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CASE REPORT

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Folliculotropic mycosis fungoides associated with follicular mucinosis: A case report and mini review

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Key Clinical Message

F-MF is a rare non-classic variant of MF. In the case of hair loss, this should be a diagnostic consideration. The essence of the diagnosis of F-MF is a careful medical history, physical examination, and a combination of immunohistological and molecular analyses (*Cureus*. 2022; 14:e21231, *Ann Saudi Med*. 2012; 32:283, *Oman Med J*. 2012; 27:134, *Int J Dermatol*. 2016; 55:1396, *Saudi Med J*. 2018; 39:994 and *Case Rep Oncol*. 2018; 11:436).

Abstract

Mycosis fungoides (MF) is a primary cutaneous T-cell lymphoma with multiple subtypes. Follicular MF (F-MF) is a non-classic variant of MF. Histological features entail folliculotropism and damage of the epithelium lining of the hair follicles with or without mucin deposition. A 52-year-old male patient complained of recurrent skin lesions on the scalp over 8 months. The lesions appeared suddenly, enlarged over time, and became itchy. A skin punch biopsy was performed. Histological features included mucin deposits in the epithelium of the hair follicles and dense, predominantly perifollicular atypical lymphocytes infiltrating the follicular epithelium. The lymphoid cells were composed of CD3-positive T cells (CD4/CD8-positive T cells) with a shift in favor of the former. The case was diagnosed as F-MF on an immunohistological basis. The diagnosis of F-MF is often difficult for dermatologists and dermatopathologists alike. Not only clinicopathological correlations but also immunohistochemical and molecular analysis are required.

KEYWORDS

folliculotropic, fungoides, mycosis, skin

1 | INTRODUCTION

1.1 | Mycosis fungoides

Mycosis fungoides (MF) is a primary cutaneous T-cell lymphoma (CTCL). It is a common type of extranodal non-Hodgkin lymphoma.[1,2] Follicular or folliculotropic MF (F-MF, also called follicular T-cell lymphoma, follicular MF, MF-associated mucinosis, or pleiotropic MF) is an under-recognized subtype of MF. On histology, there is folliculotropism with neoplastic T cells, with or without mucin deposits in the epithelium of the hair follicles.[3] In 2005, WHO/EORTC considered F-MF as a variant of MF in their classification.[4–7]

1.2 | Mycosis fungoides in Saudi Arabia

In Saudi Arabia, few studies are available about MF and F-MF.[1,8–12] Al Ghamdi et al examined the clinical and pathological findings of MF in 43 cases of MF. The disease affected adults with an average age of 33.5 years. The male-to-female ratio was 2:1. Most of the cases have been presented in an early stage (I and II) of the disease. Most of the patients had classic MF whereas few patients had other subtypes including the hypopigmented variant of MF. The patients were followed up and only a few of them recovered; whereas MF skin lesions persisted in most of them.[8]

Alojailand and his colleagues examined the clinical and pathological findings in 34 patients with MF. The patients had the features of several variants including hyperpigmented MF (11 patients), hypopigmented MF (21 patients), poikilodermatous MF, or pagetoid reticulosis (a single patient, each). Therapy consisted of phototherapy Narrowband UVB, topical corticosteroids, and systemic acitretin.[1]

Alghubaywi et al examined 73 patients with classic or hypopigmented variants of MF at the dermatology clinic (King Abdulaziz Medical City, Saudi Arabia). MF was slightly more common in females. Most of the patients presented to the dermatology clinics at an early stage of the disease (IA, IB, and IIA). There was a delay in the diagnosis of MF because some of the patients were initially misdiagnosed with chronic dermatitis. This may be reasoned to the fact that MF and chronic dermatitis can have overlapping clinical manifestations.[13] On immunohistology, the neoplastic T cells had CD4-positive/CD8-positive phenotype with a predominance of CD8.[13] Therapy consisted of topical corticosteroids. Table 1 summarizes these previous studies.

