Folliculotropic mycosis fungoides associated with follicular mucinosis: a case report and minireview

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October 5, 2023

INTRODUCTION

Mycosis fungoides: Mycosis fungoides (MF) is a primary cutaneous T-cell lymphoma. It represents the most common type of extranodal non-Hodgkin lymphomas [12]. Follicular or folliculotropic MF (F-MF, also known as follicular T-cell lymphoma, follicular MF, MF-associated mucinosis, or pleiotropic MF) is an under-recognized subtype of MF. It is characterized histologically by folliculotropism (histologically analogous to epidermotropism) with malignant T cells, with or without associated follicular mucinosis[3]. In 2005, The WHO/EORTC considered F-MF as a variant of MF in their classification[4-7].

Mycosis fungoides in the Kingdom of Saudi Arabia: In the Kingdom of Saudi Arabia, few studies are available about MF and F-MF[1,8-12]. AlGhamdi et al examined the clinicopathologic features of MF in 43 cases of immunohistologically confirmed MF. The average age was 33.5 years was reviewed. The male-to-female ratio was 2:1. Most of the cases presented in an early-stage (I and II) MF. Most of the patients had classic MF and other subtypes included hypopigmented MF and other variants. The patients were followed up for a duration of 27.6 months. The follow-up data indicated that few patients recovered (9.5%) patients recovered; whereas the majority (83.3%) had persistent MF skin lesions. A single patient had the extracutaneous disease; whereas only two patients died of MF [8].

Al-Dawsari et al examined the surgical pathology records of Saudi patients from 1995 to 2014 at the Johns Hopkins Aramco Healthcare Center (Eastern Province of KSA). This medical facility is the healthcare provider for the employees working at Saudi Aramco company and their dependents in the Eastern Province of Saudi Arabia. The total number of primary skin tumors was 204 and out of them 22 cases were MF[10]. Albasri et al examined the pattern of skin cancer in the Madinah region of KSA. Among the 202 cancer cases examined in their series, there were 14 (6.8%) cases of MF. The mean age of the patients was 30.7 years with a male-to-female ratio of 11:3. The distribution of the MF skin lesions included: 4 cases (head and neck), 3 cases (upper limb), and 7 cases (lower limb) [11].

Alsaif et al described the Leser-Trelat sign (sudden appearance of seborrheic keratosis) in a 60-year-old Saudi male patient with MF. The lesions appeared on the face and back [12]. Alojail et reported the clinical features and treatment regimens in 34 cases of MF in KSA. The cases included both hyperpigmented (11 cases) and hypopigmented (21 cases) MF, poikilodermatous MF, and pagetoid reticulosis (a single, each). The treatment regimens included phototherapy Narrowband UVB (NB-UVB) in combination with topical corticosteroids, phototherapy NB-UVB in combination with the topical corticosteroid, and phototherapy NB-UVB with topical corticosteroid and systemic acitretin [1].

Alghubaywi et al examined all MF cases diagnosed at King Abdulaziz Medical City in KSA (January 2016

to July 2022). A total of 73 patients were included in their study. The incidence of MF was slightly higher in females (male to female ratio: 1: 1.3). The average age was 44 years. The most common MF subtypes included classic MF, followed by hypopigmented MF. Most of the cases were presented at an early-stage MF (IA, IB, and IIA). The treatment option was mainly in the form of topical steroids. Immunohistological staining of CD4+/CD8+ with CD8 predominance was common and this may reason for the favorable disease outcome [13]. These authors also indicated that MF was under-recognized with 20% of the patients with MF initially misdiagnosed as atopic dermatitis. The correct diagnosis of MF was rendered within a mean of 33 months from the time of presentation to the Dermatology clinics. The authors reasoned the delay in the diagnosis of MF the fact that chronic dermatitis and MF share several clinical manifestations such as the presence of pruritic, erythematous, scaly plaques [13]. A summary of the previous studies is shown in Table 1.

Follicular mucinosis: Follicular mucinosis, i.e. accumulation of mucin in the epithelium of the hair follicles can be either a primary idiopathic disorder or an associated event with several inflammatory conditions (such as chronic spongiotic dermatitis), benign or malignant neoplasms[14-16]. In 1957, Pinkus first described mucin deposits in the follicular epithelium (alopecia mucinosa) that are associated with folliculotropism, i.e., infiltration of the epithelial cells of the outer hair sheath by atypical lymphocytes[17]. In 1959, the term follicular mucinosis was introduced by Jablonska [18]. There are two clinical types of follicular mucinosis: idiopathic follicular mucinosis and lymphoma-related follicular mucinosis, i.e., F-MF. The latter can be separated from the classical MF on a clinical and histological basis[2,19,20]. Currently, there is no specific therapy for idiopathic follicular mucinosis and the skin lesions can resolve spontaneously within a period of 2 to 24. Some therapeutic options include steroids (topical, intralesional, and systemic steroids), photodynamic therapy, antimalarials, interferon, and dapson[21,22].

