Folikulotropna oblika mycosis fungoides: kliničnopatološke značilnosti

Folliculotropic mycosis fungoides: Clinicopathological features

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Izvleček

Folikulotropni tip fungoidne mikoze (MF) je redka oblika T-celičnega limfoma kože, ki prizadene manj kot 10 % pacientov z MF. Običajno se pojavlja pri starejših osebah. Najpogosteje prizadene glavo, vrat in zgornji del trupa. Diagnoza se postavi s pomočjo klinične slike, histološkega videza in monoklonalnosti T-celic. Pomembna je prepoznava te oblike bolezni zaradi slabše prognoze in posledično potrebe po intenzivnejšem zdravljenju.

Abstract

Folliculotropic variant of mycosis fungoides (MF) is a rare type of cutaneous T-cell lymphoma, detected in less than 10% of patients with MF. It occurs mostly in elderly adults, and usually involves the head, neck region, and upper trunk. The diagnosis of this disease is based on a combination of clinical presentation, histology, and T-cell monoclonality. Identification of this variant of disease is important because it may imply worse prognosis and require more intensive treatment.

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BACKGROUND

Mycosis fungoides (MF) accounts for nearly 50% of all cases of primary cutaneous T–cell lymphoproliferative skin diseases. The cause of MF is unclear, and current hypotheses include genetic and epigenetic abnormalities. The incidence of MF is approximately six cases per million per year and about 4% of all cases of non–Hodgkin lymphoma. The clinical features of MF include persistent or slowly progressive skin lesions consisting of erythematous, infiltrating patches, and ulcerating plaques, which vary in size and shape and are often located on sun–protected skin. Classic MF is characterized by typical light microscopic changes, marked epidermotropism of atypical T–lymphocytes, or band–like infiltrate containing abnormal lymphocytes in the upper dermis, which can eventually have some degree of follicular involvement. Besides, sharply marginated, discrete clusters of lymphocytes in close apposition with one another within the epidermis (Pautrier's microabscess) are evident characteristics of MF. In some cases, a marked lichenoid reaction with histology resembling lichen planus is observed. The dermal infiltrate usually contains a small number of eosinophils and sometimes plasma cells, and early MF can mimic common dermatoses. The atypical variants of MF show the clinical features and histologic patterns of all the major inflammatory skin diseases (1–7). Folliculotropic MF (FMF) has been categorized as a distinct entity among classic MF by the World Health Organization / European Organization for Research and Treatment of Cancer, and includes pilotropic MF, follicular MF, and MF–associated mucinosis (1–7).

CLINICAL FEATURES

FMF is the most common subtype of MF in adults, and can also affect children and adolescents (9, 10), with men being more commonly affected than women. The clinical characteristics of FMF include infiltrated plaques affecting head and neck area. Besides, involvement of the trunk is also common, and keratotic follicular papules and acneiform lesions are evident. The lesions often have follicular–based and tumid appearance, and commonly present as a combination of comedo–like lesions and small pustular lesions. In addition, FMF is often associated with hair loss within the lesions and patients experience significant pruritus. The defining criterion for the diagnosis of FMF is the presence of progressive clinical lesions with a dominant histologic pattern of folliculotropism (8–19) (Figure 1).