1.3 | Follicular mucinosis

Follicular mucinosis, that is, accumulation of mucin in the follicular epithelium may be an idiopathic disorder or secondary condition. The latter may be associated with several inflammatory conditions such as chronic spongiotic dermatitis. Other cases can be associated with several neoplastic conditions.[14,15] In 1957, Pinkus described the deposition of acellular mucin in the epithelium of the hair follicles (alopecia mucinosa). In this condition, there is an associated infiltration of the epithelial cells of the outer root sheath of the hair follicles by atypical lymphocytes (i.e., folliculotropism).[16] In 1959, Jablonska coined the terminology "follicular mucinosis"[17] which includes both idiopathic follicular mucinosis and lymphoma-related follicular mucinosis (F-MF).[2,18,19] The skin lesions of the idiopathic follicular mucinosis can resolve spontaneously. In resolving lesions, the therapy consists of steroids (topical, intralesional, or systemic steroids). Other therapeutic modalities include photodynamic therapy, antimalarials, interferon, or dapson.[20,21]

TABLE 1 Mycosis fungoides in the Kingdom of Saudi Arabia: some previous studies.

Studies	Location of the study	Total number of cases	Average age (Years)	Male to female ratio	References
1	King Khalid University Hospital, Riyadh	43	33.5	2:1	8
2	Johns Hopkins Aramco Healthcare Center (Eastern Province)	22patients (out of 204 cases with skin cancers) had MF	–	–	10
3	The western region of KSA	14 cases of MF out of 202 cases of skin cancer	30.7	11:3	11
4	College of Medicine, King Saud University, Riyadh	A single case of MF	–	–	12
5	King Faisal University, Al Ahsa	34 cases	44	1: 1.3	1

1.4 | Folliculotropic mycosis fungoides

F-MF is a common non-classic variant of MF. It represents about 10% of the cases of MF.[22] It has a male predominance and usually affects adults.[23] The clinical manifestations include follicle-based infiltrated erythematous papules resembling acne or keratosis pilaris. The skin manifestations include patches, plaques, or tumor-like lesions with follicular accentuation.[2,19,24] Also, the clinical findings include prurigo-like lesions, pseudotumors, or lichen spinulosus-like lesions. Other F-MF lesions may resemble rosacea or lupus tumidus.[25] The lesions of F-MF can be solitary or extensive leading to the appearance of a leonine face.[22] Pruritis is a common complaint that may be aggravated by staphylococcal auras infection resulting in pyoderma.[24]

In F-MF, the head and neck area is the most affected region. Other affected areas include the trunk and extremities.[16] The clinicopathologic features of F-MF are observed in nearly 10% of MF patients.[2,19,24] The hallmark histological features of F-MF include perivascular and adnexal infiltration by atypical lymphocytes and destruction of the follicular epithelium by small, medium, or large lymphocytes with convoluted nuclei (cerebriform nuclei). The epidermis is usually spared. Additional histological findings include follicular mucinosis, Pautrier's micro-abscess, follicular plugging, atypical lymphocytes residing along the basal layers of the follicular epithelium, and perieccrine infiltration of atypical lymphocytes.[22,25] Immunohistochemistry usually shows a prominent CD3-positive T-cell infiltrate, with a predominance of CD4-positive T lymphocytes over rare CD8-positive T cells. CD7 expression may be reduced or even completely lost. Molecular analysis (T cell receptor-γ gene rearrangement) may show monoclonal T cells.[22,25–27] Treatment options for F-MF include photochemotherapy in combination with interferon alpha-2a and retinoids. Other options include local radiotherapy, topical imiquimod, and whole-body electron irradiation.[22]

Several F-MF case reports have been described in the literature. Monopoli et al. described two adult patients with F-MF. Clinical manifestations included alopecia, follicular erythematous papules or comedones, and cysts. Histological findings included a follicle-based atypical T-cell infiltrate extending into the epidermis. There was no associated mucinosis. Clonality analysis revealed the oligo/monoclonal nature of the T-cell lymphocytic infiltrate.[26]

