Folliculotropic Mycosis Fungoides: Clinical and Histologic Features in Five Patients

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Abstract

Background: Alopecia can be a manifestation of mycosis fungoides (MF); however, the prevalence is unknown. Aims: We sought to describe the clinicopathologic presentation of alopecia in patients with diagnosis of MF. Methods: A retrospective analysis of patients with biopsy-proven MF, who were evaluated at our cancer center from 2002 to 2012, was performed to identify patients with alopecia. Results: Five patients with alopecia were identified from reviewing of 157 patients with MF. The male:female ratio was 3:2, and the mean age of patients was 42.8 years. Two of these patients showed patchy hair loss on scalp which was clinically identical to alopecia areata. In remaining three patients, hair loss was seen in areas of MF lesions, and epidermal changes consisted of patch- and plaque-type lesions of MF, tumors, and follicular lesions (follicular MF) were also present. In two of these patients, lymphadenopathy without any visceral involvement was detected. Conclusions: Alopecia was observed in 5 (3.18%) patients with MF, which makes it a rare finding, which included alopecia areata-like patchy loss in 2 and alopecia within MF lesions in 3.

Key Words: Alopecia, folliculotropic mycosis fungoides, mycosis fungoides

Introduction

Primary cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of skin-homing T lymphocytes malignancies. Mycosis fungoides (MF) accounts for nearly 50% of all cases. The classic type of MF is characterized by infiltration of atypical T lymphocyte with cerebriform nuclei in the papillary dermis and evidence of epidermotropism (i.e., the presence of atypical T-cell lymphocytes in the epidermis without significant spongiosis). Classic MF typically exhibits slow progression in 1st year after diagnosis and rarely progresses to extracutaneous involvement or disease-related death. Alongside this classic type, three subtypes of MF have been recognized in the World Health Organization (WHO)-European Organization for Research and Treatment of Cancer (EORTC) classification of CTCL: A superficial, pagetoid Woringer-Kolopp type; a granulomatous slack skin disease; and a folliculotropic variant of MF (F-MF). F-MF is considered less common variant of MF which is characterized histologically by atypical T lymphocytes that preferentially infiltrate the follicular epithelium and the interfollicular epidermis is usually spared. Mucin deposition within the follicular epithelium (i.e., follicular mucinosis) may or may not be present in F-MF lesions. Furthermore, one study concluded that there is no any difference in the clinical presentation and behavior of F-MF with or without associated follicular mucinosis. Patients with conventional MF usually present with patch- or plaque-type lesions on sun-protected skin whereas patients with F-MF usually manifest with acniform lesions, grouped follicular papules, and indurated plaques that preferentially involve the head and neck areas. F-MF is considered to have a worse prognosis and more aggressive disease course than conventional MF. Due to the paucity of F-MF, data regarding detailed findings in these patients are

What was known?
Alopecia can be a manifestation of mycosis fungoides (MF); however, the prevalence is unknown. Alopecia is a typical consequence of folliculotropic variant of MF (F-MF), although due to the paucity of F-MF, data regarding detailed findings in these patients are limited.

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mainly based on case reports, and a few case series with limited follow-up times.\(^5\)

To evaluate alopecia and F-MF among patients with MF, we studied hereon 157 patients with MF referred to our institution from 2002 to 2012.

**Methods**

The study protocol was reviewed and approved by the Tehran University of Medical Sciences Research Center. We conducted a retrospective analysis of 157 patients with biopsy-proven MF, who were evaluated at our cancer center from 2002 to 2012. Clinical data collected included age at the onset of cutaneous symptoms leading to the diagnosis of MF, age at the onset of alopecia, sex, locations of alopecia, clinical presentation of alopecia, presence of lymphadenopathy and visceral involvement, and stage of MF at the time of diagnosis were also included. Patients with alopecia due to chemotherapy or radiation therapy and patients suffering from androgenic alopecia were excluded from the study.

Histology slides from available biopsy specimens were stained by hematoxylin and eosin and were reevaluated by our dermatopathologists. The presence of atypical T lymphocytes within the follicular epithelium (i.e., folliculotropism) and the presence of mucin within the follicular epithelium (i.e. follicular mucinosis) were evaluated in biopsy specimens. Immunohistochemical (IHC) studies of CD4\(^+\) and CD8\(^+\) cells were also recorded.

