Mycosis Fungoides: A Clinicopathological Study of 60 Cases from a Tertiary Care Center

Saira Fatima, Sabeehuddin Siddiqui, Muhammad Usman Tariq, Hira Ishtiaque, Romana Idrees, Zubair Ahmed, Arsalan Ahmed

Abstract

Background: Mycosis fungoides (MF) is the most common primary cutaneous lymphoma. It affects usually the covered areas of the body in elderly males in 6th and 7th decades of life. Atypical dermal lymphoid infiltrate is seen along with epidermotropism. Nuclei of neoplastic cells are convoluted. The neoplastic cells demonstrate positivity for CD3 (Pan T) immunohistochemical stain. Majority show increased CD4 to CD8 ratio. The present study was done to study the clinicopathological features, which might be of help in reaching a correct diagnosis in these cases.

Materials and Methods: A retrospective descriptive study was conducted on 60 reported cases of MF. The retrieved slides were reviewed for clinical and histopathological features and immunohistochemical profile.

Results: The ages ranged from 20–84 years, mean age was 47 years. Majority (75%) of patients were male. Trunk and extremities were the sites most commonly affected. There was significant inverse correlation between epidermal thickness and tumor stage ($P = 0.02$). Thickened epidermis was seen in patch stage and thickness reduced with progressing stage. The intensity of dermal infiltrate and cell size was also statistically significantly linked to stage progression ($P < 0.001$ each). In addition, proliferation index also correlated significantly with tumor stage ($P = 0.002$).

Conclusion: Clinical information and histological features are equally important in the accurate diagnosis of MF. Papillary dermal fibrosis is a useful diagnostic clue. CD4:CD8 ratio is not increased in all cases; it may be decreased or remain unchanged.

Key Words: Histologic features, immunohistochemical profile, mycosis fungoides

Introduction

Primary cutaneous T-cell lymphoma comprises of a heterogeneous group of T-cell lymphomas and accounts for 4% of all Non-Hodgkin lymphomas. Its incidence rate in the US population was reported to be 7.7 per 1,000,000 person-years. Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL), accounting for 50% of them.

The clinical as well as histopathological diagnosis of MF, especially in the early stage, can be challenging in the face of overlapping features with inflammatory dermatoses plus the fact that patients usually have received multiple treatments. As a result, biopsy at a given point in time may be inconclusive. MF has been described as an indolent disease in its classic form, men being affected more than the women. The exact etiology is unknown. Genetic mutations, environmental factors such as microorganisms, occupational agents, etc. have been implicated in the pathogenesis.

MF usually presents in the 5th and 6th decades of life, but children and adolescents may also be affected. The genetic alterations detected in MF patients include a gain of DNA in regions of chromosomes 7 and 17 and loss of DNA in region of chromosomes 9 and 10. Other studies have found an association between MF and HLA Class II antigens. The tumor cells in MF have T-RM (Tissue Memory Cells) profile and this may explain their tendency to remain confined to the skin. On the other hand, Sézary syndrome has T-CM (Central Memory cell) profile and show spread to the regional lymph nodes and peripheral blood.

The classical case of MF manifests as erythematous scaly patches slowly progressing into plaques over a period of years and into nodules over a prolonged period.

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Definitive diagnosis in patch and early plaque stages remains the greatest source of referral skin biopsy cases. A large majority of the patients may have been treated as chronic eczema or psoriasis before being finally diagnosed as MF. A high index of clinical suspicion of MF allows a pathologist to look closely for subtleties. There has been a constant addition in clinical variants and parallel increase in the diversity of histopathological findings. Classically, MF cells have been described as moderately enlarged lymphocytes with convoluted nuclei and a marked tendency to localize in the basal layer of epidermis either singly or in collections (Pautrier’s microabscesses). At times, they may have perinuclear clear halo. Papillary dermal fibrosis has been described as another important feature. Morphological mimics often make cases difficult in the histologic diagnosis of MF and ancillary studies may be required for a definitive diagnosis.

There is extensively published literature on the epidemiology and clinicopathological features of MF in the western population, but data is limited in Asia, especially in south Asian countries. In Pakistan also, due to the lack of a central cancer registry, data is scarce. We present a study of 60 cases diagnosed as MF over a period of 10 years with an aim to describe clinicopathological features of these patients.