Rajalakshmi et al. investigated four cases of F-MF affecting the facial skin.[28] The mean age of the patients was 17.5 years. Hypopigmented patches or erythematous macules were the presenting skin lesions. Two patients had concurrent alopecia. The histological findings included folliculotropism, perifollicular mucin deposition, and lymphocyte tagging of the follicular epithelium. Some of the atypical lymphocytes were surrounded by haloes. The atypical lymphocytes had convoluted (cerebriform) nuclei. The atypical lymphocytes also infiltrated the eccrine and sebaceous glandular epithelium.[28]

Magro et al. reported six cases of unilesional follicular MF. All patients were males, with a mean age of 28 years. Patients presented with single lesions on the face and scalp (five patients) or trunk (a single patient) that persisted for several months. Follicular prominence and alopecia were observed. Routine histology revealed an atypical folliculotropic lymphocytic infiltrate associated with follicular mucin deposits. Immunohistochemistry revealed a high CD4:CD8 T-cell ratio and loss of CD7 protein expression. In a single untreated case, similar lesions re-appeared on the skin of the thighs and buttocks 3–4 years later.[27]

F-MF occurs most commonly in adults, with an average age of 60 years at diagnosis. It is extremely rare in children and adolescents.[29] Mantri et al. reported a case of F-MF in a 16-year-old boy who had a 6 × 7 cm plaque on his forehead that lasted for 2 months. Immunohistochemistry revealed a high density of atypical T cells that infiltrated and destroyed the epithelium of the hair follicles. Follicular mucinosis was also observed. Most neoplastic cells were CD4-positive T cells, and there were few CD8-positive T cells around the hair follicle. Treatment included a targeted electron beam. The lesions completely disappeared within 2 months.[29] Interestingly, Emge et al. reported a case of F-MF in a 6-year-old boy. This lymphoma was associated with idiopathic follicular mucinosis.[30]

Taken together, previous reports suggest that F-MF is a rare and highly malignant MF, with a poor prognosis compared with classic MF. In adults, the head and neck are usually affected. It has distinct histological features and may or may not be associated with follicular mucinosis. F-MF has multiple overlapping not only clinical manifestations but also many histological aspects with chronic dermatitis. Therefore, it is often misdiagnosed or diagnosed late in advanced stages compared to traditional MF.[26,27,29,30]

Here, we report a case of F-MF in a middle-aged male patient. The clinicopathological features were addressed and the relevant literature was discussed.

2 | CASE REPORT

2.1 | Clinical features

A 52-year-old Saudi man presented to the Dermatology clinics (Armed Forces Hospitals Southern Region) in 2020 with recurrent pruritic scalp lesions for eight months. The

skin lesions developed suddenly and increased in size over time. There were no constitutional symptoms such as fever, night sweats, or weight loss. Also, there was no joint pain, muscle pain, or loss of appetite. The patient was otherwise healthy and had no history of drug use or other comorbidities. There was no family history of similar dermatological conditions.

Physical examination revealed multiple well-defined erythematous telangiectatic infiltrative nodules and plaques on the scalp and forehead associated with hair loss. There was a poikilodermatous patch over the skin of the chest. The clinical examination revealed no other abnormalities. A summary of these findings is shown in Figures 1 and 2. Clinical impressions included F-MF, follicular lymphomatoid papulosis, follicular eczema, and pseudolymphomatoid folliculitis. All laboratory tests including hematological (complete blood count with fractionated and peripheral blood) and biochemical (liver function, urea, electrolytes, and lactate dehydrogenase) parameters were within normal limits. A computed tomography scan showed multiple bilateral cervical lymph nodes, the largest measuring 1.1×0.9 cm, with preserved fatty hilum. Topical steroids slightly alleviated the itching, but this treatment did not improve the lesions. The patient disappeared and refused further treatment at our medical facility.

