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Histopathologic Findings in Early Mycosis Fungoides with Prognostic Correlation

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ABSTRACT

Background: Mycosis fungoides (MF) is a primary cutaneous T-cell lymphoma that usually presents clinical indolent behavior, although some patients evolve towards advanced stages of the disease, despite adequate treatment, having therefore worse prognosis. The refinement of the prognostic evaluation of these patients is considered of interest.

Aim: Evaluate histopathological factors with prognosis importance.

Methods: We proceed a cross-sectional study based on the review of the first histopathological examinations of patients with early stage MF (IA and IB), with at least 5 years follow-up. Several histopathological variables were analyzed and related to progression of disease and death. Prevalence ratios and their respective confidence intervals were calculated as association measurements; a p value of 5% was adopted.

Results: Sixty-one patients, with medium follow-up of 8.2 years, presented 26.2% of staging progression and 6.6% of MF related death. Parakeratosis (PR: 2,636, p=0.03 e CI 95%: 1.1-6.0) and superficial and deep perivascular pattern of the lymphoid infiltrate (PR: 3.056, p=0.036 e CI 95% 1.4-6.5) were associated with disease progression and death (PR: 27.50, p=0.02 e CI 95%: 3.3-224.6). On the other hand, histopathological features usually related to poor prognosis, such as the presence of Pautrier's microabscesses, folliculotropism and enlarged nuclei atypical lymphocytes, were not associated with the outcomes studied.

Conclusion: Parakeratosis and a superficial and deep lymphoid infiltrate pattern may have prognostic value. Retrospective character and small sample are limitations of this study. These findings should be tested in prospective studies with different samples.

Keywords: Lymphoma, Lymphoma, T-cell, Cutaneous, Mycosis fungoides

INTRODUCTION

Mycosis fungoides (MF) is a low-grade malignant T-cell epidermotropic lymphoma that onsets on the skin. It is the most prevalent form of primary cutaneous T-cell lymphoma (CTCL), which accounts for approximately 50% to 65% of cases. The disease often takes an indolent course, but in approximately one-third of the patients, the disease progresses to an aggressive malignancy with a poor prognosis [1,2].

The staging classification system for MF is known as TNMB and it is based on the evaluation of skin involvement patterns (T), lymph node involvement (N), disease extension to other organs (M) and, finally, to peripheral blood (B). TNMB stage represents the main prognostic factor for patients with MF [3].

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Early-stage MF (Stages IA, IB and IIA), which represents the majority of the patients at the time of the diagnosis, shows a favorable prognosis, with 10-years specific survival rates of more than 95% for stage IA and about 80-85% for stage IB [4-7].

While the majority of patients with early-stage MF will not advance to late-stage disease, such progression may occur. Rates of progression may vary between 4-13% of patients with clinical stage IA and 21 to 27% with stage IB [5-9].

Therefore, it is essential to distinguish this group of patients that are at greater risk of having worse outcomes. It is of interest to investigate other possible factors capable of refining prognostic evaluation, besides the TNMB staging system.

Histopathological exams of patients diagnosed with early-stage MF from the Photo dermatology Sector of the University Hospital Clementino Fraga Filho (HUCFF) of the Federal University of Rio de Janeiro (UFRJ), were reviewed in order to investigate possible histopathological features that could be related to prognosis.

MATERIALS AND METHODS

The current research is an observational, cross-sectional study based on the review of histopathological examinations performed in patients diagnosed with early-stage MF.

Inclusion criteria

- Early-stage MF, defined by Pimpinelli et al. [10]. The aforementioned criteria were retrospectively applied based on the first biopsy examination performed at our institution. Four points at least were required (as proposed by the algorithm). We highlight that our institution does not have access to clonality T-cell receptor gene rearrangements examination. In this way, clinical, histopathological and immunohistochemical criteria (CD 2, 3, 5 and 7) were used;
- Adult patients, with 18 years old or more;
- TNMB staging IA or IB (Disease restricted to the skin);
- Five-year follow up or more.

