The Egyptian Journal of Hospital Medicine (October 2021) Vol. 85 (2), Page 4331-4337

Mycosis Fungoides Diagnosis Using TOX Versus Old Panel Immunohistochemical Markers

Mai Ahmed Gobran, Abeer Hafeez*, Mohamed Ali Alabiad, Sabah Mohamed Hanafy, Amira Salem
Departments of Pathology, Faculty of Medicine, Zagazig University, Egypt
***Corresponding Author:** Mai Ahmed Gobran**, Mail:** magibran@medicine.zu.edu.eg

ABSTRACT

Background: For primary cutaneous lymphoma, mycosis fungoides (MF) is the most prevalent form with skin-homing T cells plus clonal proliferation of CD4. In many CTCLs, thymocyte selection associated with the HMG-box (TOX) is an uncontrolled gene, together with MF in comparison with controls. Early mycosis fungoides is difficult to diagnose, and, its distinction from inflammatory diseases is sometimes impossible.

Objective: In this study, we compared the TOX vs C7 and CD4 expression as an early mycosis fungoides diagnostic markers & to assess their ability to differentiate Mycosis fungoides from benign cutaneous inflammatory diseases (BCID).

Materials and methods: 60 patients who had been previously diagnosed as MF (30 cases) and BCID (30 cases). All were evaluated histopathologically using H & E and immunohistochemically staining for TOX, CD7 & CD 4.

Results: There was statistically significant difference between MF and BCID with increased TOX, CD7 & CD4 expression among MF than among BCID and ability of TOX to detect all true positive cases (100.0%) compared to 83.3% for CD4 and 13.3% for CD7. TOX had the highest sensitivity (100.0%) and accuracy (88.3%) followed by CD4 with sensitivity of 88.3% and accuracy of 66.7%, ($P < 0.001$).

Conclusion: TOX had the highest sensitivity (100.0%) & accuracy (88.3%) followed by CD4 with sensitivity of 88.3% and accuracy of 66.7%. Our results suggest that TOX is a useful marker in diagnosis of MF & differentiating it from BCID.

Keywords: TOX, CD7, CD4, Mycosis fungoides (MF), Benign cutaneous inflammatory diseases (BCID), Immunohistochemistry.

INTRODUCTION

Skin diseases are not only affecting the overall look of the patient but also could cause serious health complications. Mycosis fungoides (MF) is initially affecting the skin and is considered as a widespread type of primary cutaneous lymphoma (PCL) [(1)]**.** Atypical CD4+ skin-homing T cells are the hallmark of MF, which is a low-grade lymphoma. It is possible that MF grows into tumors over its lengthy clinical history, which begins with MF-infiltrated plaques. MF mainly affect the skin in the early stage, but could disseminate to visceral organs, peripheral blood, and lymph nodes in the advanced stages. In MF patients, the prognosis is heavily influenced by the disease's stage. Clinical and histological criteria was used for MF diagnosis through an integrated algorithm [(2)]**.**

Histology of MF shows a lichenoid infiltrate or band-like mononuclear cells within the papillose dermis with covering epidermotropism. In many cases, these lymphocytes are bordered by a clear halo (Pautrier microabscesses), but they could be produced in groups or individually within the epidermis. Irregular and hyperchromatic nuclear contours are shown after high-power analysis of mononuclear cells. Focal parakeratosis and hyperkeratosis-associated psoriasiform epidermal hyperplasia pattern are commonly shown from the epidermis. Hematoxylin and eosin-stained sections remain the diagnostic gold requirement, but the early stages diagnosis may be challenging as it is like other chronic inflammatory dermatoses [(3)]**.**

Thymocytes election-related high-mobility set family (HMG) box (TOX), is an unfettered gene in MF-skin biopsies, which encodes an HMG-domain DNA interacting nuclear protein, which governs the developing differentiation of T-cells [(4)]**.** Prior to the evacuation of CD4+ T cells from the thymus, TOX is down regulated in the thymus. Peripheral lymphoid tissue expresses proteins and TOX mRNA at a very low level [(5)]**.** At a higher frequency, TOX staining was observed in several vaired subtypes of CTCLs such as Peripheral T-cell lymphoma, not otherwise required (PTCL-NOS), Sézary Syndrome (SS), and MF [(6)]**.** It was found that TOX was the target gene of miR-223 in CTCL [(7)]**.** Moreover, a study confirmed the high expression of TOX gene in early MF lesions compared to controls [(8)]**.** In another study, rare expression of TOX gene was obtained in numerous tumors, such as leukemia, breast cancer and lung cancer [(9)]**.**