2.2 | Pathological findings

A 6-mm punch skin biopsy from the scalp lesions was performed. Sections showed mucin deposition in the follicular epithelium in both hematoxylin–eosin and PAS/Alcian blue-stained preparations. There was a dense, predominantly perifollicular lymphocytic infiltrate. The slightly hyperplastic follicular epithelium was infiltrated by atypical small to medium-sized lymphocytes (folliculotropism). Other mononuclear cells included eosinophils and histiocytes. There was epidermal thinning. Epidermotropic lymphocytes were absent. Mucin deposition occurred

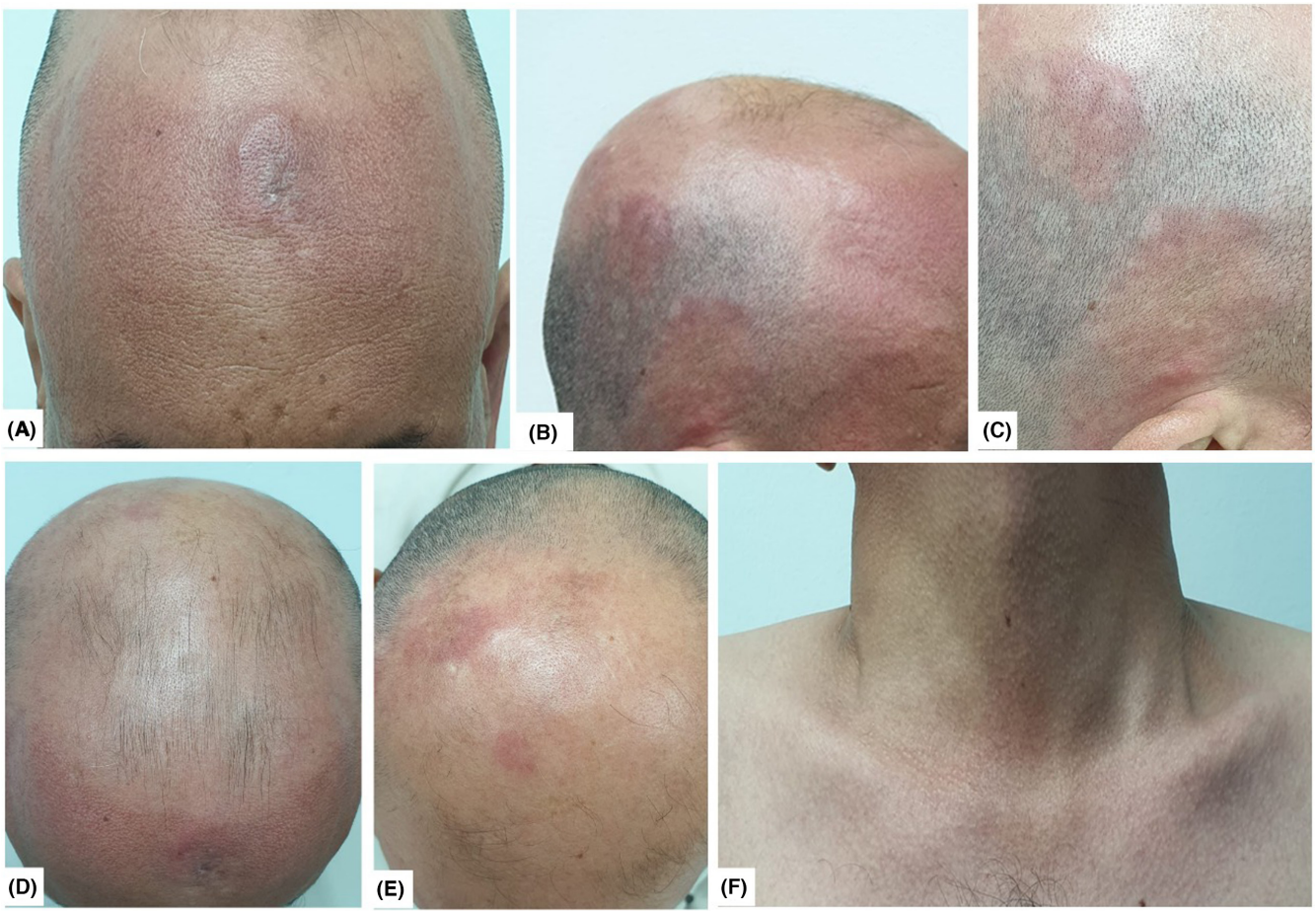

FIGURE 1 Clinical findings of follicular mycosis fungoides of the scalp (A)- This image shows a well-defined erythematous non-scaly infiltrative plaque across the forehead with poikilodermatous changes. (B, C) This lateral view of the patient's face shows multiple distinct erythematous non-scaly alopecic patches over the temporal side of the scalp. (D, E) This image of the patient's scalp shows multiple erythematous patches with poikilodermatous changes over the vertex. (F) This image of the patient's upper chest shows poikilodermatous changes.