**Results**

In all, 157 patients (54 men and 103 women) with MF were evaluated for evidence of alopecia. The mean age of patients was 57.5 ± 17.75 (range 18–98) years. Lymphadenopathy was present in 62 patients; however, visceral involvement was detected in only three patients. Most of the patients were in Stage IIa and Stage Ib (36.9% and 27.4%, respectively).

Five (3.18%) patients with alopecia were identified from reviewing of 157 patients with MF. The male:female ratio was 3:2, and the mean age of patients was 42.8 years [Table 1]. Two of these patients showed patchy hair loss on scalp which was clinically identical to alopecia areata. In these patients, overt MF and F-MF lesions were not present within areas of baldness but were present elsewhere on their bodies and there were no epidermal changes in alopecic area except for mild erythema in one of them. In remaining three patients, hair loss was seen in areas of MF lesions and epidermal changes consisted of patch- and plaque-type lesions of MF, tumors and follicular lesions (F-MF) were also present [Figure 1]. In two of these patients, lymphadenopathy without any visceral involvement was detected. TNM stages, histologic and IHC findings [Figure 2] and other features of patients are summarized in Table 1.

**Discussion**

In the recent WHO-EORTC classification, F-MF has been determined as a rare variant of MF with distinct clinical and histological findings, treatment responses, and survival rates.\(^2,4\) The overall 5-year survival rate of F-MF has been estimated to vary from 60% to 87% compared with >90% 5-year survival rate for the classic patch- or plaque-type MF.\(^5\)

Hair loss was identified in only 5 (3.18%) of 157 patients with MF in our study. Although the prevalence of alopecia in MF was lower than expected, we distinguished two clinically different types of hair loss: (1) Hair loss clinically similar to alopecia areata, (2) hair loss within localized MF lesions. Regardless of the clinical presentation of alopecia, the existence of atypical T lymphocytes in the follicular epithelium or epidermis indicates that MF contributed to hair loss in these patients.\(^6\)

| Patients | Sex/age at diagnosis of MF | Age at diagnosis of alopecia | Location | Clinical presentation | Histology/IHC | Lymphadenopathy | Visceral involvement | Stage |
|----------|---------------------------|-----------------------------|----------|----------------------|---------------|-----------------|---------------------|-------|
| 1        | Male/66                   | 74                          | Scalp, trunk | Plaques, tumors with alopecia | Epidermotropism without folliculotropism P-CD4\(^+\) | No              | No                  | IIb   |
| 2        | Male/54                   | 55                          | Scalp     | Alopecia areata-like hair loss | Folliculotropism P-CD4\(^+\) | Yes             | No                  | IIA   |
| 3        | Female/36                 | 38                          | Scalp     | Alopecia areata-like hair loss | Folliculotropism P-CD4\(^+\) | No              | No                  | Ia    |
| 4        | Male/41                   | 46                          | Trunk, extremities | Follicular papules, plaques with alopecia | Folliculotropism with follicular mucinosis P-CD4\(^+\) | Yes             | No                  | IIA   |
| 5        | Female/64                 | 68                          | Trunk, extremities | Plaques and acneiform lesions with alopecia | Folliculotropism with follicular mucinosis P-CD4\(^+\) | Yes             | No                  | IIA   |

IHC: Immunohistochemical, MF: Mycosis fungoides, P-CD4\(^+\): Predominance of CD4\(^+\)
In our study, patients with alopecia and MF were predominantly male (male:female, 3:2) and had a mean age of 52.2 ± 13.4 years at diagnosis of MF, which is consistent with previous studies. However, we only selected F-MF patients among alopecic cases who had diagnosis of MF previously; hence, the total number of patients was limited.

The head and neck are usually spared in classical MF; however, they are predilection sites for F-MF involvement. In our study, in patients with alopecia areata-like hair loss, scalp was the most common site of alopecia; however, in other three patients, only one had scalp alopecia with concurrent plaque-type lesions and trunk was the predilection site for hair loss in regions of MF lesions. These findings are similar to some other case series reported in literature.