However, MF is difficult to be diagnosed, especially in early stages, distinction between MF and inflammatory diseases can be impossible. It was discovered that the permeating lymphocytes in MF were mostly CD4, with a section of CD8 T-cells, but CD4 was also conveyed by histiocytes, which can be abundant in this situation [(10)]**.** A quantitative assessment of CD4:CD8 ratio (normal value of 2:1) was performed beside evaluation of CD marker expression in terms of quality (negative, decreased, and positive). In classic patch stage MF/CTCL, a higher CD4:CD8 ratio is common, but lowers as the disease progresses. T-cells can be identified by a reduced CD4:CD8 ratio with unique CTCL mutations. CD7, which is generally the first CD marker to lose expression in CTCL, can be used to diagnose the disease [(11)]**.**

However, it has been discovered that CD7 depletion can occur in BCID processes as well. CTCL patients also

Received: 20/8/2021
Accepted: 2/10/2021

experienced a loss of additional indicators [12]. Immunopathology diagnostic criteria of MF include expression of lower than fifty percent of T cells, CD7 expression lower than ten percent of T cells and epidermal discordance from representation of CD7 on dermal T cells [13].

In this study, we compared the TOX vs C7 and CD4 expression as an early mycosis fungoides diagnostic markers & to assess their ability to differentiate mycosis fungoides from benign cutaneous inflammatory diseases (BCID).

MATERIALS AND METHODS

This retrospective-cross sectional study was achieved on punch biopsy taken from 60 cases of patients. 30 of them had early patch and plaque stages of MF and the other 30 cases had BCID inflammatory dermatoses. Samples were collected from Pathology and Dermatology Departments, Faculty of Medicine, Zagazig University Hospitals through the duration between April 2019 and April 2021. Elected specimens were purchased by 4 mmpunch biopsy.

The clinical data concerning sex and age were collected from the patients' files. Sections with thickness of 3-4 micron were cut from the formalin fixed paraffin-embedded blocks and stained with routine Hematoxylin and eosin stain to confirm the diagnosis. Serial sections from the same blocks are submitted for immunohistochemical staining for TOX, CD4 & 7.

Inclusion criteria: used in the current study were: 1) Patients with active lesion of early-stage MF and 2) Patients with active lesion of BCID inflammatory dermatoses.

Exclusion criteria: 1) Lactating and pregnant women, 2) Patients with tumor stage of MF, and 3) Patients with other kinds of cutaneous B or T- cell lymphoma.

Histopathology examination: The 30 cases of MG-associated lesions (including 10 cases of plaque stage MF and 20 cases of patch stage MF), and 30 cases of BCID inflammatory dermatoses (15 cases chronic dermatitis, 10 cases psoriasis, and 5 cases lichen planus).

Immunohistochemical staining:

The streptavidin–biotin immunoperoxidase method was used to conduct this test (Dako- Cytomation, Glostrup, Denmark). Formalin-fixed, paraffin-embedded blocks were cut into 3–4 mm sections and placed on slides that are positively charged, used xylene for deparaffinization, then alcohol graded for rehydration. A citrate buffer (pH 6.0) was used to heat the segments for 20 minutes before PBS was used to rinse them (pH 7.3). Then, peroxidase activity was stopped by H_2O_2 (6%) in MeOH. Then, the segments were hatched overnight with monoclonal antibodies: TOX: rabbit polyclonal antibody (dilution 1:50) (Clone TOX, lab vision corporations). Positive controls for TOX were (strong nuclear) positivity in the germinal center and interfollicular zone. The negative samples were achieved by omission of the initial antibody.

CD7 & CD4 mouse monoclonal antibody (Dilution 1:100) (Clone 4A4, lab vision corporation, Santa Cruz, California, USA). A secondary antibody was used, and the chromogen was diaminobenzidine substrate (Research Genetics, Huntsville, Alabama, USA). Dako-Cytomation was used to picture the results. Counterstaining with Mayer's Hematoxylin (BioGenex Laboratories, California, USA) was then applied and the segments were washed twice each in dH_2O and PBS. In the germinal center and interfollicular zone, CD7 (cytoplasmic or nuclear) positivity in the tonsil was a positive control for CD4. The negative controls were taken by omission of the initial antibody.

Analyzing the immunohistochemistry staining results:
TOX immunostaining:

Total lymphocyte infiltration and brown nuclear staining cells were utilized to determine TOX expression. Following is a semi-quantitative scale for grading the staining; negative when lower than ten percent, weak positive when range between 10 to 30 percent and strong positive when reaches more than thirty percent of total infiltrating lymphocytes. A minimum of 10 microscopic HPF were used to total CD4 and CD7 in the epidermis of invading lymphocytes (brown staining). When CD7 is expressed in fewer than 10% of epidermotropic cells, this assay is beneficial in MF diagnosis (CD7-negativity). Immunostaining for CD7 & CD4 was rated semi-quantitatively as follows: Grade 0: none, Grade1: weak, Grade2: moderate, Grade 3: strong. The fragments were evaluated by three various pathologists working singly. All discrepancies were discussed, and consensus reached.