Folliculotropic mycosis fungoides: F-MF represents the most common non-classic variant of MF, representing approximately 10% of the cases of MF [23]. It usually shows a male predominance and most of the cases occur in adults [24]. Its clinical findings include follicle-based infiltrated erythematous grouped papules resembling acne or keratosis pilaris, patches, plaques, and tumor-like lesions with follicular accentuation [2,20,25]. Other clinical presentations include prurigo-like lesions, pseudotumors, lichen spinulosus-like lesions, rosacea-like lesions, and lupus tumidus-like plaques [26]. Pruritis is a common complaint and it is aggravated by superinfection by staphylococcus auras resulting in pyoderma [25]. The lesions of F-MF vary from solitary lesions to extensive lesions giving the appearance of a leonine face [23]. The head and neck region is the most commonly affected site. Other sites include the trunk, and the extremities [17]. The features of F-MF are seen in nearly 10% of the patients with MF [2,20,25]. The salient histological features of F-MF include perivascular and peri-adnexal dermal lymphocytic infiltrates with variable infiltration and destruction of the follicular epithelium by small, medium-sized, or large-sized lymphocytes with hyperconvoluted nuclei (cerebriform

nuclei). The epidermis is usually spared. Other histological findings include follicular mucinosis, Pautrier's Micro-abscess, follicular plugging, tagging of the atypical lymphocytes along the follicular epithelium, peri-eccrine infiltrate of atypical lymphocytes[23,26]. Immunohistochemistry usually reveals prominent CD3 positive infiltrate, with

a predominance of CD4 positive lymphocytes over rare CD8 positive T-cells. CD7 expression is reduced or completely lost. Molecular analysis (T-cell receptor-γ gene rearrangement) reveals a monoclonal T-cell population[23,26-28]. The therapeutic options in F-MF include photochemotherapy combined with interferon alpha-2a and retinoids. Other options include local radiotherapy, topical imiquimod, and total body electron beam irradiation [23].

Several F-MF case reports were presented in the literature. Monopoli et al described two adult patients with F-MF. The clinical manifestations included alopecia and follicular erythematous papules, and comedones and cysts, respectively. The histological findings included folliculotropic atypical T-cell infiltrate that extends to the epidermis. There was no associated mucinosis. Clonality analyses revealed the oligo/monoclonal nature of the T-cell lymphocytic infiltrate [27].

Rajalakshmi et al examined four cases of F-MF affecting the skin of the face. The mean age of the patients was

17.5 years and there were no differences in gender distribution. The lesions were in the form of hypopigmented patches or erythematous plaques. Two patients had associated alopecia. The salient histological finding included folliculotropism, mucin deposition around the hair follicles, lymphocyte tagging with haloes, atypical lymphocytes with hyperconvoluted/cerebriform nuclei, and infiltration of the eccrine and sebaceous glands by atypical lymphocytes. Other histological features included the presence of epithelioid cells, parakeratosis, and a prominent infiltrate of eosinophils [29]. Magro et al reported 6 cases of unilesional follicular MF. All the patients were males with a mean age of 28 years. The patients were presented with a solitary lesion on the face and scalp (five patients) and trunk (a single patient) that persisted for a few months. There were follicular prominence and alopecia. On histology, there was an atypical folliculotropic lymphocytic infiltrate associated with follicular mucinosis. Immunohistology revealed a high CD4: CD8 ratio and loss of CD7 expression. A single untreated case developed similar lesions over the skin of the thigh and buttock after 3-4 years [28]. F-MF usually occurs in adults with an average age at the time of diagnosis of 60 years [30]. F-MF is exceptionally rare in children and adolescents. Mantri et al reported a case of F-MF in a 16-year-old boy who presented with 6x7 cm plaque on the forehead for a 2-month duration. Immunohistological examination revealed dense atypical T-cell lymphocytes invading and destroying the hair follicles. Follicular mucinosis was also seen. Most of the neoplastic cells were CD4-positive T- T-lymphocytes with scarce CD8-positive T cells around the hair follicles. Treatment was in the form of a spot electron beam and the lesion completely resolved within 2 months [30]. Interestingly, Emge et al reported a case of F-MF in a 6-year-old boy. The lymphoma was associated with idiopathic follicular mucinosis[31].