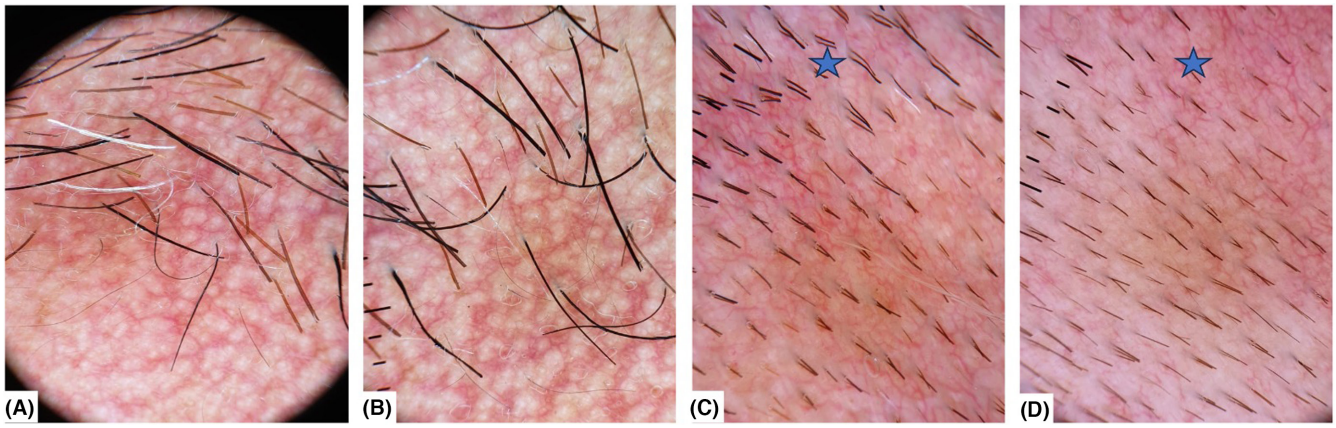

FIGURE 2 Clinical findings of folliculotropic mycosis fungoides of the scalp and chest. (A–C). These are dermoscopy images of the patient's skin lesions showing areas of hypopigmentation, hyperpigmentation, telangiectasia, and atrophy associated with terminal hair thinning. (D) This dermoscopy image shows a comparison of diseased and normal skin.