Ethical consent:

An approval of the study was obtained from Zagazig University academic and ethical committee. Every patient signed an informed written consent for acceptance of the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value < 0.05 was considered significant.

RESULTS

The age of the studied cases ranged from 20-55 years, and the mean was 38.8 ± 11.6 years for the BCID group and 41.8 ± 9.0 years for MF group. Most studied cases were male (57 % in MF and 60 % in BCID).

TOX expression: There was a significant difference in TOX expression with a higher expression in MF group than in BCID group. Expression was strong in 70.0% of the MF group and only 6.7% of the BCID group. Regarding CD4 expression, we found that a significant difference between MF and BCID in CD4 was also found, with higher expression in MF lesions than in BCID group. Strong expression was observed in 33.3.0% of MF group and only in 20.0 % of BCID group and the result was statistically significant ($P \leq 0.05$) (Table I & II and Figures 1, 2 & 3).

CD7 expression:

It was found that there were very-highly statistically significant differences in CD7 with increased negative staining in MF more than in BCID (P<.001), (Table III, Figure 4).

The diagnostic performance of the markers:

We found that the ability/sensitivity of TOX to detect all true positive cases was 100.0%. TOX had the highest sensitivity (100.0%) and accuracy (88.3%) followed by CD4 with sensitivity of 83.3% and accuracy of 66.7%. The ability of CD4 to detect true positive cases was 83.3%. Sensitivity of CD4 was 83.3% with specificity of 50%. The ability of CD7 to detect true positive cases was 13.3% with false negative cases of 86.7%, with 13.3% sensitivity and 20% specificity (Table IV).

Table (I): TOX expression in MF patients' vs BCID

TOX expression, n, (%)	MF	BCIDs	Chi-squared for trend	*P*-value
	n=30	*n=30*		
Negative	**0(0%)**	**23(76%)**	**χ^2=42.6**	**<0.001**
Weak positive	**0(0%)**	**3(10%)**		
Moderate positive	**9(30%)**	**2(6.7%)**		
Strong positive	**21(70%)**	**2(6.7%)**		

Table (II): Comparing CD4 expression between MF and BCIDs

CD4 expression	MF No (30) %	BCIDs No (30) %	χ^2	p-value
Negative	5 16.7	15 50.0	10.2	**0.01***
Weak	14 46.7	6 20.0		
Moderate	1 3.3	3 10.0		
Strong	10 33.3	6 20.0		

Table (III): Comparing CD7experssion between MF and BCIDs

CD7 expression	*Total (60)*	MF No (30) %	BCID No (30) %	χ^2	P-value
Negative	20	26 86.7	6 20.0	27	**0.001****
Weak	20	4 13.3	20 66.7		
Moderate	4	0.00 0.00	4 13.3		
Strong	16	0.0 0.00	0.0 0.00		

Table (IV): predictive value of TOX, CD3, CD4& CD7 in early MF detection

Variable	Sensitivity	Specificity	PPV	NPV	Accuracy
TOX	100.0%	76.7%	81.1%	100.0%	88.3%
CD4	83.3%	50.0%	62.5%	75.0%	66.7%
CD7	13.3%	20.0%	14.3%	18.8%	16.7%