Taken collectively, these previous reports indicated that F-MF is a rare and aggressive form of MF that has a worse prognosis compared to conventional MF. It usually affects the head and neck region in adults. It has distinct histological features and may or may not be associated with follicular mucinosis. F-MF has several clinical presentations and many histological faces. Therefore, it is often misdiagnosed, or diagnosed with much delay at an advanced stage as compared to the conventional MF.

Herein, we report a case of F-MF in a middle-aged male patient. To date and to be best of our knowledge, this is the first case of F-MF to be reported in the Southern region (Asir region) of the KSA. The clinicopathologic features were discussed.

CASE REPORT

Clinical features: A 52-year-old Saudi male presented to the Dermatology Clinic at the Armed Forces Hospitals Southern Region, KSA in 2020 with an eight-month history of recurrent itchy scalp lesions. These skin lesions developed suddenly and increased in size with time. There was no history of fever, night sweating, weight loss, joint pain, muscle pain, or loss of appetite. The patient was otherwise medically free with no history of taking medication or other comorbidities. There was no family history of similar dermatological problems.

Physical examination revealed multiple well-defined erythematous telangiectatic infiltrated nodules and plaques associated with hair loss over the scalp and forehead. 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. The clinical impressions included F-MF, follicular lymphomatoid papulosis, follicular eczema, and pseudolymphomatous folliculitis. All the laboratory investigations including hematological (complete blood cell count with differential and peripheral blood) and biochemical (liver function, urea, electrolyte, lactate dehydrogenase) parameters were within normal limits. CT scan revealed multiple bilateral cervical lymph nodes the largest measuring 1.1 x 0.9 cm with preserved fatty hilum. Although itching was slightly ameliorated with the application of topical steroids, the lesions did not improve on this treatment. The patient disappeared and refused any further treatment at our medical facility.

Pathological findings: A skin 6 mm punch biopsy was obtained. Sections show deposition of mucin in the follicular epithelium both in hematoxylin-eosin and PAS/Alcian blue-stained preparations. There was a dense predominantly perifollicular lymphoid infiltrate. folliculotropism with infiltration of the mildly hyperplastic follicular epithelium by atypical small-to-medium-sized lymphocytes infiltrating the follicular epithelium

was seen in all cases. The infiltrate was composed essentially of lymphocytes with few histiocytes but no eosinophils (Figure 2-A-F). Infiltration was accompanied by eosinophils and histiocytes at various rates. There was attenuation of the epidermis without atypia. There was no epidermotropism. Immunophenotyping revealed dense dermal (predominantly perifollicular) CD3 and CD4 positive lymphoid infiltrate (Figure 2-G-H). Occasional CD8-positive dermal T lymphocytes were seen (CD4: CD8 ratio was more than 7:1) (Figure 2-I). CD20 showed focal expression in some of the diffusely scattered lymphocytes. CD30 was negative. A summary of these findings is shown in Figure 3.

DISCUSSION

MF is the most common type of cutaneous T cell lymphoma accounting for 50% of all primary cutaneous lymphomas [4,5]. MF includes several variants based on the clinical and immunohistological characteristics [1 32]. Some clinical variants of MF such as bullous MF and hyperpigmented MF or hypopigmented MF have clinical behavior similar to that of the classic MF. Accordingly, they are not considered separately. In contrast, some variants of MF such as F-MF, pagetoid reticulosis, and granulomatous slack skin have distinctive clinicopathologic features and therefore are considered distinct entities [4,5,29,32].

F-MF is a very aggressive subtype of MF and usually, the patients need aggressive interventions in contrast to classic MF [29]. Gender distribution in F-MF shows a male-to-female ratio of 3:1 and a mean age of 55 years at the time of presentation. F-MF is very rare in adolescents and children with few cases being reported in the literature to date [20,30].

The clinical features of the case reported here concur with the previous studies [14,27-29]. Bonta et al reported a case of a 44-year-old male patient with a generalized pruritic eczematous eruption. The patient developed an aggressive, rapidly progressive F-MF involving the scalp, eyebrows, and axillae. This was associated with follicular mucinosis, alopecia, and lymphomatous involvement of the inguinal lymph node. Histological examination of the skin biopsy revealed follicular mucinosis, folliculotropism of atypical cells, and intrafollicular Pautrier's microabscesses [14].