Exclusion criteria

- Insufficient data on medical charts;
- Unavailable histopathological exams for revision or insufficient material on paraffin blocks to perform immunohistochemical analysis;
- Positive serology to HTLV 1 and 2.

Study population comprised MF patients diagnosed, treated and followed-up in the Photo dermatology Sector of HUCFF/UFRJ, between January 2000 and December 2015. Early stage cases were selected based on the current TNMB staging system [3]. All patients underwent laboratory exams (complete blood white count, serum LDH and beta-2-microglobulin) and imaging exams (chest x-ray and abdominal ultrasound for the majority and, more recently, computed tomography scans including thorax, abdomen and pelvis).

The first histopathological examinations that which confirmed a diagnosis of MF were selected. All patients were stage IA or IB at the time of diagnostic confirmation. All the exams were reviewed by two dermato pathologists, who did not know the original medical report and together performed and accorded the analysis of the specific established histological parameters. Only histological sections stained with hematoxylin and eosin were evaluated. Some patients had more than one biopsy taken from different anatomical sites at the same time; in these cases, samples were evaluated together and the evaluation was set considering the conjoint of histopathological findings.

The dependent variables evaluated were:

- Disease progression (staging) treated in a qualitative, dichotomous and nominal manner. Since patients at stages IA or IB were included in the study, all those who progressed to stage IIA onwards were categorized as disease progression.
- MF-related death (due to lymphoma or to complications arising from systemic therapies). This variable was also treated in a qualitative, dichotomous and nominal manner.

Histopathological independent variables are summarized in **Table 1**.

Table 1. Variables studied, summarizing materials and methods.

Histopathological variables		Classification	Definitions
Epidermis	Hyperkeratosis Parakeratosis	Qualitative, dichotomous and nominal	
	Normal Epidermis Atrophic Epidermis Acanthosis Psoriasiform Acanthosis	Qualitative and nominal	
	Vacuolar alteration of the basal layer	Qualitative, dichotomous and nominal	
	Apoptotic keratinocytes	Qualitative, nominal and dichotomic	
Lymphoid Infiltrate (LI)	Superficial Perivascular LI Superficial and Deep Perivascular LI Lichenoid LI Confluent and Diffuse LI LI affecting the Hypodermis	Qualitative and nominal	According to its predominant distribution pattern
Lymphoid exocitoses	Epidermotropism Pautrier's Microabscesses Folliculotropism	Qualitative, dichotomous and nominal	Lymphocytes aligned along the basal layer and in the epidermis, isolated, with halo. Pautrier's microabscesses: cluster of at least 4 atypical lymphocytes inside the epidermis [11]. Folliculotropism, equivalent to epidermotropism, but inherent to the epithelium of the hair follicle.
Lymphoid Atypia	Convolution of the lymphocyte nucleus in the epidermis and/or dermis Increase of the size of the lymphocytes nuclei, also in the epidermis and/or dermis	Qualitative, dichotomous and nominal	Lymphoid atypia criteria follow the diagnostic algorithm [10] Lymphoid nucleus were considered increased when equal or greater than the nuclei of the basal keratinocytes [11]
Dermis	Papillary dermal fibrosis Melanophages Extravasated erythrocytes	Qualitative, dichotomous and nominal	

Data were gathered in Excel (Microsoft® Excel® for Mac 2011/Version: 14.2.0) and analyzed in the SPSS statistical software, version 24.0. The chi-square test (X^2) or Fischer's exact test, were applied to investigate the association between qualitative independent variables.

Prevalence ratios and their respective confidence intervals (CI: 95%) were calculated as association measurements. The significance criterion was 5%. Finally, *Multivariate Poisson* regression was performed to help identify independent predictors for the events and to estimate their corresponding prevalence ratio.

The current study complies with the National Health Council Resolution 466/12; it is registered in *Plataforma Brasil* (Brazil Platform) and was approved by CEP-HUCFF/UFRJ - CAAE: 59235916.9.0000.5257.

