

CASE REPORT

Follicular mycosis fungoides: a report of 2 cases in Filipino octogenarians

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Introduction: Folliculotropic mycosis fungoides is a rare and aggressive subtype of mycosis fungoides characterized by small to medium-sized malignant T-cells that typically infiltrate the hair follicle. It represents 4% of primary cutaneous lymphomas and less than 10% of patients with MF.

Case Summary: We report 2 cases of 80-year old female, who presented with a 3-year history of an erythematous plaque on the left infraorbital area and forehead, and the other with an 8-month history of multiple erythematous indurated plaques on the left cheek, left eyebrow and malar area. Clinical presentation, histopathology and immunohistochemistry findings revealed a diagnosis of folliculotropic mycosis fungoides.

Conclusion: Folliculotropic mycosis fungoides has distinct clinical and microscopic features. Evaluation of clinical, pathologic, and immunophenotypic findings are important to identify this rare form of cutaneous T-cell lymphoma.

Keywords: *Mycosis fungoides, cutaneous T-cell lymphoma, Follicular mucinosis*

INTRODUCTION

Mycosis fungoides (MF) is the most predominant type of cutaneous T-cell lymphoma characterized by small to medium-sized malignant T cells that typically infiltrate the epidermis. In folliculotropic mycosis fungoides (FMF), neoplastic T-lymphocytes infiltrate the hair follicle, often sparing the epidermis. It has been classified as a separate entity to classic Mycosis Fungoides in the World Health Organization/European Organization for Research and Treatment of Cancer (WHO/EORTC) classification because it has distinctive clinical and histological features, is more resistant to standard therapies, and has a worse prognosis. Herein, we report 2 cases of FMF with one case displaying follicular mucinosis and the other displaying epidermotropism, which is not commonly seen in FMF.

CASE 1

An 80-year-old woman presented with a 3-year history of multiple erythematous plaques on the left infraorbital area extending to the malar area and on the forehead (Figure 1a). No clinically palpable lymphadenopathy was observed.

Skin punch biopsy reveals mild hyperplasia of the epidermis but particularly of the upper part of the hair follicle with hyperkeratosis and parakeratosis. Follicular mucinosis and exocytosis of atypical lymphocytes within the upper part of the hair follicles could be observed (Figure 2). Immunohistochemical examination showed pan T-helper phenotype (CD2, CD3, CD4 and CD5-positive) with some loss of CD7 in most of the cells in the infiltrate. A few of the larger cells within the hair follicles are positive for CD30. Clinicopathologic features were consistent with the diagnosis of folliculotropic cutaneous T-cell lymphoma.

The patient was advised therapeutic options but has refused any form of treatment erythrocyte sedimentation rate, thyroid function test and non-reactive hepatitis profile. A chest x-ray did not reveal any abnormality.

CASE 2

An 80-year-old woman presented with an 8-month history of a violaceous plaque on the left cheek and a 1-month history of multiple erythematous indurated plaques on the left eyebrow and malar area (Figure 1b).

Skin punch biopsy showed parakeratosis and scale crusts in the stratum corneum. There is atrophy of the

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epidermis, neutrophilic microabscesses in the granular layer and a prominent epidermotropism of medium sized atypical lymphocytes surrounded by a perinuclear halo. The dermis reveals a dense inflammatory infiltrate of lymphocytes, some large and atypical, and plasma cells. Numerous pigment-laden macrophages are seen. By immunohistochemistry, most of the cells of the infiltrate are positive for CD2, CD3 and CD4 with some loss of expression of CD5 and alpha beta chain with hardly any cells positive for CD30 (Figure 3). A small percentage of the T cells, mainly the reactive T lymphocytes, are positive for CD8. CD45RA and RO have reduced expression.

The patient responded initially to methotrexate but there was recurrence characterized by edema and erythema. Presently, patient is maintained on intermittent low dose systemic steroids and topical steroids during flares with modest improvement although complete resolution is not observed.