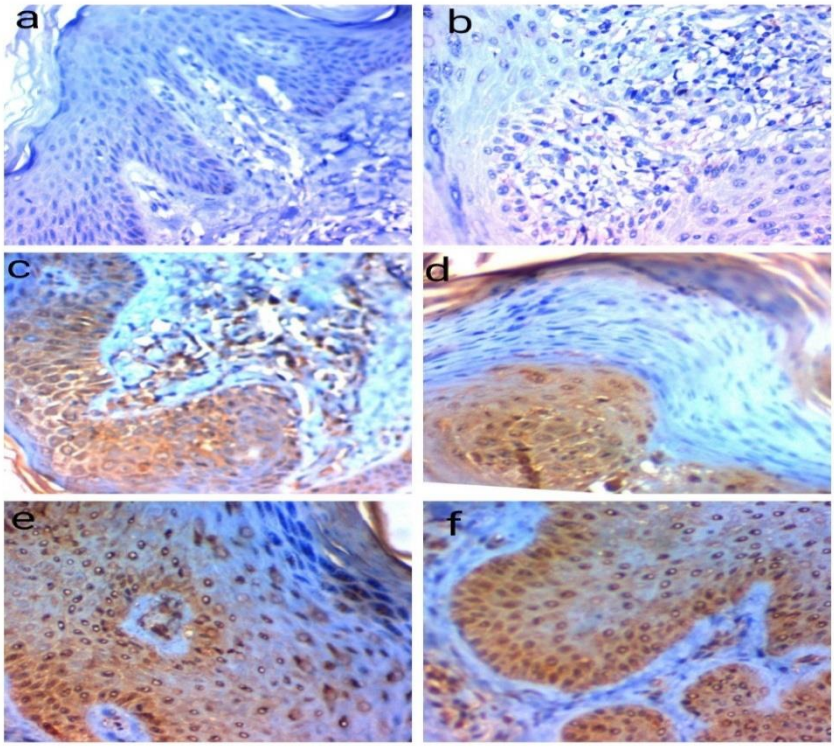

Figure (1): TOX immunoreactivity in MF& BCID lesions: (a) A case of chronic dermatitis showing negative TOX immunoreactivity (Immunoperoxidase stain, X 100). (b) A case of lichen planus showing negative TOX immunoreactivity (Immunoperoxidase stain, X 400). (c) A case of MF showing weak TOX immunoreactivity (Immunoperoxidase stain, X 400). (d) A case of mycosis fungoides showing moderate positivity of TOX immunoreactivity (Immunoperoxidase stain, X 400). (e) A case of mycosis fungoides showing strong positivity of TOX immunoreactivity (Immunoperoxidase stain, X 400). (f) A case of mycosis fungoides showing strong positivity of TOX immunoreactivity (Immunoperoxidase stain, X 400).

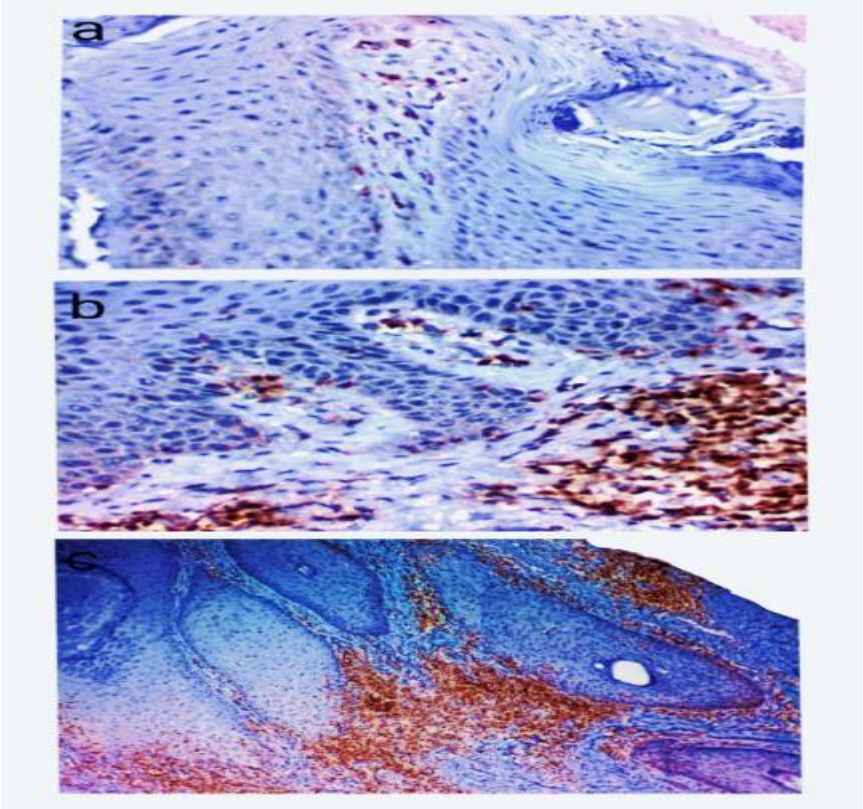

Figure (2): CD4 immunoreactivity in BCID lesions: (a) A case of psoriasis showing weak CD4 immunoreactivity (Immunoperoxidase stain, X 400). (b) A case of psoriasis showing moderate CD4 immunoreactivity (Immunoperoxidase stain, X 400). (c) A case of psoriasis showing severe CD4 immunoreactivity (Immunoperoxidase stain, X 400).

