Early mycosis fungoides vs. inflammatory mimics: How reliable is histology?

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ABSTRACT

Background: The histologic diagnosis of early mycosis fungoides (MF) and its distinction from inflammatory dermatoses is challenging, owing to the overlap of several features. **Aims:** 1) To assess the efficacy of histologic criteria to diagnose early MF, 2) to study their utility in differentiating inflammatory mimics of MF. **Methods:** We retrospectively reviewed slides from 50 cases clinically/histologically suspicious for MF. The diagnoses were established based on response to treatment and follow-up. The slides were analyzed double-blinded by two observers independently. Twenty-eight histologic criteria were assessed and each criterion was graded. Univariate analysis was performed on the results. **Results:** There were 17 cases of MF and 33 of inflammatory dermatoses. Of the 28 criteria, the following 15 achieved significance on univariate analysis: disproportionate epidermotropism, tagging of lymphocytes along the basal layer, haloed lymphocytes, convoluted lymphocytes, Pautrier's abscesses, larger epidermal lymphocytes, wiry dermal collagen, absence of edema, eccrine infiltration, folliculotropism, follicular mucin, involvement of papillary and reticular dermis, monomorphous infiltrates, and atypia of dermal lymphocytes. The criteria that were 100% specific for MF included convoluted lymphocytes, eccrine infiltration, and follicular mucin. Absence of edema was 100% sensitive and specific in distinguishing MF from its inflammatory mimics. **Conclusions:** A combination of histologic patterns and cytology of lymphocytes is reliable in distinguishing MF from inflammatory dermatoses. No single criterion is effective in achieving this. Rather than merely recording the presence or absence of a criterion, grading each of them adds objectivity to the diagnosis.

Key Words: Histology, Mycosis fungoides, Patch stage

INTRODUCTION

Mycosis fungoides (MF) is a cutaneous T-cell lymphoma. Traditionally, three stages have been described - the patch, plaque, and tumor. While the plaque and tumor stages are diagnosed with relative ease, the diagnosis of MF in the patch stage continues to be a vexing issue to both clinicians and pathologists alike. The patch stage has a wide clinical spectrum that overlaps with several inflammatory dermatoses, and it carries an excellent prognosis with conservative management.[1-3] Till about two decades ago, there were no morphologic criteria that were deemed sensitive enough to diagnose such early lesions. Many authors considered them to be 'pre-malignant' and used (some still do) confusing terms like small plaque and large plaque parapsoriasis to denote these lesions.[4,5] Following pioneering work by Sanchez and Bernard Ackerman, the criteria for diagnosis of patch-stage MF have been put forth and evaluated for sensitivity and specificity in several studies.[6] Unfortunately, no single criterion is strong enough to accomplish this task. But the combination of these histologic criteria with clinical and immunohistochemical data is found to have sensitivities of 80% and above in several studies.[6,7] Analysis of clonality by T-cell receptor gene rearrangements in the epidermotropic lymphocytes and also sometimes in the peripheral blood and lymph

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nodes, clinches the diagnosis.[7,8]

In the recent past, there have been several studies stressing the histological parameters that help in diagnosing MF.[1,2,7,9-11] Despite this, there has been no consensus regarding the histological criteria for a definite diagnosis of patch stage of MF. The International Society for Cutaneous Lymphoma (ICSL) has integrated the histologic, immunophenotype, and molecular findings of various studies and proposed a score to bring uniformity.[12] The data on MF from India is limited mainly to case reports.[13,14] There have been no studies in the Indian context relating to this topic. The paucity and non-availability of resources for performing confirmatory tests stresses the need for a meticulous histologic evaluation. Most pathologists are not yet comfortable making this diagnosis, therefore we undertook this study to assess the efficacy of histologic criteria for diagnosis of MF.

METHODS

We retrospectively reviewed slides from 50 skin biopsies that were clinically/histologically suspicious for MF, which were sent to the Department of Pathology between the years 2001 and 2006. Of the 50 cases studied, 17 were MF and 33 were inflammatory lesions. The diagnoses were established based on response to treatment, repeat biopsies (where present), staging, and follow-up. Where there were biopsies from multiple sites, only the patch-stage lesions were chosen. The slides were mixed randomly by a person not participating in the study and analyzed double-blinded by two observers independently. Twenty-eight histologic criteria were assessed, and each criterion was graded semiquantitatively as depicted in the table of results. These criteria were defined based on previous studies prior to evaluating the slides in order to minimize inter- and intra-observer variations.[2,12,15] Features scoring 6 to 10 or more in cases of numeric values for cell counts were taken for statistical analysis. Statistically significant results are highlighted.