RESULTS

One hundred and thirty-five (135) patients were selected at the outpatient clinic; however, only 102 early-stage MF patients were included based on medical reports analysis.

Among the 33 excluded patients, 17 were due to insufficient clinical data, 10 received a different diagnosis after revision (lymphomatoid papulo Sixty-seven of the 102 patients selected had their first histopathological examinations available for adequate revision along with paraffin blocks containing biopsied tissue sufficient for subsequent immunohistochemical analysis of CD 2, 3, 5 and 7.sis and granulomatous slack skin lymphoma) and 6 had positive HTLV serology.

Of those 67 patients, 61 scored 4 points after retrospective application of Pimpinelli's criteria, therefore corresponding to the total sample [10].

Table 2 summarizes clinical aspects of our sample.

Table 2. Clinical epidemiological profile.

Gender	Male: 49.2%	30/61
	Female: 50.8%	31/61
Age at diagnosis (years)	Mean: 53.46 (dp*: 16.4)	
	Median: 57	
	Mode: 48	
	Range: 18 to 79	
Skin lesion	Patches: 36.1%	22/61
	Plaques: 63.9%	39/61
Affected body surface area	<10%: 47.5%	29/61
	10 a 80%: 52.5%	32/61
CLIPi score	Low risk: 44.3%	27/61
	Intermediary risk: 37.7%	23/61
	High risk: 18%	11/61
TNMB staging	IA: 44.3%	27/61
	IB: 55.7%	34/61

** dp: deviation pattern*

Table 3 shows the outcome variables and reflects the evolution of the studied sample during outpatient follow-up.

Table 3. Studied outcomes during follow up.

Follow-up (years)	Mean: 8.25 (dp*: 4.38)	
	Median: 6	
	Mode: 5	
	Range: 2 to 26	
Staging progression	16/61 (26.2%)	Mean time to progression (years): 3.53
MF-related death	4/61 (6.6%)	

Minimum follow-up: 5 years. Although cases that progressed or even evolved to death in inferior periods were included in the analysis
** dp: deviation pattern*

Out of the 16 patients who progressed in staging, 25.0% advanced to IIA (N1); 12.5%, to IIB (T3); and 50%, to IIIA (T4). Of the 2 remaining patients, 1 progressed to stage IIIB (T4 + B1) and 1, to stage IVA (T4 + B2).

Eight (8) patients died along the follow up period and the outcome was associated with MF in 4 of them. All had progressed in staging and died due to infectious complications associated with chemotherapy.

Results of association measurements between independent histopathological and dependent variables are shown in **Table 4**.

Table 4. Prevalence ratio for the studied variables.

Independent Variables		**Dependent Variables**					
		Progression			**MF-related Death**		
		PR*	**p**	**CI 95%****	**PR***	**p**	**CI 95%****
Hyperkeratosis	No	1.0	0.250	0.6-4.9	1.0	0.638	0.09-4.0
	Yes	1.816			0.605		
Parakeratosis	No	1.0	0.03	1.1-6.0	-	-	-
	Yes	2.636			-		
Normal Epidermis	No	1.0	0.196	0.1-1.5	1.0	0.279	0.4-18.3
	Yes	0.402			2.813		
Atrophic Epidermis	-	-	-	-	-	-	-
Acanthosis:	No	1.0	0.557	0.5-3.5	1.0	0.643	0.09-4.3
	Yes	1.427			0.649		
Psor. Acanthosis	No	1.0	0.179	0.8-5.3	-	-	-
	Yes	2.115			-		
Vacuolar alt. basal layer:	-	-	-	-	-	-	-
Apopt. Keratinocytes	No	1.0	1.0	0.1-4.5	-	-	-
	Yes	0.747			-		
Sup. Periv. LI:	No	1.0	0.203	0.2-1.2	1.0	0.073	0.01-1.2
	Yes	0.538			0.140		
Sup. and Deep Periv. LI	No	1.0	0.036	1.4-6.5	1.0	0.02	3.3-224.6