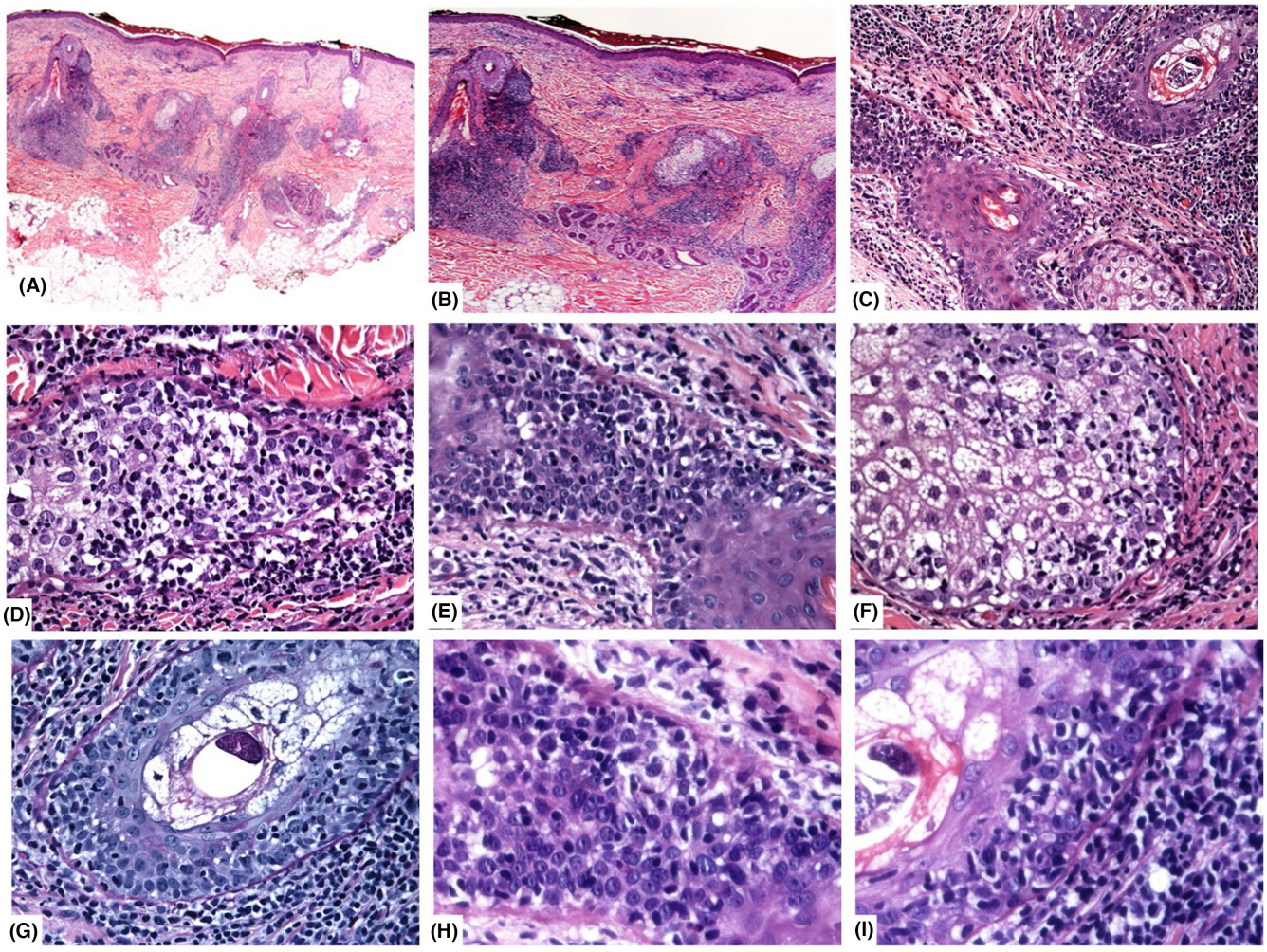

FIGURE 3 Histological features of follicular mycosis fungoides. (A, B) Dense superficial and deep dermal lymphocytic infiltrate with a predominantly perifollicular/folliculocentric distribution extending into the mid-dermis. Atypical lymphocytes are located along the basal cell layer of the hair follicle epithelium. Some neoplastic lymphocytes are surrounded by a halo. Although there is epidermal thinning, there is no atypia or epidermotropism, or Pautrier microabscesses. The interfollicular epidermis is not involved. (hematoxylin and eosin staining, original magnification, A:×20, B:×40). (C, D) Exocytosis of small and medium-sized hyperchromatic lymphocytes into the follicular epithelium of the bulbar and isthmic portions of the hair follicle with disproportionate spongiosis and destruction of the hair follicles. The follicular epithelium is focally spongiotic. The sebaceous epithelium is also infiltrated by the atypical lymphocytes (hematoxylin–eosin stain, original magnification, C: ×200, D: ×400, E–G:×400, and H–I:×600).

in the dermal interstitial spaces and around the hair follicles (PAS/Alcian blue spots). Immunophenotyping revealed a dense dermal (mainly perifollicular) CD3- and CD4-positive lymphocytic infiltrate. There were rare CD8-positive cutaneous T lymphocytes. CD4:CD8 ratio was >7:1. SomeCD20-positive lymphocytes were present. Atypical large CD30-positive cells were absent. The number of CD2-positive, CD5-positive, and CD7-positive T cells decreased. Molecular analysis was not performed. A summary of these results is shown in Figures 3 and 4.