We used the following definition of the various histologic criteria:

a) *Spongiosis:* Presence of widened intercellular spaces with stretched intercellular bridges with/without formation of microvesicles containing plasma.

b) *Epidermotropism:* Lymphocytes disposed as solitary units within the basal layer of the epidermis in foci.

c) *Tagging:* Four or more lymphoid cells closely opposed to basal keratinocytes in a linear arrangement.

d) *Pagetoid spread:* Epidermotropic lymphoid cells occupying the entire thickness of the epidermis.

e) *Pautrier's microabscess:* Collections of 4 or more lymphoid cells in the epidermis with no significant cytopathic changes in the surrounding keratinocytes.

f) *Haloed lymphocytes:* Single epidermotropic lymphocytes having no tendency to coalesce, separated from the surrounding keratinocytes by clear spaces.

g) *Disproportionate epidermotropism:* Epidermotropism as a function of spongiosis. Lymphocytes scattered in the epidermis in association with little or barely detectable spongiosis.

h) *Papillary dermal fibrosis (wiry collagen):* Thickened bundles of collagen in haphazard array in the papillary dermis.

i) *Monomorphous dermal infiltrate:* Cellular infiltrate composed of more than 75% of lymphoid cells.

j) *Atypia of dermal lymphocytes:* Lymphocytes showing high nuclear-cytoplasmic ratio with irregular, folded nuclear margins.

k) *Stuffed dermis:* Dermal papillae packed completely with lymphoid cells.

Statistical analysis

Data was tabulated and statistically analyzed using Minitab Release 15 package. A univariate analysis was performed on each criterion by Chi-square/Fischer's exact test. The *P* value, sensitivity, specificity, and positive predictive value were calculated for each of the parameters.

RESULTS

The results, including number of cases of MF and inflammatory dermatoses under each of the evaluated histologic features and their statistical analyses, are depicted in Table 1.

Of the 50 cases studied, 17 were classified as MF and 33 as inflammatory dermatoses. The common inflammatory mimics included pityriasis lichenoides, lichenoid purpura, contact/nummular dermatitis, and arthropod bite reactions.

The criteria which were 100% sensitive for MF include epidermotropism and absence of dermal edema. One hundred percent specificity was achieved by convoluted lymphocytes, infiltration of eccrine units, follicular mucin, folliculotropism of lymphocytes, and absence of dermal edema. Rest of the features were as evident in Table 1 and are discussed subsequently.

Table 1: Histologic features assessed in mycosis fungoides (MF; n = 17) and inflammatory dermatoses (Inflm; n = 33) with *P* value, sensitivity, and specificity for each parameter

Feature (with grading)	MF-17	Inflm-33	*P* value	Sensitivity	Specificity
Pattern: Spongiotic lichenoid	2	1	0.218		
Spongiotic psoriasiform	6	16	0.373		
Lichenoid psoriasiform	4	3	0.163		
Spon-pso-lichenoid	1	1	100		
Compact orthokeratosis	11	25	0.4		
Elongated parakeratosis	7	11	0.5		
Spongiosis (none/<10%/10-50%/>50%)	15	22	0.1		
Epidermotropism (40 x - none/1-5/6-10/>10)	17	4	0	100	87
Lymphocyte tagging (absent/focal/extensive)	16	4	0	96	87
Pagetoid spread (absent/present)	3	2	0.196		
Pautrier microabscess (absent/present)	7	1	0	41	96
Haloed lymphocytes (100 x - none/1-5/6-10/>10)	10	1	0	58	96
Disproportionate epidermotropism(absent/present)	14	2	0	82	93
Larger epidermal lymphocytes(100 x - none/1-5/6-10/>10)	12	1	0	70	96
Convoluted lymphocytes none/focal/extensive)	8	0	0	47	100
Mitoses (per 10 hpf - none/1-5/6-10/>10)	1	0	100		
Interface dermatitis (none/focal/extensive)	1	3	0.6		
Wiry collagen (none/focal/extensive)	9	3	0.001	52	90
Dermal edema (none/focal/extensive)	0	12	0.004	100	100
Eccrine infiltration (40 x - none/1-5/6-10/>10)	3	0	0.013	17	100
Mucin within follicle (none/focal/extensive)	3	0	0.013	17	100
Follicular infiltration (40 x - none/1-5/6-10/>10)	6	1	0.002	35	96
Involvement of papillary+reticular dermis	8	5	0.015	47	84
Monomorphous infiltrate	15	18	0.017	88	45
Eosinophils (40 x - none/focal/extensive)	4	10	0.613		
Plasma cells (40 x- none/1-5/6-10/>10)	1	3	0.692		
Extravasated RBCs (none/focal/extensive)	2	4	0.971		
Melanophages (none/focal/extensive)	4	6	0.654		
Atypia of dermal lymphocytes (none/focal/extensive)	10	1	0	58	96
Stuffed dermis (none/focal/extensive)	7	6	0.079		