	Yes	3.056			27.50		
Lichenoid LI	No	1.0	1.0	0.1-2.7	-	-	-
	Yes	0.729			-		
Confl./Dif. LI	No	1.0	1.0	0.2-6.7	-	-	-
	Yes	1.289			-		
Hypodermis	-	-	-	-	-	-	-
Epidermotropism	No	1.0	0.312	0.5-8.9	1.0	1.0	0.1-8.7
	Yes	2.283			0.978		
Folliculotropism	No	1.0	0.422	0.5-4.2	-	-	-
	Yes	1.529			-		
Pautrier's Microab	No	1.0	1.0	0.1-4.5	-	-	-
	Yes	0.747			-		
Melanophages	No	1.0	0.368	0.2-1.3	1.0	0.146	0.02-1.8
	Yes	0.605			0.202		
Lymphoid Atypia	No	1.0	0.193	0.6-10.6	1.0	1.0	0.1-10.3
	Yes	2.705			1.159		
Multinucl. giant cells	No	1.0	0.459	0.4-8.4	-	-	-
	Yes	1.967			-		
Eosinophils		-		-		-	
Papillary derm. Fibrosis	No	1.0	0.153	0.5-27.9	-	-	-
	Yes	4.063			-		
Extrav. erythrocytes	No	1.0	0.668	0.06-2.9	1.0	0.439	0.2-18.7
	Yes	0.442			2.208		

** Prevalence Ratio (PR)*
*** Confidence Interval 95% (CI 95%)*

The incidence of hyperkeratosis did not show correlation with disease progression or death. On the other hand, the incidence of parakeratosis indicated higher prevalence of staging progression (PR=2.636, p=0.03 and CI 95% 1.1-6.0).

Epidermal changes (epidermis presenting normal thickness, atrophy, acanthosis, psoriasiform acanthosis, vacuolar changes in the basal layer and, finally, apoptotic basal keratinocytes) did not correlated with dependent variables.

Superficial perivascular-pattern lymphoid infiltrates was present in 77% of the patients, whereas the lichenoid-pattern was found in 13.1% of them. Superficial and deep perivascular infiltrates, were found in 9.8% of the cases. It is worth emphasizing that the lymphoid infiltrates was classified by taking into consideration the predominant pattern in comparison to another more focal pattern eventually combined. There was statistically significant correlation between the identification of the lymphoid infiltrate of superficial and deep perivascular pattern and the incidence of both disease progression (PR: 3.056, p=0.036 and CI 95% 1.4-6.5) and disease- related death (PR: 27.50, p=0.02 and CI 95% 3.3-224.6). The same outcome was not observed in other lymphoid infiltrate patterns investigated in the current study.

Variables such as Pautrier's microabscesses (PM), folliculotropism and lymphocytic atypia did not show statistically significant correlation to the analyzed dependent variables.

No statistically significant association was found in the multivariate regression test when all variables were studied **(Table 5)**.

Table 5. Multivariate regression analysis.

Independent Variables	**Dependent variables:**	
	Progression	**MF-related Death**
	p	***P***
Gender	0.867	0.908
Age at diagnosis	0.981	0.894
Skin lesions (patches × plaques)	0.816	0.967
Affected body surface area	0.743	0.971
CLIPi score	0.950	x
TNMB staging	0.882	0.981
Hyperkeratosis	0.787	0.765
Parakeratosis	0.614	0.828
Normal epidermis	0.876	0.975
Atrophic epidermis	-	-
Acantosis	0.784	0.846
Psoriasiform acantosis	0.889	0.942
Vacuolar alteration of the basal layer	-	-
Apoptotic Keratinocytes	0.650	0.832
Superficial perivascular lymphoid infiltrate (LI)	0.781	0.870
Superficial and deep perivascular LI	0.752	0.739
Lichenoid infiltrate	0.745	0.859
Confluent and diffuse LI	0.818	0.870
Hypodermis	-	-
Epidermotropism	0.839	0.838
Pautrier Microabscesses	0.929	0.954
Folliculotropism	0.933	0.682
Melanophages	0.804	0.833
Lymphoid atypia	0.798	0.951
Multinucleated giant cells	0.606	0.992
Eosinophils	0.562	0.756
Papillary dermal fibrosis	0.366	0.801
Extravasated erythrocytes	0.939	0.776

DISCUSSION

We carried out an observational, cross-sectional study focused on reviewing the first histopathological exams performed in 61 patients diagnosed with early-stage (IA and IB) MF, based on criteria set by Pimpinelli et al. [10].