3 | DISCUSSION

MF is the most common form of cutaneous T-cell lymphoma, accounting for 50% of all primary cutaneous lymphomas.[4,5] MF includes several variants based on clinical and immunohistological features.[1,31] Some clinical variants of MF, such as bullous MF and hyperpigmented or hypopigmented MF, exhibit clinical behavior similar to classic MF. Therefore, they are not considered separately. In contrast, some variants of MF, such as F-MF, pagetoid reticulosis, and granulomatous slack skin have distinctive clinicopathological features and are therefore considered as distinct entities.[4,5,28,31]

F-MF is a highly aggressive subtype of MF, and patients usually require aggressive intervention in contrast to classic MF.[28] The gender distribution of F-MF shows a 3:1 male-to-female ratio and a mean age of 55 years. F-MF is very rare in adolescents and children, with only a small number of cases described in the literature.[19,29]

The clinical features of the case reported here are consistent with previous studies.[14,26–28] Bonta et al. reported the case of a 44-year-old male patient who suffered from a generalized pruritic eczematous rash. The patient developed a rapidly progressive F-MF in several areas including the scalp, eyebrows, and axilla. This was associated with follicular mucinosis, alopecia, and lymphomatous involvement of the inguinal lymph nodes. Histological examination of the skin biopsy revealed follicular mucinosis, folliculotropism with atypical cells, and intrafollicular Pautrier'smicroabscesses.[14]

The histological differential diagnosis of the case presented here encompasses follicular lymphomatoid papulosis, follicular eczema, and pseudolymphomatous folliculitis. Follicular lymphomatoid papulosis is characterized clinically by the "waxing and waning" nature of skin lesions and histologically by the presence of eosinophils and expression of CD30 protein.[17,32] Follicular eczema is characterized by marked spongiosis of the interfollicular epidermis and lack of lymphocytic atypia. Pseudolymphomatous folliculitis, which may be drug-induced, is separated from F-MF by the presence