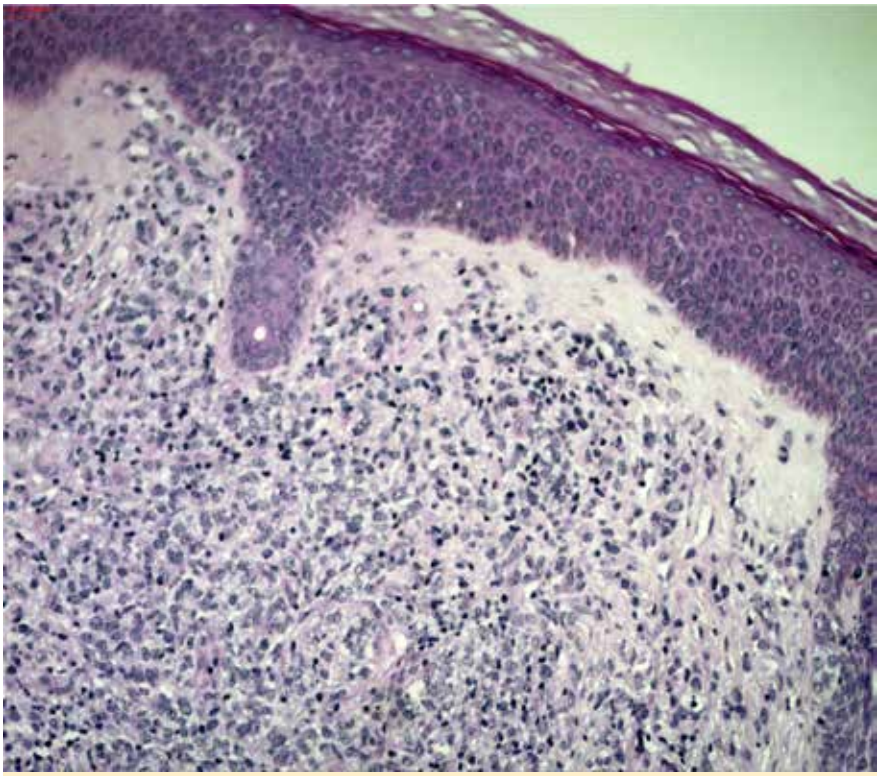

Figure 1. *MF: A dense dermal infiltrate with atypical lymphocytes in the basal epidermis (HE)*

HISTOPATHOLOGICAL FINDINGS

FMF is histologically characterized by pronounced infiltration of malignant T–cells in the follicular epithelium, and often lacks evidence of epidermotropism. Although most of the cases show mucinous degeneration of the hair follicles, it is more likely a secondary phenomenon (11). Many biopsies have revealed histologic features associated with pruritus, including the presence of superficial excoriations, acanthosis, spongiosis, and lamellar fibroplasias. Histological skin sample analysis comprises examination for the presence of mucin in tissue samples stained with hematoxylin and eosin (HE) as well as Alcian–blue. Although many characteristic histological patterns are known, including the classic pattern of folliculotropism, eosinophilic follicle-like pattern, cystic pattern, granulomatous pattern, and basaloid folliculolymphoid hyperplasia, histologic identification of FMF is exacerbated by nondiagnostic biopsies with neutrophilic pustular lesions or lichenoid lesions. Hence, immunohistochemical (IHC)–stained sections for detecting CD2, CD3, CD4, CD5, CD7, CD8, CD20, and CD30 are used to support or confirm the results of routine histology. Immunophenotyping can help distinguish MF from reactive or inflammatory lymphoid infiltrates in the skin.

FMF is histologically characterized by the presence of atypical $CD3^+$, $CD4^+$, and $CD8^-$ T–lymphocytes that surround and infiltrate the hair follicles usually without evidence of epidermotropism. An increased CD4/CD8 ratio of interfollicular lymphocytes is a typical feature of FMF. Moreover, scattered large atypical $CD30^+$ or $CD30^-$ cells are commonly seen, which may get transformed to a $CD30^+$ large cell lymphoma. In addition, accumulation of $CD1a^+$ cells (Langerhans cells) within the follicular epithelium has also been reported (8–22). Histology and IHC findings should be always correlated with clinical manifestations, and one or multiple skin biopsies are obtained with additional follow–up biopsies. Analyses of the morphometric parameters have revealed that the perifollicular infiltrates are significantly heavier and their vertical depth is significantly greater in advanced–stage lesions, when compared with those in early–stage lesions (Figure 2, Figure 3, Figure 4).

MOLECULAR FINDINGS

From each paraffin–embedded sample, DNA is isolated for the detection of T–cell receptor (TCR) gene rearrangement by using PCR. The incidence of clonal TCR rearrangement varies by the clinical stage of FMF. As the percentage of suspected neoplastic T–cells is usually low in skin biopsies, it is recommended to assess the PCR target in duplicate to demonstrate reproducibility of the signals. The results should be interpreted based on clinical, histologic, and IHC data. It must be noted that T–cell monoclonality can also be found in various inflam-