DISCUSSION

The diagnosis of early/patch-stage MF has always posed a challenge to dermatologists and pathologists alike.[1-3] The subtle histologic changes of early MF often comprising of minimal lymphoid infiltrates show variable overlap with inflammatory mimics of MF such as pityriasis lichenoides chronica, drug eruptions, etc.[1,3] Although there have been many studies on early MF, there is a lack of consensus on what constitutes specific histologic criteria, leading to low agreement rate in reporting early MF among dermatopathologists.[2,10,12] Though immunophenotyping and clonality by T-cell receptor gene rearrangement clinch the diagnosis, they have failed to identify early lesions as immunophenotypic aberrations seen in advanced stages may not be evident in early lesions and molecular techniques detect only a certain percentage of cases with variable results.[10] Moreover, clonality may be present even in inflammatory lesions like pityriasis lichenoides chronica, and none of the molecular techniques may prove useful in differentiating this from MF.[16] In such cases, only the response to treatment and evolution of lesions on follow-up will help. Thus, light microscopy with clinical correlation and follow-up remains the gold standard for evaluating early lesions of MF.[10]

Mycosis fungoides is deemed to be rare in the Indian population. A reason for this may be the fact that the disease is underdiagnosed in the early stages. It has been documented that the hypopigmented variant of MF is quite common in the Asian population.[15] Such lesions often mimic pityriasis alba, leprosy, or vitiligo, which are more prevalent. The lack of clinical suspicion, coupled with limited experience in interpreting these biopsies, is

a major confounder. There are no Indian studies that have addressed the value of histologic criteria in such lesions. We have attempted to tackle this issue in the present study.

In our study we found epidermotropism in all 17 cases of MF (100%), whereas only 4/33 (12%) cases in the inflammatory group showed this feature. The commonest pattern of epidermotropism was the tagging of lymphocytes along the basal layer, which was observed in 96% of cases [Figure 1]. This finding agrees with the findings of Santucci *et al.* and Smoller *et al.*[2,9] At this point, one should also note that epidermotropism disproportionate to the degree of spongiosis is very useful. Spongiosis was seen in both MF and its mimics to varying extents, and its presence does not imply an inflammatory cause. Haloed lymphocytes were found in 58% of cases of MF and in only 3% of the inflammatory mimics, proving to be highly specific (96%) though less sensitive (58%), in concurrence with the findings of Ackerman and Smoller *et al.*[9,10] Pautrier's microabscesses were highly specific (96%) but had a low sensitivity (41%), which is reasonable as this feature is more often encountered in advanced stages of MF and our study included only the early lesions. Hence tagging is a more reliable feature in early MF.

Some authors claim the presence of larger, convoluted epidermal lymphocytes and the concomitant presence of atypia to be the most useful histopathologic markers of MF.[2]

We did not find these to be very sensitive [Refer Table 1]. We would like to stress that in early lesions of MF, it is architecture rather that cytology that guides us to the correct diagnosis.

Several important distinguishing factors emerged from this study. We observed that infiltration of eccrine units and follicular infundibula by lymphocytes were highly specific for MF (100% and 96% respectively). Infundibulotropism and sebaceotropism of lymphocytes are well known attributes of MF. Our findings highlight the concept that lymphocytes in MF are epitheliotropic and not just epidermotropic.[10] In two cases, we found the degree of folliculotropism of lymphocytes in far excess when compared to the rest of the epidermis. Diagnosis of early MF may be missed if we bank only on epidermotropism, and the adnexae are not keenly observed. We also found that the presence of follicular mucin is 100% specific for MF. The finding of mucin within the follicular unit together with an infundibulotropic lymphocytic infiltrate heightens the suspicion for MF.

An important clue to diagnosis was the presence of a monomorphous, deep dermal lymphoid infiltrate. In 47% of the cases, the infiltrate was seen in the papillary and reticular dermis showing a specificity of 84% as compared to a more superficial pattern of infiltration in the inflammatory mimics. The probable explanation for this is again the adnexotropism of lymphocytes that is well seen in MF.

At scanning magnification, all types of architectural patterns of epidermis and cellular infiltrate such as spongiotic-lichenoid, psoriasiform-lichenoid, and spongiotic-psoriasiform-lichenoid were observed in various combinations in MF, and no single pattern achieved statistical significance in discriminating from the non-MF group, as stated by authors preceding us.[1] Features such as elongated mounds of parakeratosis, interface dermatitis, and stuffed dermis did not achieve discriminatory statistical significance. We observed that a certain degree of interface dermatitis may be seen in MF also, and it should not lead one astray.