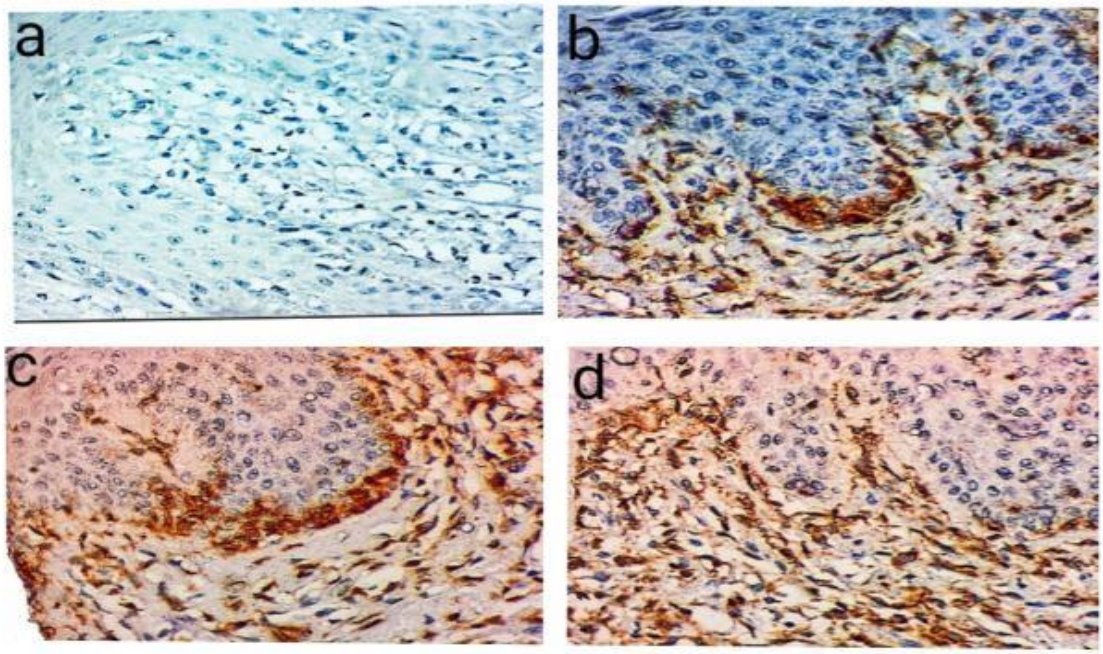

Figure (3): CD4 immunoreactivity in mycosis fungoides: (a) A case of mycosis fungoides showing negative CD4 immunoreactivity (Immunoperoxidase stain, X 400). (b) A case of mycosis fungoides showing weak positivity of CD4 immunoreactivity (Immunoperoxidase stain, X 400). (c) A case of mycosis fungoides showing moderate positivity of CD4 immunoreactivity (Immunoperoxidase stain, X 400). (d) A case of mycosis fungoides showing strong positivity of CD4 immunoreactivity (Immunoperoxidase stain, X 400)