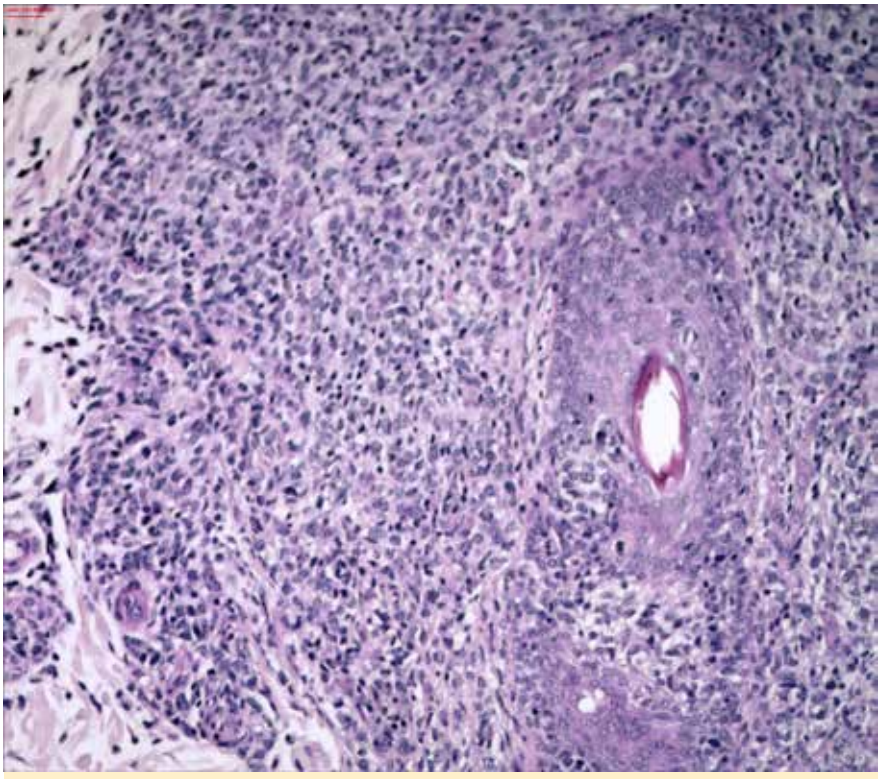

Figure 2. *FMF: Follicle with atypical lymphoid infiltrate (HE)*

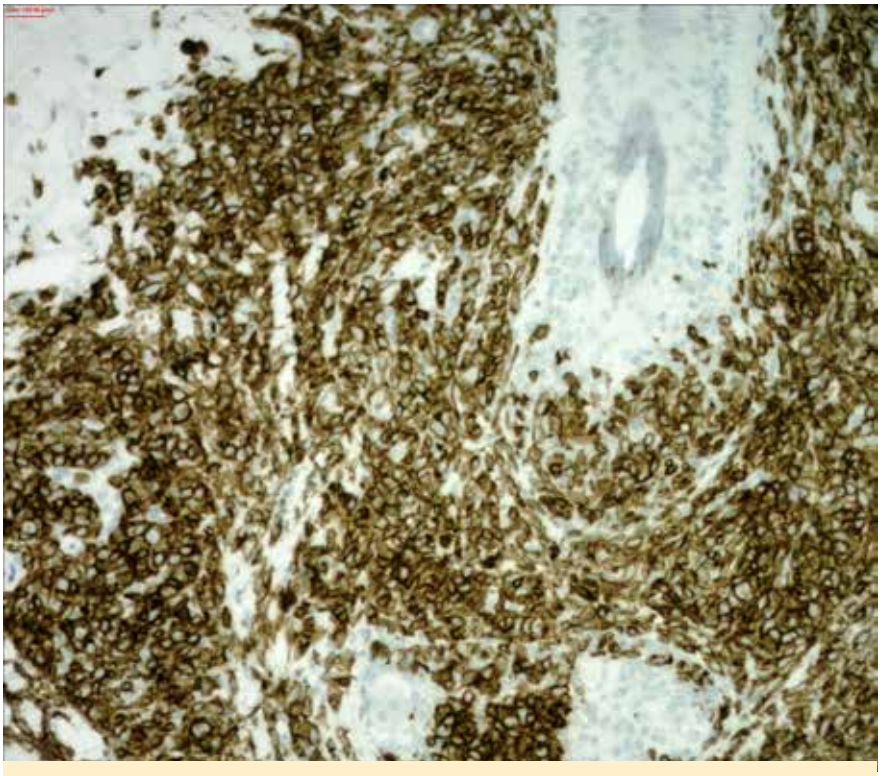

Figure 3. *FMF: Most of the infiltrating cells present CD4+ phenotype*

matory dermatoses such as cutaneous lymphoid hyperplasia, cutaneous drug reactions, lupus-associated dermatitis, or lichen planus (4, 18, 19).

TREATMENT

Treatment of FMF should be stage–adapted (24). FMF, with its polymorphic clinical presentation, is usually diagnosed at a later stage than classic MF. The skin lesions are often unresponsive to standard treatments owing to deep localization of the T–cell infiltrate. The modalities for the treatment of early FMF include application of topical corticosteroids, psoralen, and ultraviolet light therapy. Second–line treatments of FMF comprise localized and total–body beam irradiation therapy, chemotherapy, and cytokines therapy. Patients with early–stage FMF may benefit well from standard skin–directed therapies (25, 26), whereas those in advanced stages may require chemotherapy, biological therapy, radiotherapy, and allogenic bone marrow transplant (27).