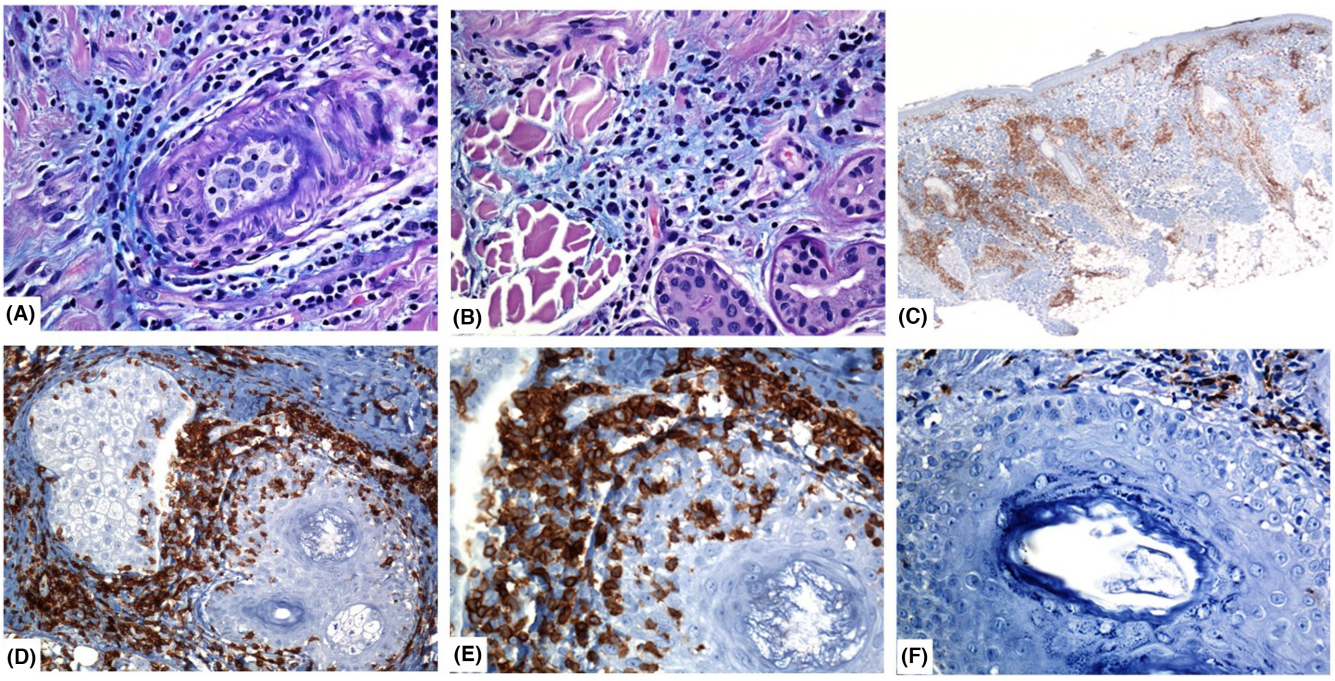

FIGURE 4 Ancillary studies in folliculotropic mycosis fungoides. (A, B) Examination of PAS/Alcian blue stained sections reveals mucin deposition in the hair follicles and the interstitial spaces (PAS/Alcian blue, original magnification, A, B: ×400). (C–E) Dense CD4-positive perifollicular lymphoid aggregates with marked infiltration of the follicular epithelium (folliculotropism) by small to medium-sized T- T-lymphocytes (original magnification, C: ×20, D:×200 and E:×400). (F): Minimal CD8-positive T- T-lymphocytes are seen (original magnification, F:×400).

of lymphoid follicles with germinal centers. The folliculotropic infiltrates are predominantly CD20-positive and admixed with S100, and CD1a-positive cells.[16] Some experts in the field of dermatopathology (Gerami and Guitart, and Mitteldorf) have proposed five histomorphologic patterns for F-MF including a "prototypical" pattern with intact hair follicles, folliculotropism with or without follicular mucinosis, eosinophilic folliculitis, basaloid folliculolymphoid hyperplasia with folliculotropism, granulomatous dermatitis associated with follicular destruction, and follicular cysts with folliculotropism.[16,23] Consistent with other studies, we found mucin deposition in the follicular epithelium. Mucin deposition represents the response of the follicular epithelium of the host to harmful agents and is associated with a variety of conditions including follicular eczema, granulomatous rosacea, Ofuji's disease, contact dermatitis, F-MF, and angiolymphoid hyperplasia with eosinophilia. These pathological conditions are collectively grouped under the term"alopecia mucinosa or follicular mucinosis." Some authorities consider follicular mucinosis as an "abortive cutaneous lymphoma."[4,5,28]

In conclusion, F-MF is a rare and under-recognized variant of MF. Salient clinicopathologic findings include frequent head and neck involvement, folliculotropism, nuclear atypia, and mucin deposition in the follicular epithelium. The prognosis of FTMF is poor compared to classic MF. The 10-year survival rate for early-stage disease is 82% and the 15-year survival rate is 42%. The prognosis for late disease is similar to classic MF (91% both at 5 and 10 years).[29] The diagnosis of F-MF requires a high degree of suspicion by both the dermatologist and dermatopathologist.

AUTHOR CONTRIBUTIONS

Majed Saleh Aldayhum: Methodology; resources; supervision; writing – review and editing. **Mohammed Saad Alshahrani:** Resources; supervision; visualization; writing – review and editing. **Mahmoud Rezk A. Hussein:** Formal analysis; software; supervision; validation; writing – original draft; writing – review and editing. **Abdulmajeed Saad Alshahrani:** Methodology; software; writing – original draft. **Toka M. R. Hussein**: Critical revision of the manuscript and textual review.

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None to declare.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

All data and materials are included inside the manuscript.

ETHICS STATEMENT

Ethics approval was received for this article.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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