PM incidence, atypical lymphocytes with cerebriform nuclei in the dermis, folliculotropism and large cells suggesting progression to large-cell transformation are acknowledged as the worst histopathological prognostic factors [12-14].The aforementioned factors were compiled from different studies and not all of them are unanimous among the authors.

Disease progression presented statistically significant association between the incidence of parakeratosis and the superficial/deep perivascular pattern of the lymphoid infiltrate.

Patients presenting parakeratosis recorded higher prevalence of disease progression than patients who did not present it. The magnitude of the increased prevalence reached 2.6x. Likewise, the superficial/deep perivascular pattern was significantly associated with increased prevalence of staging progression during follow-up.

Superficial and deep perivascular infiltrate was the only variable associated with disease-related death, the prevalence being 27 times higher. The likelihood of certainty of this finding is low given the small numbers involved.

Studies focused on analyzing histopathological prognostic factors remain scarce. Vonderheid et al. [4] investigated possible histopathological and immunohistochemical factors with prognostic influence and found association between worse outcomes and factors such as the incidence of large MPs (clustering of 10 or more atypical lymphocytes) and lymphocytes with hyperchromatic and vesicular nuclei in the dermis. However, there was no association between infiltrate structure and the investigated events [4].

Smoller et al. investigated 24 histopathological criteria in patients belonging to 2 MF groups: 21 patients with stable disease who followed a usual and slowly progressive course versus 26 patients who were rapidly progressive and had worse prognosis. The incidence of parakeratosis and the lymphoid infiltrate pattern were taken into consideration among the investigated criteria. There was no statistical significance in any of the two parameters; the degree of epidermal acanthosis was the only factor likely to have prognostic influence. Rapidly-progressive patients tended to have a canthotic epidermis. Their distinct findings as compared to ours may be related to sampling. Although total number was similar, Smoller et al. [15] study involved a larger number of patients with rapidly-progressive disease course.

The degree of infiltration of clinical lesions correlates to the intensity and depth of the lymphoid infiltrate [16]. According to Marti et al. [17] the greater the infiltrate thickness (measured from the granular layer to the end of the dermal infiltrate), the worse the prognosis. Four of the 6 cases classified as superficial and deep perivascular lymphoid infiltration had focal lichenoid pattern. Thus, worse prognosis may be associated with the increased number of lymphoid cells infiltrating the skin, which corresponds to increased tumor burden. In fact, the concept is taken into account in the TNMB staging since it considers spots, plaques or tumors clinical lesions. On the other hand, there was no association between lichenoid infiltrate and the evaluated outcomes.

Parakeratosis is an abnormal epithelial cell-maturation process that leads to nuclei retention in the stratum corneum, which is normally anucleate. It is observed in many pathological skin conditions, accompanied or not to changes in the malpighian layer though its association to an accelerated cell turnover, and is often seen in patients with early-stage MF [18,19]. Based on results of the exploratory analysis conducted after the identification of such association, we found that the incidence of parakeratosis was associated with epidermal acanthosis (RP: 1.623; p=0.006; CI 95%: 1.2-2.1), which in turn was more often, although not significantly, associated with epidermotropism (p=0.3). So, we hypothesize that a greater epidermal lymphoid permeation with sequent epidermal reaction could lead to parakeratosis. Therefore an increased tumor burden in this setting could justify such unprecedented association. From another point of view, intense pruritus correlates to worse MF prognosis [13]. Scratching can cause excoriation and histopathologically result in spongiosis and tissue healing, parakeratosis included in the process. Since “pruritus” was not a clinical variable it was not possible to test such hypothesis at this time.