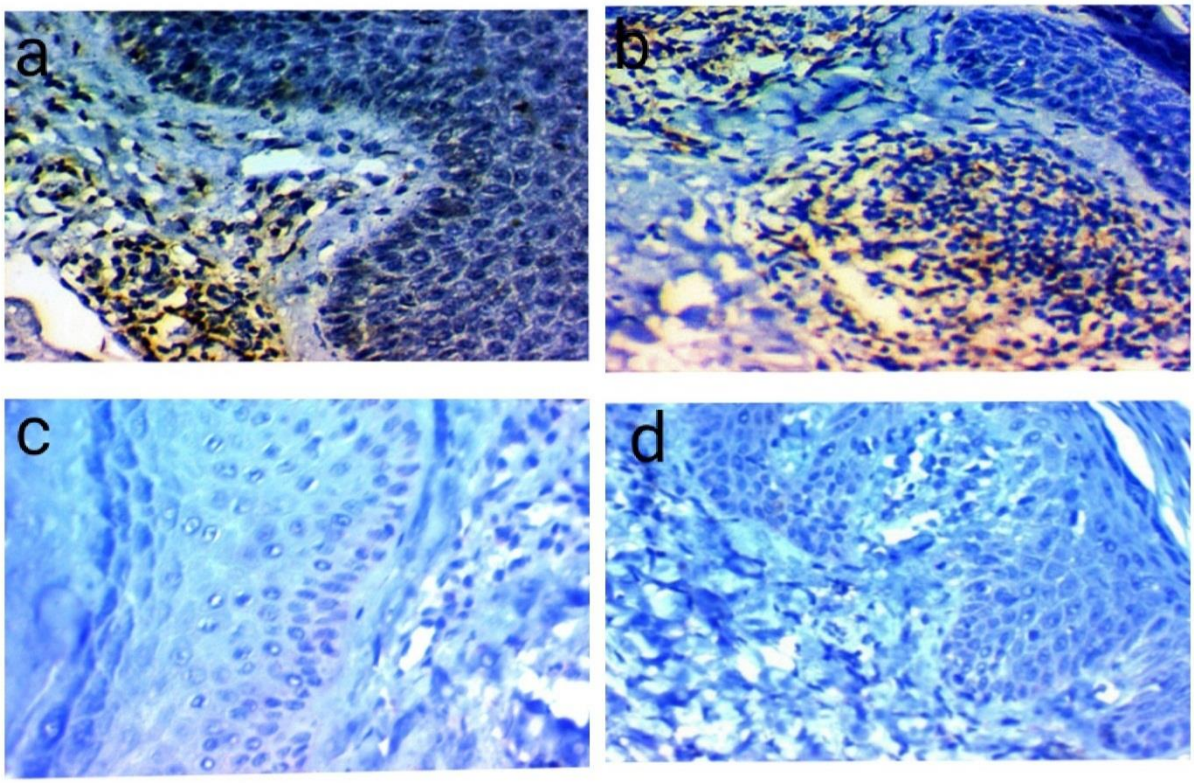

Figure (4): CD7 immunoreactivity in MF & BCID: (a) A case of psoriasis showing weak CD7 immunoreactivity (Immunoperoxidase stain, X 400). (b) A case of chronic dermatitis showing moderate positivity of CD7 immunoreactivity (Immunoperoxidase stain, X 400). (c) A case of mycosis fungoides showing negative CD7 immunoreactivity (Immunoperoxidase stain, X 400). (d) A case of mycosis fungoides showing negative CD7 immunoreactivity (Immunoperoxidase stain, X 400).

DISCUSSION

In the present study, we made a comparative analysis of the initial MF-stage versus BCIDs with respect to TOX, CD4 & CD 7 immuno-histochemical expression. A 30 patient with MF and 30 patients with BCIDs were involved in this study. The MF study group revealed that it was more communal in males (57 %) than in females (43%). The BCIDs study group showed that it was more communal in males (60 %) than in females (40%) and the result was statistically insignificant (P =0.7).

TOX indicated a significant representation in initial MF-lesions against the biopsies from dermatitis. The abnormal TOX-expression in MF was also consequently proved in the early and chronic dermatitis, but did not adequately show the more advanced disease of MF. For MF diagnosis and prediction, the TOX could be used **[14].**

Herein, we noted that a highly statistical significant difference in the TOX-expression was found, with a greater expression in MF group than in BCID group. The expression was strong in 70.0% and 6.7% of MF and BCID groups respectively. These results are in agreement with the results of **Huang *et al.*** **[14]** and **Yu *et al.*** **[4],** who validated that TOX was extremely stated in MF-lesions. A blot for TOX is a diagnostic marker for MF and may have a role in disease progression. In 32 from 35 (91%) biopsies, the neoplastic T-cells indicated a clear nuclear, where only 6 from 30 (20%) in the BCID-cases noted a positive staining. A significant difference between MF and BCID was also noticed ($P < 0.0001$, Chi-square test). TOX-expression in MF and BCID differed significantly, according to our findings. In comparison with BCID, the MF TOX expressions peaked. **McGirt *et al.*** **[15]** also showed that MF have been boosted the expression of thymocyte election-related of HMG box-protein (TOX). While, TOX has been intended to be a diagnostic indicator for MF. Additional confirmation studies are demanded. Meanwhile, TOX-expression was positively detected in 73.6% and 31.6% of MF and BCID/NS cases, separately.

Concerning the CD4, we herein noted that a highly statistically significant difference between MF and BCIDs was also found, with superior CD4-expression in MF-lesions than the BCID one. The CD4-expression was sturdy in 33.3% and 20.0% of the MF and BCID groups orderly with a statistical significance between them ($P \leq 0.05$). These results are matching with the results of **Burg *et al.*** **[16]** and **Ortonne *et al.*** **[17],** whose CD4 dominance was identified preferring MF to MF diagnosis, if the results are obtained in epidermal lymphocytes but not dermal lymphocytes, one is more likely to see them. **Kelati and colleagues** **[18]** also disclosed that the immunophenotypic analysis displayed that 93.3% (28 out 30) of MF-patients were a CD4-positive. **Scarisbrick *et al.*** **[19]** also noticed that no difference among the means (%) of CD4-circulating cells for the normal control (5.8%) or BCID (9.3%) was statistically reported, with no difference between BCID and MF. The cause for the inconsistency may be owing to the mycosis fungoides stage, the inflammatory dermatoses type, and the patients' number involved in the study.