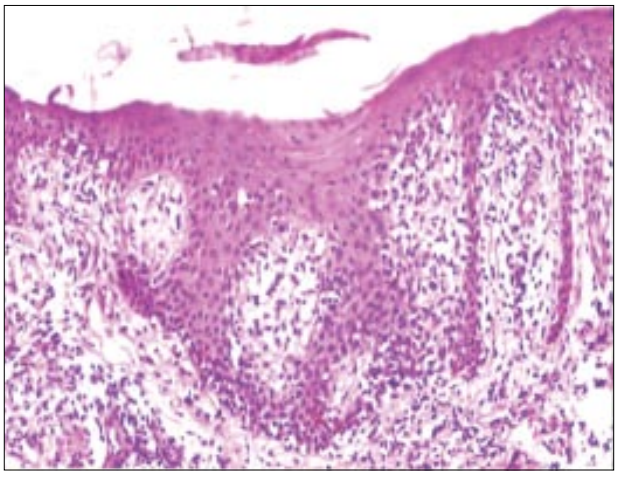

Figure 1: Tagging of lymphocytes in a linear array along the basal layer of the epidermis (H & E, ×200)

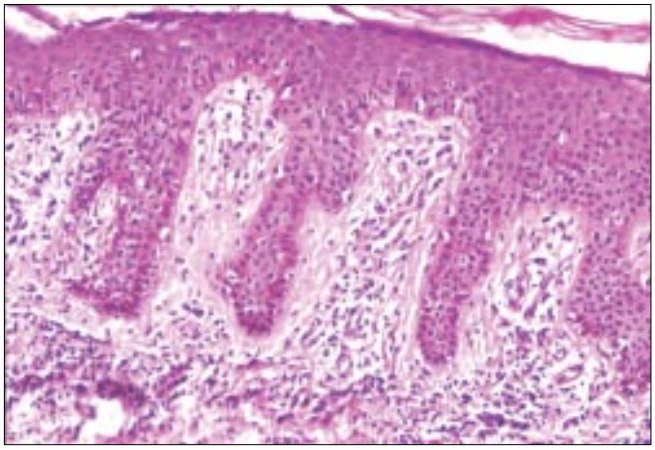

Figure 2: Thick, haphazardly oriented fibers of collagen in the papillary dermis accompanied by a monomorphous dermal lymphoid infiltrate. A few haloed lymphocytes are observed in the overlying epidermis (H & E, ×200)

Papillary dermal fibrosis/wiry collagen [Figure 2] was another significant and specific feature in MF. It was relatively rare in inflammatory dermatoses. While some authors have stated that dermal fibrosis is a characteristic feature of MF, others have refuted this saying that it is commonly seen in advanced lesions and not in early stages.[1,2,9,11] We have included both early and late patches in our study. When present, dermal fibrosis mirrors the chronicity of the infiltrate, a warning bell by itself.

One feature which achieved 100% specificity and sensitivity in our study was the absence of dermal edema. This is in stark contrast to other studies where dermal edema was neither sensitive nor specific.[10]

In the dermis, the presence of eosinophils, plasma cells, extravasated RBCs, and melanophages was found in a variable proportion of cases of MF and its mimics. On numerical grading, these features were more extensive in the mimics. Rather than merely documenting the presence or absence of a particular feature, it is more useful to semi-quantitatively grade each parameter, adding objectivity to the diagnosis. Also, numerical grading helps the eye to familiarize oneself with the multitude of patterns encountered, as the emphasis here is not on a single feature but on the right constellation of findings. We are still within the learning curve for diagnosing early MF at histology, and grading will help minimize inter- and intra-observer variability.

In the present study, we found that histology is quite reliable in picking up early MF. Disproportionate epidermotropism/epitheliotropism, tagging of lymphocytes, haloed lymphocytes, larger epidermal lymphocytes, convoluted lymphocytes, eccrine infiltration, follicular infiltration, absence of dermal edema, papillary dermal fibrosis and monomorphous lymphoid infiltrate were the histological features useful in discriminating MF from inflammatory skin diseases. This assumes significance in our population, where access to, and affordability for, immunohistochemical and clonality studies are limited. Of course, one cannot overemphasize the importance of making this diagnosis in the right clinical setting, with the right constellation of cyto-architectural features. One should also make an attempt to grade these features every time, which will help us appreciate the histology better. One should not be overenthusiastic in rendering a specific diagnosis every time, as there is always a significant gray zone. It is better to follow up these patients meticulously; and to carry out re-biopsy when necessary.

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