These features were not found in the patients with conventional MF ($n=30$). Additional features in FMF were: exocytosis with atypical T cells in the epidermis with occasional Pautrier's abscesses ($n=3$), syringotropism ($n=4$), and follicular mucinosis ($n=2$) (Fig. 2). A dermal granulomatous inflammation was seen in one patient. Invariably, the atypical T cells displayed a CD3+, CD4+, CD8- immunophenotype. Loss of CD7 expression was noted in 7 of 14 patients. Loss of CD5 expression was noted in 3 patients. In one patient, the immunophenotype of the atypical lymphoid infiltrate could not be analysed with certainty because of a pronounced mixture of reactive T- and B-lymphocytes. A variable number of scattered small B cells were observed in the other patients. Monoclonal T-cell receptor gamma gene rearrangement was shown in 10 of 12 patients.



*Fig. 1.* Folliculotropic mycosis fungoides patient with diffuse erythema on the face, and leonine facies with predominant infiltrating plaques and alopecia of the eyebrows. Lichenified dermatitis of the upper trunk was also present. (Publication without masking has been approved in writing by the patient.)

Table I. *Clinical characteristics and treatment of patients with folliculotropic mycosis fungoides*

| Pat. no. | Sex/age (years) | Clinical presentation | Localization | Stage at diagnosis and last stage | Therapy |
|---|---|---|---|---|---|
| 1 | M/65 | Multiple infiltrating/ulcerated erythematous plaques and tumours | Head/trunk | IA–IVB with mucosa infiltration | PUVA, chlorambucil, LESB, vorinostat, allogeneic BSCT |
| 2 | F/51 | Early bullae, ulcerated nodules; later hidradenitis-like pustules, papules, nodules and plaques | Lower extremities | IIB–IVA | n.a. |
| 3 | M/57 | Diffuse erythema, confluent erythematous, desquamated psoriasiform plaques, alopecia | Head/neck, face, trunk, inguinal | IA | Topical steroids, PUVA |
| 4 | M/53 | Ulcerated crusted plaques and tumours + alopecia (head) + eczema nummular-like plaques (upper and generalized) | Head, upper and whole body | IIB–IVB with mucosa infiltration | PUVA, re-PUVA, CHOP, allogeneic BSCT |
| 5 | F/67 | Multiple infiltrating and ulcerating erythematous plaques and tumours | Head, trunk | IIB | TESB/fractionated LESB, IFNα, gemcitabine |
| 6 | F/78 | n.a. | n.a. | n.a. | n.a. |
| 7 | F/55 | Cystic comedo-like or basal cell carcinoma-like lesion | Face | IA | Excision |
| 8 | M/70 | Multiple generalized erythematous, indurated plaques | Head, generalized | IB | n.a. |
| 9 | M/60 | Indurated plaques, alopecia and eczema nummular-like lesions | Face/eyebrow, trunk and extremities | IA | Topical steroids, fractionated LESB |
| 10 | M/65 | Generalized erythematous eczema nummular-like plaques and ulcerated tumours | Face/eyebrow, abdomen, extremities, sacrum | IA–IIB | Topical steroids, PUVA, fractionated LESB, re-PUVA, IFNα |
| 11 | M/86 | n.a. | n.a. | n.a. | n.a. |
| 12 | M/79 | Confluent erythematous/infiltrated plaques, diffuse erythema, leonine facies, alopecia, lichenified dermatitis, subcutaneous tumour | Face/eyebrows, trunk, extremities | IVA | Topical steroids + PUVA combined with MTX |
| 13 | M/26 | Erythematous plaques with scale | Face/eyebrows, extremities | IIA–IB | Topical steroids |
| 14 | M/82 | Erythematous/infiltrated plaques | Trunk | IB | TESB |
| 15 | F/90 | Multiple tumours ulcerated | Face and extremities | IIB | Fractionated LESB |

n.a.: not available; BSCT: blood stem cell transplantation; TESB: total-body beam therapy; LESB: localized radiation (beam) therapy; IFNα: interferon alpha; MTX: methotrexate; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; PUVA: psoralen plus ultraviolet A light.

## Treatment

Patients were given variable treatment modalities according to stage (Table I). Treatment consisted of local steroids and psoralen and ultraviolet light treatment (PUVA) as first-line treatments. Second-line treatments, such as total-body electron beam irradiation therapy (TSEB), localized electron beam irradiation therapy (LESB), chemotherapy, cytokines, such as interferon alpha (IFNα), were given as shown in Table I. Chemotherapy was given either as a monotherapy (chlorambucil, gemcitabine or high-dose methotrexate) or combination chemotherapy (CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone). More innovative therapy, such as treatment with histone deacetylase inhibitors (Vorinostat) were given in one patient (patient 1) and allogeneic blood stem cell transplantation after reduced conditioning (RIC-allo-SCT), according to a protocol developed at the National Cancer Institute, Bethesda, USA (18), in 2 patients (patients 1 and 4) after multiple conventional therapeutic approaches for MF had failed. The effect of treatment with Vorinostat in patient 1 could not be evaluated because therapy was discontinued early due to fatigue and emesis. Eventually patient 1, as well as patient 4, received allogeneic RIC-allo-SCT. Although both patients attained complete remission at 6 months, both patients died within one year, one due to myocardial infarction and one due to pulmonary infection and bronchiolitis obliterans.