Regarding the CD7-expression in the current study, we realized that very-highly statistically significant differences in CD7-expression were found, with increases in the negative staining of MF-lesions more than that of the BCID-lesions ($P < .001$). **Balmer *et al.*** **[20]** found an epidermotropic CD4+ and CD7- small cribriform of T-cell infiltrate, and morphologically matched with M. fungoides. **Kelati *et al.*** **[18]** also noticed the loss of pan-T-cell markers (CD2, CD5, and CD7) preferring a diagnosis of MF. **Basir *et al.*** **[21]** observed that tumor cells of M. fungoides regularly deficiency expression of CD7, and this is a valuable feature that helps in differentiating reactions from neoplastic procedures. However, **Murphy *et al.*** **[22]** noted that gradual loss of CD7-expression in BCID is the probable expansion outcome of antigen-elected +CD4+CD7- T-cells. The spongiosis dermatitis displayed a gradual decline in mean of CD7-counts from severe to subacute to chronic stages (50, 35, and 30%, respectively). This may be since these inflammatory CD4+CD7- T-cells may signify the physiologic equivalent to the neoplastic lymphocyte of MF. In addition, **Aslani *et al.*** **[23]** also informed that BCID-inflammatory dermatoses can display a low CD7-expression, but hardly fits that of patch MF-stage and that minimal CD7-expression, which is a particular result for patch MF-stage.

Concerning the diagnostic performance of the indicators, we noted that a statistically significant difference between MF and BCID in TOX, CD4, and CD7 expressions was found. The ability/sensitivity of TOX to reveal all true positive cases was 100.0%. The TOX specificity was 76.7%, with a positive prognostic-value of TOX of 81.1%, a negative prognostic-value of 100%, and accuracy of 88.3%. The TOX had the maximum sympathy (100.0%) and accuracy (88.3%) monitored by CD4 with a sensitivity and accuracy of 83.3 and 66.7%, respectively. The capability of CD4 to identify the true positive cases was 83.3%. Meanwhile, sensitivity of CD4 was 83.3%. Specificity of CD4 was 50%, positive prognostic-value of CD4 was 62.5%, negative prognostic value of CD4 was 75%, and accuracy of CD4 was 66.7%. The capability of CD7 to measure the true positive cases was 13.3% with false negative cases of 86.7%, with a 13.3% sensitivity, 2% specificity, 14.3% positive prognostic value, 18.8% of negative prognostic value, and 16.7% accuracy. TOX positive prognostic-value (PPV) for any TOX expression (Grade 1–3) was 86.7 percent and negative prognostic value (NPV) was roughly 48.1 percent by **Mcgirt *et al.*** **[15]**, which are in agreement with our findings. 33 of 53 MF-cases had a strong TOX expression (Grade 2–3) (62.3 percent). In terms of PPV and NPV, they scored 97.1% and 47.4% for each of them. In contrast, six of the 19 BCID/NS samples were positive for TOX expression (31.6 percent). TOX expression was detected in only one of the 19 BCID samples (5.3 percent) with an extremely positive TOX expression. In contrast, 75% of those surveyed had some level of expertise and 90.3 percent had a high level of sensitivity, which was reported by **Huang *et al.*** **[14].** Because they had a larger sample size, more

genetic methods, and a lower threshold value, they were able to analyze a larger number of instances. **Pimpinelli *et al.*** [(24)] stated that the shortfall CD5 in T-cells though their scarcity is involved in ISCL-criteria to explain the early-MF, only 10% subtle, despite its 100% specificity. The CD7 lacking is about 40 and 80% sensitive and specificity orderly in general.

Florell *et al.* [(25)] discovered that for MF, the sensitivity and specificity of the epidermal CD4/CD8 ratio at 1:1 were 79% and 69% respectively, at 2.4:1 were 69% and 93%, respectively and at 9:1 were 24% and 98% respectively. In the patch MF stage, **Aslani *et al.*** [(23)] found the lowest mean CD7-counts. A sensitivity of 75% and a predictive value of 100% were found for lymphocytes with less than 10% CD7 expression. Patch MF-stage diagnosis has a dismal prognosis with a specificity and negative predictive values of 100% and 83.3%.

CONCLUSION

The TOX had the uppermost sensitivity (100.0%) and accuracy (88.3%), which was tracked by CD4 with a sensitivity and accuracy of 88.3% and 66.7% respectively. Our outcomes proposed that the TOX may be believed as a valuable marker in MF-diagnosis. The test had 100% sensitivity, 76.7 percent specificity, and 88.3% accuracy. It is more irrefutable and valued in differentiating MF from BCID than CD4 & 7.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