**Materials and Methods**

This was a descriptive study. Since this was a retrospective review of surgical pathology reports and slides, exemption from ethical approval was granted by the institution’s Ethics Review Committee (4656-Pat-ERC-17). We searched the Surgical Pathology database of the section of Histopathology through “Integrated Laboratory Management System (ILMS)” software for cases diagnosed as “Mycosis Fungoides” between January 2008 and December 2017. The slides of 65 cases stained with hematoxylin and eosin (H and E) and immunohistochemical (IHC) stains on glass slides were reviewed by two pathologists (Saira F and Tariq MU). Inclusion criteria were the presence of epidermotropism by atypical lymphoid cells and CD3 positive atypical lymphoid infiltrate in the dermis. Post-treatment cases and those with fixation and processing artifacts were excluded. Finally, 60 cases met the inclusion criteria and were included.

Clinical information regarding age, sex, distribution, biopsy site, and presenting complaints was obtained from the pathology reports. Slides were reassessed for histological features which were broadly divided into epidermal and dermal features. The epidermal features included degree of epidermal thickness, intensity and pattern of epidermotropism, the presence of spongiosis, parakeratosis, basal vacuolar damage, Pautrier’s microabscesses, and mucinous change in hair follicles. The dermal features included the degree of dermal fibrosis, intensity of dermal infiltrate, predominant cell size of atypical lymphoid infiltrate, the percentage of large cells, periannexal distribution, pigment incontinence, granuloma formation, and histologic stage. Expression of CD3, CD4, and CD8 immunohistochemical stains by atypical lymphoid cells and their ratio (CD4:CD8) was assessed in all cases. Ki-67 (Mib-1) index, CD5 and CD30 IHC expression by atypical cells was assessed in cases where these had been performed. Prospective IHC staining was not performed.

Descriptive statistical analysis of quantitative and qualitative variables was performed. The mean and the standard deviation were calculated for age, Ki-67 (Mib-1) index, and percentage of large cells in atypical lymphoid infiltrate. Frequency and percentages were calculated for different clinical presentations, and histological and IHC features. Pearson Chi-Square and ANOVA tests were applied to determine whether clinical, histological, and IHC features differed in different histologic stages of the disease. *P* value < 0.05 was considered statistically significant.

**Results**

A total of 60 patients were included in the study. The age of patients ranged between 20 and 84 years with mean age of 47 years. The majority of patients were male (75%). Affected sites were known in 32 cases. Trunk (43.75%) and extremities (37.5%) were the most common sites affected. The face was involved in 12.5% and hands in 15.6% cases.

**Clinical presentation**

The most common presentation was erythema (63%), mainly generalized followed by scaliness (57%) and pruritis (47%). The rashes were clinically categorized as patch (62%), plaque (28%), and nodule (10%). Skin ulceration was seen in 15% cases. Alopecia, photosensitivity, keratoderma and nail changes were less common. Systemic symptoms such as weight loss and lymphadenopathy were present in 5 cases [Table 1].

**Histopathological features**

The pathological findings were broadly divided into two groups, epidermal and dermal. Increased epidermal thickness was seen in large majority of cases (87%), including psoriasiform in 13%. Epidermal thinning was present in 13% of cases [Table 2]. Epidermotropism was present in all cases; it was mild in 53% and moderate in 47% [Figures 1 and 2]. Mucinous change was seen in 3 (5%) cases. Dermal features were subdivided as the degree of inflammatory infiltrate, cell size, and perianexal distribution [Table 3]. The degree of papillary dermal fibrosis was also noted [Figures 3 and 4].
Unusual histological patterns included band-like infiltrate (27%), followed by pityriasis lichenoides chronica-like change (6.7%) and verruciform hyperplasia (5%). A poikilodermatous pattern was rarely observed (3%). One case demonstrated a folliculotropic pattern [Figures 5 and 6]. Immunohistochemical profile was in accordance with the pattern reported in the literature. In 73% of cases, CD4 expression was increased. CD8 expression was increased in 15% cases. CD4:CD8 ratio was maintained in 12% of the cases [Figures 7, 8 and 9].

The pathological features that correlated with the stage were analyzed for statistical significance. Epidermal thickness correlated significantly ($P = 0.02$). Thickened epidermis was seen in patch stage and thickness reduced with progressing stage. The intensity of dermal infiltrate and cell size was also significantly linked to stage progression ($P < 0.001$ each). Small to intermediate-sized cells were most prevalent in the patch stage while medium-sized cells increased in the plaque stage. Large cells were found only in plaque and tumor stages. Mean age did not vary significantly with stage progression. Proliferation index correlated significantly with the stage ($P = 0.002$).

**Discussion**

MF is difficult to diagnose in the early stage. However, a detailed clinical history and inclusion of MF in the differential diagnosis by the physician alert the pathologist to the possibility and to the need to perform ancillary (immunohistochemistry) in order to reach a correct diagnosis. However, the gold standard remains the clinicopathological correlation with a good H and E slide. Immunophenotypical profile characteristically seen in plaque and tumor stages may not be evident in the early stage. A single biopsy during a particular stage may not yield conclusive results and a serial biopsy may be required. Early stage of MF is simulated by a variety of inflammatory dermatoses including eczema and psoriasis.