However, it is worth highlighting that Smoller et al. [15] investigated the prognostic value of parakeratosis and did not find such association.

We did not find statistically significant association between the incidence of Pautrier’s microabscesses and disease progression, despite the positive Pautrier’s microabscess prevalence ratio, which would denote tendency to higher progression prevalence.

Folliculotropism is pointed out as worse prognosis factor, being one of the criteria adopted in the CLIP score [5,12,20]. According to the study conducted by Nikolau et al. [13] with 473 patients from two different lymphoma centers, the incidence of folliculotropism was associated with disease progression to more advanced stages in patients with early-stage MF. However, similar to the large-cohort study conducted by Talpur et al. [20] we did not find significant association between the incidence of folliculotropism and the two investigated outcomes. It is important to note that

only a few patients had folliculotropism, making it unlikely to find a significant association with the studied events.

The finding of enlarged lymphocytes (representing at least 25% of the lymphoid infiltrate) was associated with worse prognosis, based on the literature [20-22]. Cytologic criteria of lymphocytic atypia, such as increased lymphocyte nuclear size, were not significantly associated with the investigated outcomes.

Important limitations of the present study are: retrospective nature, small sample, and relatively low incidence of events. Our findings with statistically significant associations should be interpreted and acquired effect in the context of the total histological picture that describes early MF and in parallel to previous reported changes that were also associated with progression of the disease.

CONCLUSION

Prospective studies conducted with meaningful samples have shown most patients with early-stage MF evolve slowly and characteristically have a good prognosis. Yet, a small group of patients follow a rapidly-progressive course with considerable higher morbidity and mortality. Thus, it is essential to identify relevant factors to contribute to better prognostic analysis besides the current staging model.

After focusing on analyzing histopathological aspects of the first biopsies conducted in a group of early-stage MF patients, it is possible to suggest that parakeratosis and superficial and deep perivascular lymphoid dermal infiltrate pattern are additional features that may play a prognostic role. New studies are needed to get deeper insights on the subject.

AUTHORS CONTRIBUTIONS

1. Gustavo Moreira Amorim: Project development, data collection, data analysis, writing (ORCID number: 0000-0001-6067-9463).
2. Danielle Carvalho Quintella: Histopathological review. Interpretation of the collected data, text correction (ORCID number: 0000-0001-90139417).
3. João Paulo Niemeyer Corbellini: Contribution to the project design, interpretation of the collected data, text correction (ORCID number: 0000-0001-81043915).
4. Marcia Ramos-e-Silva: Contribution to the project design, text correction (ORCID number: 0000-0003-1625-0760).
5. Tullia Cuzzi: Contribution to the project design, histopathological review, interpretation of the collected data, text correction (ORCID number: 0000-0002-3331-5290).