The histological differential diagnoses in the case presented here revolved around follicular lymphomatoid papulosis, follicular eczema, and pseudolymphomatous folliculitis [18,33]. Follicular lymphomatoid papulosis (LyP) is characterized clinically by a "waxing and waning" of the skin lesions and histologically by the presence of eosinophils and expression of CD30 protein [18,33]. Follicular eczema is characterized by prominent spongiosis of the interfollicular epidermis and the lack of lymphocyte atypia. Pseudolymphomatous folliculitis that can be drug-induced is separated from F-MF by the presence of lymphoid follicles with germinal centers, and folliculotropic infiltrate is composed predominantly of CD3 positive cells admixed with CD20-positive, S100-positive, and CD1a-positive cells[17]. Some authorities in Dermatopathology (Gerami and Guitart, and Mitteldorf) proposed the presence of five histomorphologic patterns for F-MF including the "Prototypic" 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[17,24]. In agreement with other studies, we found the deposition of mucin in the follicular epithelium. Mucin deposition represents a response of the host follicular epithelium to injurious agents and can be encountered in several conditions such as follicular eczema, granulomatous rosacea, Ofuji's disease, contact dermatitis, F-MF, angiolymphoid hyperplasia with eosinophilia. Taken together, these pathological conditions were lumped under the terminology of "Alopecia mucinosa or Follicular mucinosis". Some authorities consider follicular mucinosis as an "abortive cutaneous lymphoma" [4,529].

To sum up, F-MF is a rare and under-recognized variant of MF. Its 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 classical MF. The early disease has 10 years survival of 82% and 42% by 15 years. The late disease has a similar prognosis as classical MF (91% at both 5 and 10 years) [30]The diagnosis of F-MF requires a high index of suspicion both on the part of the dermatologist and dermatopathologists.

Table 1: Previous studies about mycosis fungoides in the Kingdom of Saudi Arabia

Studies	Location of the study	Number of cases	Mean 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)	22 cases were MF out of 204 skin cancer cases	-	-	[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]

Figure and table legends

Table 1: Previous studies about mycosis fungoides in the Kingdom of Saudi Arabia

Figure 1: The clinical findings of folliculotropic mycosis fungoides of the scalp

(A)- This picture is showing well-defined erythematous non-scally infiltrated plaque over the forehead with poikilodermatous changes.

(B-C)- This side-picture of the face of the patient shows multiple well-defined erythematous non-scaly alopecic patches over the temporal side of the scalp.

(D-E)- This picture of the scalp of the patient shows multiple erythematous patches with poikilodermatous changes over the vertex.

(F) This picture of the upper chest of the patient shows poikilodermatous changes.

Figure 2: The clinical findings of folliculotropic mycosis fungoides of the scalp and chest

(A-C) These are dermoscopic pictures of the skin lesion of the patient showing areas of hypopigmentation, hyperpigmentation telangiectasia, and hypotrophy, and are associated with thinning of terminal hair.

(D) This dermoscopic picture shows the comparison of affected skin and normal skin.

Figure 3: Immunohistological features of folliculotropic mycosis fungoides.

(A-B) Superficial and deep dense dermal monotonous lymphocytic infiltrate with predominantly perifollicular/folliculocenteric distribution extending down into the mid-dermis. There is tagging of the lymphocyte

along the basal layer of the follicular epithelium, with some lymphocytes enclosed within haloes. There is the attenuation of the epidermis, but there is no atypia or epidermotropism, Pautrier microabscess formation., tagging, haloed lymphocytes, lymphocyte atypia, or pagetoid spread in the spinous layer. The interfollicular epidermis is not involved. (hematoxylin-eosin stain, original magnification, A:x20, and B:x40).

(C-D) Exocytosis of small to 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 (hematoxylin-eosin stain, original magnification, C-D: x400).

(E-F) A close-up examination of PAS/Alcian blue stained sections reveals mucin deposition in the hair follicles and the interstitial spaces (PAS/Alcian blue, original magnification, E-F: x400)

(G-H) Dense CD4 positive perifollicular lymphoid aggregates with marked infiltration of the follicular epithelium (folliculotropism) by small to medium-sized T- T-lymphocytes (original magnification, E: x20, and F:x400).

(I): Minimal CD8-positive T- T-lymphocytes are seen. The shift of the CD4 positive folliculotropic T-cells (H) to the CD8 (I) ratio favors the diagnosis of F-MF (original magnification, I:x400). The lack of epidermotropism should not deter dermatopathologists from considering F-MF as a diagnostic possibility.

Declarations

-Ethics approval and consent to participate: Enclosed.

-Consent for publication: Enclosed.

-Availability of data and material: All data and materials are included inside the manuscript.

-Competing interests: None to declare.

-Funding: None to declare.

-Authors' contributions: The authors equally contributed to the generation of this manuscript (conception and design, acquisition of data, analysis and Interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical analysis.

-Acknowledgements: None to declare

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