REFERENCES

1. **Willemze R, Jaffe E, Burg G *et al.* (2005):** WHO-EORTC classification for cutaneous lymphomas. Blood, 105: 3768–3785.
2. **Olsen E, Vonderheid E, Pimpinelli N *et al.* (2005):** Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: European Organization of Research and Treatment of Cancer (EORTC). Blood, 110: 1713–1722.
3. **Connie A, Iriana P, Belongie G *et al.* (2007):** The Diagnosis, Staging, and Treatment Options for Mycosis Fungoides. Cancer Control, 14 (2): 102-111.
4. **Yu X, Luo Y, Liu J *et al.* (2015):** TOX acts an Oncological Role in Mycosis Fungoides. PLoS One, 10 (3): 1174-79.
5. **Wilkinson B, Chen J, Han P *et al.* (2002):** TOX: an HMG box protein implicated in the regulation of thymocyte selection. Nat Immunol., 3: 272–280.
6. **Morimura S, Sugaya M, Suga H *et al.* (2014):** TOX expression in different subtypes of cutaneous lymphoma. Arch Dermatol Res., 306: 843–9.
7. **McGirt L, Adams C, Baerenwald D *et al.* (2014):** miR-223 regulates cell growth and targets proto-oncogenes in mycosis fungoides/cutaneous T-cell lymphoma. J Invest Dermatol., 134: 1101–1107.
8. **Zhang Y, Wang Y, Yu R *et al.* (2012):** Molecular markers of early-stage mycosis fungoides. J Invest Dermatol., 132: 1698–1706.
9. **Gonzalez-Aguilar A, Idbaih A, Boisselier B *et al.* (2012):** Recurrent mutations of MYD88 and TBL1XR1 in primary central nervous system lymphomas. Clin Cancer Res., 18: 5203–5211.
10. **Ortonne N, Buyukbaba N, Delfau-Larue M *et al.* (2003):** Value of the CD8-CD3 ratio for the diagnosis of mycosis fungoides. Mod Pathol., 16: 857-862.
11. **Campbell S, Peters S, Zirwas M *et al.* (2010):** Immunophenotypic Diagnosis of Primary Cutaneous Lymphomas: A Review for the Practicing Dermatologist. The Journal of Clinical and Aesthetic Dermatology, 3 (10): 21-25.
12. **McPherson R (2001):** Overview of the immune system and immunologic disorders. In: McPherson RA, Pincus MR.Henry's Clinical Diagnosis and Management by Laboratory Methods. 20th ed. Philadelphia, Pa: WB Saunders Co, Pp: 817–820.
13. **Olsen E, Vonderheid E, Pimpinelli R *et al.* (2015):** Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: European Organization of Research and Treatment of Cancer (EORTC). Blood, 110: 1713–1722.
14. **Huang T, Yeung T, Perng C *et al.* (2017):** Folliculotropic mycosis fungoides: A case after one-year follow-up. Dermatologica Sinica , 35: 206-209.
15. **McGirt L, Degesys C, Johnson V *et al.* (2016):** TOX expression and role in CTCL. J Eur Acad Dermatol Venereol., 30 (9): 1497–1502.
16. **Burg G, Kempf W, Cozzio A *et al.* (2005):** WHO/EORTC classification of cutaneous lymphomas 2005: Histological and molecular aspects. J Cutan Pathol., 32: 647-674.
17. **Ortonne N, Buyukbaba N, Delfau-Larue M *et al.* (2003):** Value of the CD8-CD3 ratio for the diagnosis of mycosis fungoides. Mod Pathol., 16: 857-862.
18. **Kelati A, Gallouj S, Tahiri L *et al.* (2017):** Defining the mimics and clinico-histological diagnosis criteria for mycosis fungoides to minimize misdiagnosis. International Journal of Woman Dermatology, 3: 100-106.
19. **Scarisbrick J, Hodak E, Bagot M *et al.* (2018):** Blood classification and blood response criteria in mycosis fungoides and Sézary syndrome using flow cytometry: recommendations from the EORTC cutaneous lymphoma task force. Eur J Cancer, 93: 47-56.
20. **Balmer N, Hughey L, Busam K *et al.* (2009):** Primary cutaneous peripheral T-cell lymphoma with aberrant expression of CD20: case report and review of the literature.Am J Dermatopathol., 31 (2): 187-92.
21. **Basir H, Alirezaei P, Rezanejad A *et al.* (2018):** Early morphea simulating patch-stage mycosis fungoides in two cases. Dermatology Reports, 10 (1):7471-76.
22. **Murphy M, Fullen D, Carlson J (2008):** Low CD7 expression in BCID and MF cutaneous lymphocytic infiltrates: experience with an antibody reactive with paraffin-embedded tissue. Am J Dermatopathol., 24 (1): 6-16.
23. **Aslani F, Naseri M, Boub R *et al.* (2008):** CD7 Expression in Differentiating Mycosis Fungoides from BCID Cutaneous Lymphocytic Infiltrates. Iran J Med Sci., 33 (3): 144-149.
24. **Pimpinelli N, Olsen E, Santucci M *et al.* (2005):** Defining early mycosis fungoides. J Am Acad Dermatol., 53: 1053–63.
25. **Florell S, Cessna M, Lundell R *et al.* (2006):** Usefulness of Immunophenotyping in Atypical Cutaneous T-Cell Infiltrates. Am J Clin Pathol., 125: 727-736-727.