REFERENCES

1. Wilcox RA (2017) Cutaneous T-cell lymphoma: 2017 update on diagnosis, risk - Stratification and management. Am J Hematol 92: 10850-1102.
2. Amorim GM, Niemeyer-Corbellini JP, Quintella DC, Cuzzi T, Ramos-e-SilvaM (2018) Clinical and epidemiological profile of patients with early stage mycosis fungoides. An Bras Dermatol 93: 546-552.
3. Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, et al. (2007) Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: A proposal of the International Society for Cutanoues Lymphomas (ICSL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 110: 1713-1722.
4. Vonderheid EC, Pavlov I, Delgado JC, Martins TB, Telang GH, et al. (2014) Prognostic factors and risk stratification in early mycosis fungoides. Leuk Lymphoma 55: 44-50.
5. van Doorn R, Van Haselen CW, van Voorst Vader PC, Geerts ML, Heule F, et al. (2000) Mycosis fungoides: Disease evolution and prognosis of 309 Dutch patients. Arch Dermatol 136: 504-510.
6. Kim YH, Liu HL, Mraz-Gernhard S, Varghese A, Hoppe RT (2003) Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: Clinical prognostic factors and risk for disease progression. Arch Dermatol 139: 857-866.
7. Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, et al. (2010) Survival outcomes and prognostic factors in mycosis fungoides/Sézary syndrome: Validation of the revised International Society for Cutaneous Lymphomas/European Organization for Research and Treatment of Cancer staging proposal. J Clin Oncol 28: 4730-4739.
8. Eklund Y, Aronsson A, Schmidtchen A, Relander T (2016) Mycosis fungoides: A retrospective study of 44 Swedish cases. Acta Derm Venereol 96: 669-673.
9. Desai M, Liu S, Parker S (2015) Clinical characteristics, prognostic factors, and survival of 393 patients with mycosis fungoides and Sézary syndrome in the south-eastern United States: A single-institution cohort. J Am Acad Dermatol 72: 276-285.
10. Pimpinelli N, Olsen EA, Santucci M, Vonderheid E, Haeffner AC, et al. (2005) Defining early mycosis fungoides. J Am Acad Dermatol 53: 1053-1063.
11. Santucci M, Biggeri A, Feller AC, Massi D, Burg G (2000) Efficacy of histologic criteria for diagnosing

early mycosis fungoides. An EORTC Cutaneous Lymphoma Study Group Investigation. Am J Surg Pathol 24: 40-50.

12. Wernham AG, Shah F, Amel-Kashipaz R, Cobbold M, Scarisbrick J (2015) Stage I mycosis fungoides: Frequent association with a favourable prognosis but disease progression and disease specific mortality may occur. Br J Dermatol 173: 1295-1297.
13. Nikolaou V, Papavid E, Patsatsi A, Siakantaris M, Economidi A, et al. (2017) Prognostic indicators for mycosis fungoides in a Greek population. Br J Dermatol 176: 1321-1330.
14. Scarisbrick JJ, Kim YH, Whittaker SJ, Wood GS, Vermeer MH, et al. (2014) Prognostic factors, prognostic indices and staging in mycosis fungoides and Sézary syndrome: Where are we now? Br J Dermatol 170: 1226-1236.
15. Smoller BR, Detwiler SP, Kohler S, Hoppe RT, Kim YH (1998) Role of histology in providing prognostic information in mycosis fungoides. J Cutan Pathol 25: 311-315.
16. Lever WF, Schaumburg-Lever G (1990) Lymphoma and leukemia. Lever WF, Schaumburg-Lever G, eds. Histopathology of the skin 7th Edn. Philadelphia, Pa Lippincott, pp: 806-846.
17. Marti RM, Estrach T, Reverter JC, Mascaró JM (1991) Prognostic clinicopathologic factors in cutaneous T-cell lymphoma. Arch Dermatol 127: 1511-1516.
18. Ahn CS, ALSayyah A, Sangueza OP (2014) Mycosis fungoides: An update review of clinicopathologic variants. Am J Dermatopathol 36: 933-948.
19. Nagaraghi ZS, Seirafi H, Valikhani M, Farnaghi F, Kavusi S (2003) Assessment of histologic criteria in the diagnosis of mycosis fungoides. Int J Dermatol 42: 45-52.
20. Benton EC, Crichton S, Talpur R, Agar NS, Fields PA, et al. (2013) A cutaneous lymphoma international prognostic index (CLIPi) for mycosis fungoides and Sezary syndrome. Eur J Cancer 49: 2859-2868.
21. Talpur R, Singh L, Daulat S, Liu P, Seyfer S, et al. (2012) Long-term outcomes of 1.263 patients with mycosis fungoides and Sézary syndrome from 1982 to 2009. Clin Cancer Res 18: 5051-5060.
22. Vergier B, de Muret A, Beylot-Barry M, Vaillant L, Ekouevi D, et al. (2000) Transformation of mycosis fungoides: Clinicopathological and prognostic features of 45 cases. French Study Group of Cutaneous Lymphomas. Blood 95: 2212-2218.