It is also difficult to differentiate MF from parapsoriasis. There are two types of parapsoriasis. Small plaque parapsoriasis (SPP) which shows nonspecific mild changes including parakeratosis, acanthosis, spongiosis, and mild perivascular lymphocytic infiltrate. It does not simulate MF as it lacks epidermotropism. These patients have benign course with no predisposition to develop T-cell lymphoma. Large plaque parapsoriasis (LPP) on the other hand, in a proportion of cases (7.5%–14% according to various studies), can progress to T-cell lymphoma including MF. It is difficult to differentiate between LPP and MF clinically, histologically, and at molecular level.

The data on MF is scarce in Pakistan. In our study, mean age was 47 years, which was slightly lower than the 55–60 years reported by most studies. Anza et al. from India observed peaks at 41–50 and 61–70 years. In our study, no child was affected which might be due to limited number of cases. Male to female ratio was 3:1 in our study. Maha et al. from Oman reported a M:F ratio of 1.9:1, while Vonne et al. from Sweden reported a ratio of 1.6:1. An Indian study by Anza et al. described a M:F ratio of 2.5:1, which was closer to that seen in our study.
Our study showed that majority of the patients clinically presented with an erythematous patch followed by plaque. Only 10% had nodules at presentation. Anza et al.\cite{18} reported plaque as the commonest lesion, either alone or in combination. Yonne et al.\cite{20} also reported plaque as the commonest presentation. On the other hand, a study by Maha et al.\cite{19} in Saudi patients reported patch as the commonest lesion. The most frequent site of involvement in our study was trunk (44%) followed by extremities (37%). The face was affected in 12% and hands in 15% of the patients. Anza et al.\cite{18} described similar results.

### Histopathological features

Parakeratosis was present in 67% cases. Epidermal thickness was increased in the majority (87%) of the patients, a finding similar to that reported by Anza et al.\cite{18} A statistically significant ($P = 0.012$) inverse relationship was found between the thickness and stage. There was

| Dermal feature                      | Frequency | Percentage |
|-------------------------------------|-----------|------------|
| Intensity of dermal infiltrate      |           |            |
| Mild                                | 18        | 30         |
| Moderate                            | 33        | 55         |
| Marked                              | 09        | 15         |
| Cell size of dermal infiltrate      |           |            |
| Small and intermediate              | 35        | 58.3       |
| Intermediate                        | 20        | 33.3       |
| Intermediate and large              | 05        | 8.3        |
| Histologic stage                    |           |            |
| Patch                               | 40        | 66.7       |
| Plaque                              | 17        | 28.3       |
| Tumor                               | 03        | 5          |
| Degree of dermal fibrosis           |           |            |
| Mild                                | 34        | 56.7       |
| Marked                              | 26        | 43.3       |
| Periadnexal distribution            | 45        | 75         |
| Pigment incontinence                | 18        | 30         |
| Granuloma formation                 | 02        | 3.3        |

\cite{18,19,20}
a progressive decline in epidermal thickness as stage progressed from 92% in the patch and 82% in the plaque stages to 33% in tumor stage. Psoriasiform hyperplasia was seen in patch and plaque stages but was absent in tumor stage cases. Christine et al.\cite{3} described focal epidermal hyperplasia in plaque stage. Plaza et al.\cite{21} observed that epidermal acanthosis increased from patch to plaque stage. Epidermotropism was present in all our cases. It was most prevalent in the patch stage (66%) and declined with progression of stage from 28% in plaque stage to 5% in tumor stage. However, this relationship was not significant statistically. Most common patterns of epidermotropism were scattered individual cells (68%) followed by a mixture of individual cells and small clusters (32%). Pautrier’s abscesses were seen in 28%. Arafah et al.\cite{19} observed significant ($P < 0.05$) relationship between the basal alignment of neoplastic cells and Pautrier’s microabscesses in the diagnosis of MF. Christine et al.\cite{3} found focal parakeratosis and lymphocytes along the basal layer of the epidermis as a helpful clue to patch stage MF. Epidermotropism was described in 96% of patch stage MF by Massone et al.\cite{22} They also observed a disproportionate number of lymphocytes without spongiosis. Arafah et al.\cite{19} found that basal alignment had high sensitivity and moderate specificity. Combination of Pautrier’s microabscesses and basal lymphocytes correlated significantly with MF and a higher likelihood of MF was reported when these both parameters were positive. Basal alignment of lymphocytes as an important finding of MF has been reported in 23% to as high as 79% cases in patch or plaque stage by different authors.\cite{13}