## Progression-free survival

Patients with FMF and with conventional MF were staged at diagnosis and at time of last follow-up examination. Eight of 13 FMF patients showed early-stage (stage IA–IIA), 3 intermediate-stage (IIB–III) and 2 advanced-stage (IVA–IVB) disease at time of diagnosis. At follow-up, 6 of 10 patients had stable disease, while 4 had disease progression. Four of 15 FMF patients died with cause of death unknown.

In patients with conventional MF, 28 of 30 patients had early stage (IA–IIA) and 2 patients advanced stage (IVA–IVB) disease at time of diagnosis. At time of follow-up, 23 patients showed stable disease and 7 showed progressive disease. Four patients died with MF, but from an unknown immediate cause of death. No statistically significant survival difference was noted between FMF and conventional MF, although a trend towards a decreased progression-free survival for FMF patients was seen ($p = 0.089$).

## DISCUSSION

We have described the clinical and histopathological features, disease course and survival of 15 patients with FMF. Survival data were compared with those of patients with conventional MF in our database. In short, both typical and atypical clinical presentations for MF were noted. The skin biopsies showed a distinct
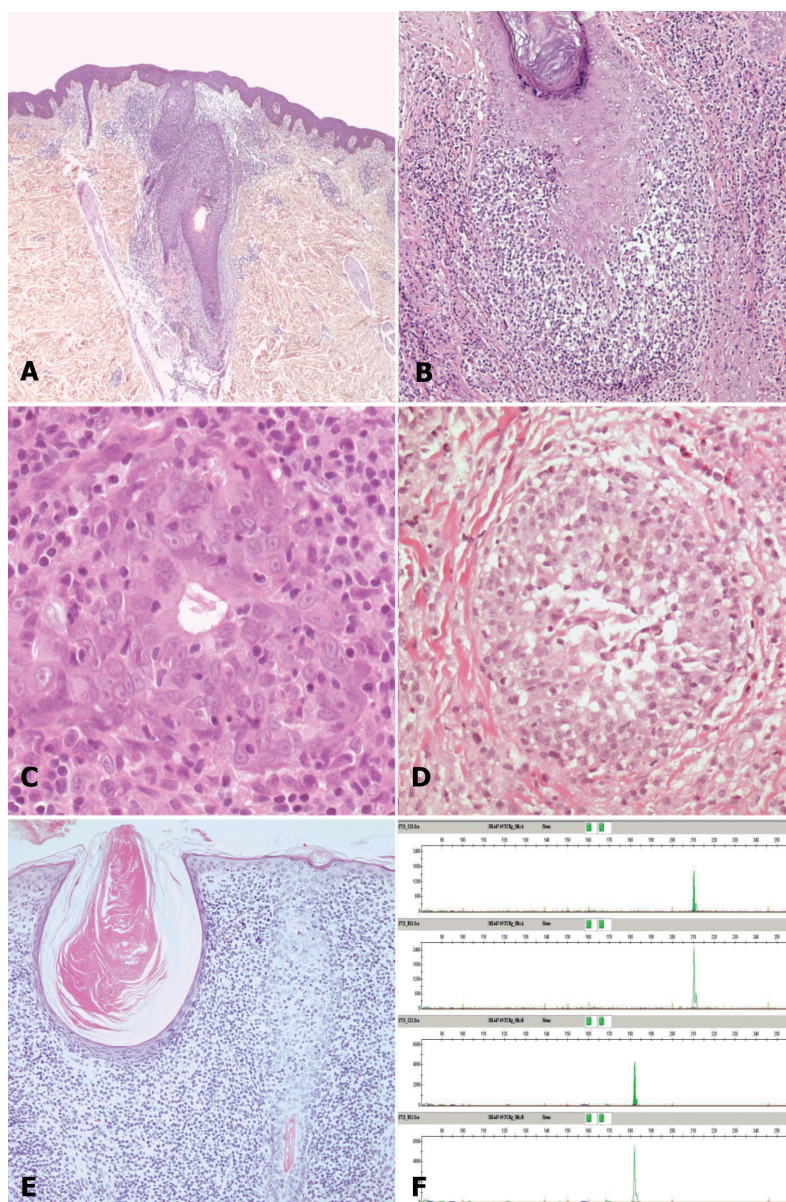
Fig. 2. (A–E) Varied histological features seen in patients with folliculotropic mycosis fungoides (FMF). (A and B) Massive infiltration of the hair follicle with atypical T cells. (C) Infiltration in an eccrine sweat gland or syringotropism. (D) A follicle with mucinosis. (E) A biopsy with a comedo (*left*) in addition to a hair-follicle with infiltration of T cells (*right*), typical of FMF. (F) Electropherogram showing monoclonal T-cell receptor gamma gene rearrangement in one of the patients.

histopathology, and the clinical course of the FMF patients was worse compared with conventional MF.