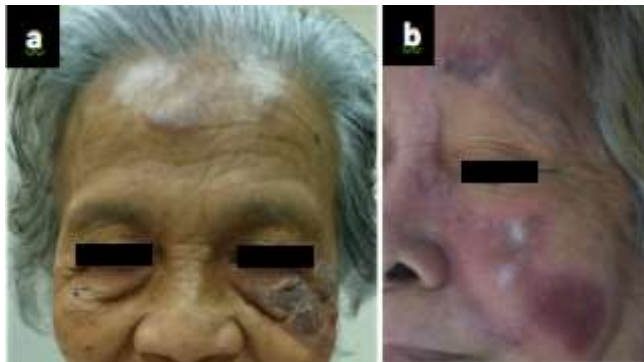


Figure 1. (a) Multiple erythematous plaques on the left infraorbital area extending to the malar area and on the forehead (Case 1); (b) Multiple erythematous indurated plaques on the left eyebrow and malar area (Case 2)

DISCUSSION

Folliculotropic mycosis fungoides is a rare form of CTCL that represents 4% of primary cutaneous lymphomas and less than 10% of patients with MF.¹

The pathogenesis of FMF is unknown, although it has been suggested that folliculotropism is mediated through intracellular adhesion molecule 1 (ICAM-1) expression by follicular epithelium and lymphocyte function associated antigen (LFA-1) expression by the lymphoid cells.^{2,4} Consistent with this possibility, *Hodak et al.* found exclusive expression of ICAM-1 in the membrane of the follicular epithelium in FMF lesions. On the other hand, classic MF lesions expressed ICAM-1 throughout the epidermis.²

It is more common in middle-aged to elderly males. Previous literature reported an average age at diagnosis of 53 years, similar to that of classic MF.¹ In a study by Lehman

et al., compared to men, the mean age at disease onset in

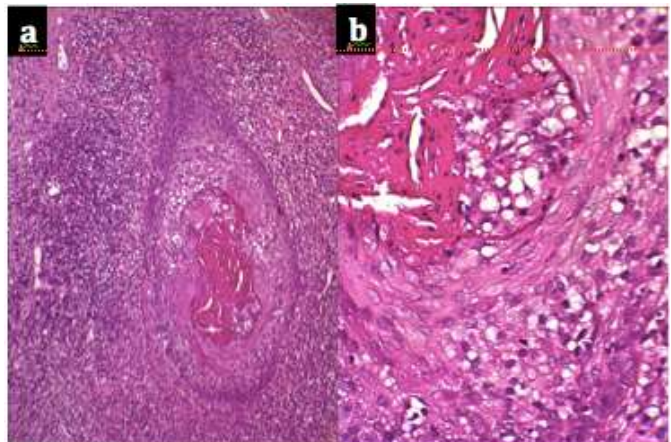


Figure 2. (a) Skin punch biopsy of an erythematous plaque on the malar (case 1) revealed exocytosis of atypical lymphocytes and destruction of the hair follicle. (H&E stain, 100x); (b) (H&E stain, 400x)

women is significantly older, as is observed in both of our reported cases. It was speculated that estrogen could serve as a protective factor (or testosterone as a predisposing factor) in patients otherwise prone to FMF.³

Folliculotropic MF cases can be a diagnostic challenge because of the great variability in their clinical presentations.² Most patients present with patches, plaques with follicular plugging, or grouped follicular papules. Less frequent are acneiform lesions such as comedone-like cyst, pustules, or milia. Tumor stage lesions may also be encountered.^{2,4} FMF has a predilection for the head and neck, particularly the face and scalp.^{1,2,3,4,6}

The histologic features of FMF are distinctive. It is characterized by the infiltration of hair follicle epithelium by medium to large cerebriform cells.⁴ Involvement of the epidermis is not present or is minimal. Collection of acid mucopolysaccharides within the involved follicles (follicular mucinosis) is present to varying degrees but is often absent.⁴ Previous studies reported follicular mucinosis in 73% of the FMF cases (ranging from 5 to 96%).¹ Van Doorn et al. found progression of the disease at 10 years in 89% of 32 patients with MF associated with follicular mucinosis compared with 32% of 277 patients with MF and no follicular mucinosis.² However, recent studies show that regardless of the presence of follicular mucinosis, no differences were observed in the clinical presentation and behavior of FMF.¹ In both our cases, the characteristic infiltration of the follicular epithelium by atypical T-cells (folliculotropism) was found. In one case, follicular mucinosis was observed and in the other case, epidermotropism. Both of which are infrequent findings in cases of FMF.