**Dermal changes**

The most consistent dermal feature found in all cases in our study was papillary dermal fibrosis which ranged from mild to severe in intensity. This microscopic feature has been consistently described in the literature and has emerged as one of the key features in the diagnosis of early MF.\cite{23} A study by Anza et al.\cite{18} had similar observations as ours. In the our study, mild fibrosis was present in 57%. Arafah et al.\cite{19} reported a significant correlation between dermal fibrosis and early MF.
The intensity of the dermal infiltrate in our study increased with the histological stage. Only mild to moderate infiltrate was present in the patch stage while plaque and tumor stages had moderate to severe degree of lymphocytic infiltrate. This was statistically significant ($P < 0.0001$). Similarly, there was statistically significant correlation between the cell size of dermal lymphocytes and the stage ($P < 0.0001$). Small to medium-sized cells dominated in the patch stage. Larger cells started to appear in the plaque stage and were the only cells in the tumor stage. Cytological atypia in the form of convoluted nuclei has been reported in the literature as the feature to look for while considering a diagnosis of early MF.\(^{(21)}\) Other patterns of atypia may include hyperchromasia as compared with the surrounding lymphocytes, scant cytoplasm, and perinuclear halos.\(^{(24,25)}\) However, Massone et al. and Pincus\(^{(22,23)}\) reported a lack of atypia in the majority of the cases, atypia was found in only 9% of their cases. Hence, diagnosis depends more upon architectural rather than cytological atypia.\(^{(26,27)}\) Periadnexal distribution of lymphoid cells correlated significantly with the stage in our study ($P < 0.001$). This was seen in 62% of the patch stage and in the cases of plaque and tumor stages. In one case, infiltrate was only perifollicular with a concomitant mucinous change in the hair follicle. Mucinous change of hair follicle was observed in two additional cases. Granuloma formation was seen in two cases.

**Immunohistochemical profile**

The IHC profile of dermal lymphoid infiltrate in our study matched the reported pattern, i.e., predominantly CD4 positive and CD8 negative population was seen in 73% and was more common in patch and plaque stages. Dual positivity was found in 12%. Reverse pattern, i.e., CD8+/CD4- was present in 15%. Tumor stage showed all three staining profiles. In a study from India by Anza et al.,\(^{(18)}\) immunohistochemical positivity was similar to ours. Of their cases, 65% showed a CD4+/CD8- pattern.

Inflammatory dermatoses demonstrate a mixture of CD4 and CD8 positive cells in a proportion of approximately 3–4:1.\(^{(28)}\) The presence of predominant CD4 lymphocytes in conjunction with epidermotropism, dermal fibrosis, and cytological atypia favor MF over an inflammatory dermatosis. There are rare reports of CD8+ MF.\(^{(29,30)}\) The behavior of these cases varied from study to study and Pincus\(^{(23)}\) concluded that CD8+ MF cases are not associated with a poorer prognosis compared to their CD4+/CD8-MF. They also found that in early MF, IHC studies are usually not helpful. A study by Hodak et al.\(^{(31)}\) reported 12% cases of MF with dual CD4-/CD8- cases in their 140 patients. However, there was no difference in prognosis. The utility of loss of CD7 in MF has not been accepted by all the authors and varying results have been reported. It is a well-known fact that loss of expression of CD7 is also observed in inflammatory dermatoses.\(^{(32)}\) Rare cases of MF with CD20 expression have been found in the literature with a variable clinical course.\(^{(3)}\) However, CD3 expression was present in these cases. Virmani et al.\(^{(33)}\) noted that sequential biopsies with increased CD20 positivity correlated with disease progression. In our study, Ki 67 proportion showed significant correlation with stage ($P < 0.002$). A greater Mib-1 labeling was seen in plaque (28%) vs. patch (16%) stage. Tumor stage showed the highest labeling (53%). Majority of the cases showed negative results with CD30 stain. A low value of less than 5% cases showed CD30 positivity in non-transformed cases.\(^{(22)}\) A higher percentage of CD30+ dermal lymphocytes was seen in higher stages. In early stage of MF, the presence of >50% CD30+ cells does not impart bad prognosis. Hence, CD30 positivity and prognosis vary with the stage.\(^{(34)}\)

**Conclusion**

The diagnosis of MF in the early stage depends on a combination of clinical findings and histological features, the latter includes presence of papillary dermal fibrosis, basally aligned lymphocytes having convoluted nuclei and perinuclear halos. In more advanced stages, classical features of MF are prominent with the formation of Pautrier’s microabscesses. IHC studies in the early stages should also be interpreted with caution.

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**Conflicts of interest**

There are no conflicts of interest.

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