FMF represented 21% of MF in our registry, which is a higher frequency than reported in other series, usually being less than 10% of all cases of MF (1, 4, 5). This is probably explained by a selection bias, since our registry is based at a tertiary care university hospital. FMF shows a slight male predominance in our series, which is in agreement with previous studies (2, 4, 10).

The head and neck was the predilection site in the majority of our patients, which is in agreement with other published series (4–10). These regions are usually spared in conventional MF. Other case series have described different predilection sites for FMF, such as the trunk and extremities (8, 9). Patches and plaques were present in more than half of our patients, in accordance with the high frequency of these lesions in published case series (4, 5, 7, 9). Features atypical for conventional MF, such as acneiform lesions, cystic comedones, alopecia and follicular papules, were observed in our, as well as in other, case series (2, 4–10). However, and to the best of our knowledge, ulcerated and crusted purulent plaques on the head, as seen in one of our patients, have not been reported previously in FMF. Two patients showed oral involvement with infiltration of the tongue. Oral lesions are reported in less than 1% of MF patients, and have been described as a distinct cutaneous lymphoma entity (19). The development of oral lesions in 2 of our FMF patients in our registry is therefore of interest. One FMF patient had bladder cancer. Second malignancies, including chronic lymphatic leukaemia, breast, bladder, lung and prostate cancer, have previously been reported to be more frequent in FMF than in conventional MF (8).

In addition to the characteristic histological finding of folliculotropism, other histological features, such as epidermotropism, syringotropism and follicular mucinosis, were seen. Epidermotropism is reported in up to 54% of FMF patients (4, 7, 9), whereas concomitant involvement of the eccrine glands or syringotropism is less frequent (8, 11). Follicular mucinosis, reported in 44–96% of FMF patients (3, 4, 7–10), is most likely a secondary phenomenon (7, 8, 10). Also, granulomatous inflammation is seen in both FMF and syringotropic MF and is probably secondary to the destruction of hair follicles or sweat glands (10, 11). Thus, histological patterns may be diverse, in parallel with the spectrum of atypical dermatological features that can be seen in FMF. Atypical histological features may even pose diagnostic problems (10). Gerami & Guitart (10) emphasized that awareness of these various histological patterns is important for the correct diagnosis of FMF. The immunophenotype of the malignant T cells seen in our patients is similar to that seen in conventional MF and is in agreement with other case series of FMF (3, 4, 7–9). Monoclonal T-cell receptor gamma gene rearrangement was demonstrated in the majority of patients, as in other case series (4–10).

In FMF, correct staging may be difficult. Firstly, the tumor, lymph node, metastasis (TNM) classification for MF does not include atypical features, such as acneiform or cystic comedo-like lesions, as seen in FMF (3, 4). Secondly, patients with FMF are probably understaged using the current TNM classification, due to the fact that the patch and plaque lesions represent deeper seated infiltrates in FMF compared with conventional MF. Van Doorn et al. (4) have suggested that solitary patch or plaque lesions in FMF should not be staged as IA, but rather as IIB, i.e. tumour stage disease. Accordingly, most FMF patients should probably receive more aggressive treatment than patients with conventional MF. This is probably a reflection of the deep localization of neoplastic infiltrates. Currently, there is no standardized treatment for FMF (4–8).

FMF patients showed more frequently intermediate- or advanced-stage disease at the time of diagnosis compared with conventional MF patients. Disease progression was seen more often in FMF patients than in conventional MF patients. Van Doorn et al. (4) showed a significantly decreased progression-free survival for FMF patients compared with conventional MF patients. Our patient series was too small to evaluate overall survival. However, Gerami et al. (7) and others (4, 8) have reported a slightly decreased overall survival for patients with FMF compared with conventional MF.

In conclusion, this case series confirms that FMF is a CTCL with a broad spectrum of clinical and histological features, and indicates that FMF has a more aggressive clinical course than conventional MF. Further studies, including genetic analyses, are needed to establish whether FMF represents a distinct type of CTCL or is only a variant of MF.

## ACKNOWLEDGEMENT

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