F-MF is clinically characterized by various cutaneous lesions such as follicular papules, alopecic plaques, acneiform or comedo-like lesions, excoriated nodules similar to prurigo nodularis, pustules, xanthomatous changes, and rarely diffuse erythroderma. In our series, 2 patients (1 male and 1 female) presented with alopecia areata-like hair loss and the only epidermal change was erythema in one of them. They were younger than patients with MF (mean age at diagnosis 46.5 ± 12.2 years) and alopecia was detected within initial years of diagnosis of MF in these patients. Therefore, alopecia may be a presenting sign of MF and multiple biopsies during the course of disease may help guide us to the correct diagnosis. In the study of Bi et al., in the series of 38 patients, 34% had patchy hair loss clinically resembling alopecia areata with predilection in scalp region.

In another three patients, indurated plaques were the most common findings along with other lesions such as tumors, follicular papules, and acneiform lesions. The mean age at the diagnosis of MF in these patients was 62.6 ± 14.7 years and the male:female ratio was 2:1. The course of the disease before diagnosis of alopecia in this group was more prolonged compared to those with alopecia areata-like hair loss.

In cases with alopecia areata-like hair loss, only limited lesions were observed on the scalp and face, but in other patients, scattered lesions were found on the trunk and extremities. These five patients included one patient with Stage Ib disease, three with Stage IIA, and one with Stage IIIb. Although, TNM classification does not meet exact staging criteria for F-MF patients. That is because of deeper infiltration in plaques of F-MF compared with classical MF.
In our series, the classic pattern of folliculotropic infiltration of atypical T-cells was the most frequent pattern (80% of subjects) which is consistent with the study of Demirkesen et al.\[10\].

This was the only pathologic feature in alopecia areata-like lesions. Although detection of atypical T lymphocytes within the follicular epithelium is the key pathologic feature for the diagnosis of F-MF, it should be kept in mind that nuclear atypia may be slight in some instances and these cells may be admixed with other inflammatory cells such as neutrophils, eosinophils, plasma cells, and even some multinucleated giant cells which may obscure the diagnosis of F-MF. The mucin deposition in follicular epithelium may be another diagnostic finding; however, it is not a constant feature.\[10,11\]

Prominent follicular mucinosis was seen in two of our patients with follicular papules and acneiform lesions. Epidermotropism of interfollicular epidermis without follicular involvement was detected in one patient with tumoral MF, although because of multiple lesions in this patient, maybe folliculotropism could have been found with additional biopsies from cutaneous lesions in different sites of the body.

The mechanism of hair loss in MF patients remains unclear; however, inflammatory damage by atypical T lymphocyte and natural killer cells to the follicular keratinocytes along with alterations in cytokines productions has been speculated to be the main cause of alopecia.\[12\]

Furthermore, antigen presentation may be important for T-cells activation, and interestingly, MF and alopecia areata are associated with similar Human Leukocyte Antigen - antigen D Related (HLA-DR) and DQ beta 1 (DQB) alleles, which could restrict antigen presentation.\[13,14\] Thus, T-cells in both disorders may be triggered by similar self-antigens or other agents. T-cells oligoclonality within alopecia areata lesions has also been observed.\[15\]

Another controversial issue is that whether hair loss with or without F-MF can be a prognostic factor in MF. In the study of Gerami et al., the 5- and 10-year overall survivals were comparable between F-MF and classic MF for disease stage less than or equal to IIa, and in stages greater than or equal to IIb, the overall survivals for classic MF and F-MF were also comparable. However, the 15-year overall survival was 91% and 41% for classic MF and F-MF, respectively.\[15\]

Conclusions

Alopecia was recognized in only 3.18% of MF patients in our study which makes it a rare finding. The clinical presentation of alopecia included patchy hair loss resembling alopecia areata and localized hair loss within existing MF lesions. Alopecia areata-like hair loss may occur during onset of MF; hence, clinical suspicion of F-MF is warranted. The alopecia areata and F-MF may have a common pathogenesis mediated by folliculotropic T lymphocytes, whether or not they are multiclonal or oligoclonal atypical lymphocytes.

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Conflicts of interest
There are no conflicts of interest.

What is new?
Alopecia was recognized in only 3.18% of mycosis fungoides (MF) patients in our study which makes it a rare finding. The clinical presentation of alopecia included patchy hair loss resembling alopecia areata and localized hair loss within existing MF lesions.

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