DISCUSSION

Previous studies suggest that FMF can be classified into two stages, an early stage and advanced stage, with some patients with early-stage FMF remaining undiagnosed. The occurrence of FMF superficial lesions as patches or

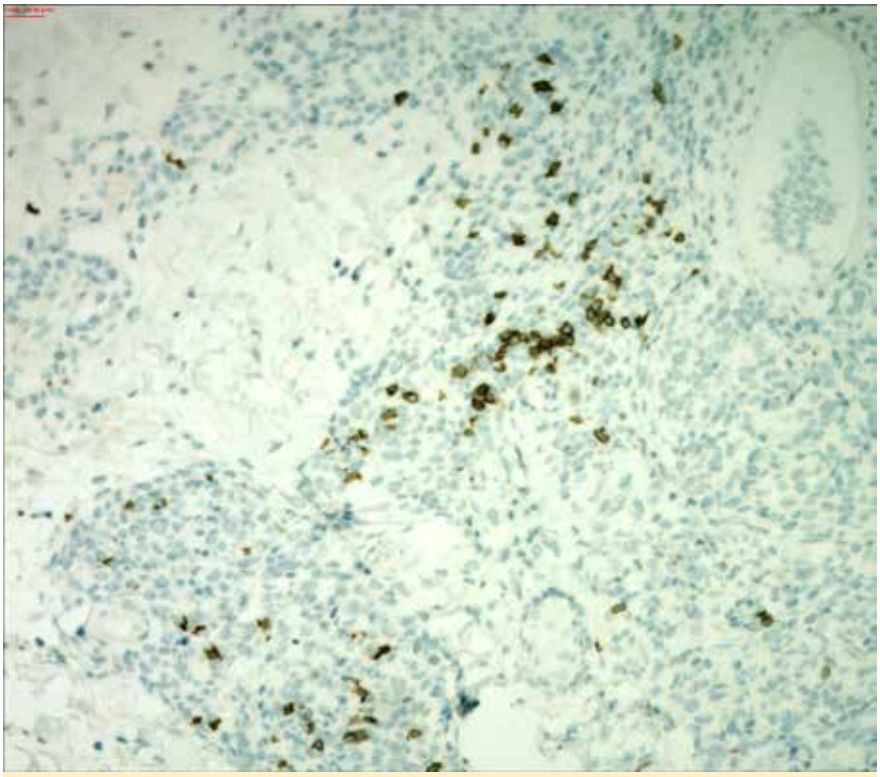

Figure 4. *FMF: Sparse interfollicular CD8+ lymphocyte infiltration*

flat plaques on extrafacial sites, mainly trunk and limbs, suggests early stage of the disease, and are mostly detected in younger patients (10). In contrast, presence of infiltrated plaques and tumors on head and neck region indicates advanced–stage FMF (20). It must be noted that Pautrier's abscess formation is rare in FMF. While follicular mucinosis could be an early sign of this disease, granulomatous inflammation might probably be secondary to the destruction of hair follicles and may compromise the final diagnosis. Besides, the role and diagnostic significance of Langerhans cell hyperplasia in FMF are not yet well understood (22). For accurate diagnosis of FMF, awareness of various histological patterns is important. A dominant T–cell clonal pattern must be detected by PCR for the analysis of TCR gene rearrangements. However, the presence of complementary clone can also occur in clonal dermatitis (19–21), making it difficult to determine the correct stage of the disease. Patch and plaque lesions represent deeper infiltrates in FMF, when compared with those in conventional MF. Moreover, intermediate- or advanced–stage FMF are more commonly detected, when compared with conventional MF (13). The most frequent initial treatment includes skin–directed therapies such as phototherapy (24, 25).

CONCLUSION

Clinical studies confirm that FMF is a variant of cutaneous T–cell lymphoma with a broad spectrum of clinical and histologic features that may lack the typical histologic attributes. Early detection of this disease, both clinically and histoIogically, is important, and correlation with total clinical information, close clinical follow–up with rebiopsy, and prudent use of laboratory studies are vital for FMF diagnosis. When compared with classic MF, FMF is considered to have a more aggressive clinical course, and patients with FMF may not respond to treatment and may require a separate therapeutic algorithm. Clinical studies confirm that FMF is a variant of cutaneous T–cell lymphoma with a broad spectrum of clinical and histologic features that may lack the typical histologic attributes. Early detection of this disease, both clinically and histoIogically, is important, and correlation with total clinical information, close clinical follow-up with rebiopsy, and prudent use of laboratory studies are vital for FMF diagnosis. When compared with classic MF, FMF is considered to have a more aggressive clinical course, and patients with FMF may not respond to treatment and may require a separate therapeutic algorithm.

ABBREVIATIONS USED:

MF: mycosis fungoides;
FMF: folliculotropic mycosis fungoides;
HE: haematoxylin and eosin
IHC: immunohistochemical;
TCR: T–cell receptors;
PCR: polymerase chain reaction

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