Immunohistochemical studies are essential for distinguishing B, T, natural killer and non-lymphoid cells and their subsets based on their immunophenotype. In FMF, the

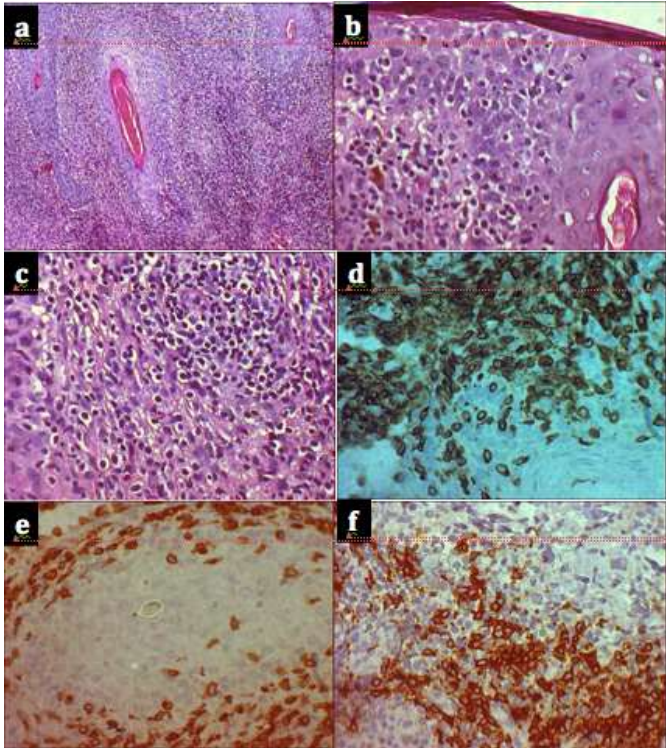


Figure 3. (a) Skin punch biopsy of an erythematous plaque (case 2) revealed a moderately dense lymphocytic infiltrate which show prominent epidermotropism to the epidermis and the hair follicle (H&E stain, x100). Epidermotropic lymphocytes are characterized by irregularly-shaped nuclei surrounded by perinuclear halo (b) (H&E stain, x400); (c) The dermis reveals a dense inflammatory infiltrate of medium-sized to large atypical lymphocytes and plasma cells; (d) CD3+ cells show epidermotropism (x400); (e) CD3+ cells infiltrating the hair follicle (x400); (f) focal CD20+ cells in the infiltrate (x400)

FMF (\leq IIA) should include phototherapy preferably PUVA in combination with a retinoid or interferon alpha. Prognosis is poor in advanced disease (\geq IIB) and aggressive therapy is required.¹

According to a WHO/EORTC consensus report, the prognosis of folliculotropic MF is worse than that of a tumor stage classical MF. The Dutch group reported 5- and 10-year disease survival rates of folliculotropic MF of 68% and 26%, respectively.² *Van Doorn et al.* reported a 5-year survival rate of 64% and a 10-year survival rate of only 14%. *Lehman et al.* reported a 1-year and 5-year overall survival rates of 96% and 62%, respectively. *Gerami et al.* found an overall survival after 5, 10, and 15 years of 87%, 82%, and 41%, respectively for early stage FMF (\leq IIA) and 83%, 67%, and 27%, respectively for late-stage FMF (\geq IIB). When compared with data on survival rates for classic MF, patients with folliculotropic MF have similar (at 5 years) or worse (at 10 years) survival than patients with tumor stage MF.¹ Calculated risk of disease progression by *Van Doorn et al.* was 37% at 5 years and 66% at 10 years.¹

CONCLUSION

Folliculotropic MF is a rare and aggressive subtype of mycosis fungoides that is refractory to standard therapies and has a poor prognosis and overall survival rate.

Although rare, this variant has distinct clinical and histopathologic features. Careful and complete evaluation of clinical, histopathologic, and immunophenotypic studies are essential for correct diagnosis.

Understanding the differences between FMF and conventional MF is important to optimize therapy and management of this rare and aggressive variant of CTCL.

neoplastic T-cells have a mature T-helper phenotype (CD3+, CD4+, CD8-) as in classical MF.^{1,2,6} There may be loss of lymphocyte antigen such as CD7, CD5 or CD2. Loss of this pan T-cell antigen is often seen as an important adjunct in the diagnosis of MF but can be nonspecific.¹ These features were seen in both our cases. A small number of dispersed CD 30+ blast cells are also frequently found. The presence of considerable number of CD30+ or CD30- blast cells (>15%) has been associated with a worse prognosis.²

Folliculotropic MF is often less responsive to skin-targeted therapies, such as PUVA and topical nitrogen mustard, than classic plaque stage MF.¹ The deep perifollicular and intrafollicular location of the infiltrates means that therapy targeting the skin is less efficacious.² Chemotherapy for patients with refractory disease may be instituted as single or multiagent chemotherapy. Single weekly doses of MTX, oral Chlorambucil, and intravenous Etoposide have each been reported to produce complete responses in up to 33% of patients.⁵ A more recent study by *Gerami et al.* suggested that initial treatment for early stage

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