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Validity of Immunohistochemical Expression of Cell Adhesion Molecule 1 (CADM1) in Differentiating Early-Stage Mycosis Fungoides from Its Benign Mimickers

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ABSTRACT

Background: Mycosis fungoides **(MF)** is the commonest cutaneous T-cell lymphoma. Early-stage MF is difficult to be differentiated from benign inflammatory dermatoses **(BIDs).** CADM1 immunohistochemical staining may be valuable in differentiating early-stage MF from BIDs. Few studies are available regarding its role in this differentiation.

Aim: To evaluate validity of CADM1 versus TOX & CD4 IHC in differentiating Early-Stage Mycosis Fungoides from Its Benign Mimickers.

Materials and methods: This retrospective cross-sectional analysis was conducted of a total 75 paraffin blocks of skin tissue that were taken from seventy five individual from the pathology department's archives at faculty of medicine in Zagazig. thirty five blocks with MF and forty blocks with other benign dermatoses (15 cases of psoriasis, 15 lichen planus, 10 chronic dermatitis). CADM1, TOX and CD4 expressions were assessed.

Results: Regarding the diagnostic performance of CADM1, TOX &CD4 in diagnosis of early stage MF and differentiating it from BIDs , we detected that CADM1 had the highest sensitivity (94.3%) followed by TOX (88.57%). While TOX had highest specificity (95%) followed by CADM1 (92.5%). Additionally, our study revealed that positive TOX expression was higher in plaque stage than in patch stage.

Conclusion: CADM1 and TOX are considered beneficial in diagnosis of early MF, as CADM1 has highest sensitivity & TOX has highest specificity. TOX can also be used as prognostic marker being significantly higher in plaque than patch stage MF.

Keywords: Immunohistochemical, CADM1, Mycosis Fungoides, Benign Mimickers.

INTRODUCTION

The most prevalent variety of cutaneous T-cell lymphomas is mycosis fungoides (MF). (CTCLs), representing almost 50% of all new cases**.** It affects males nearly twice as often as females in their late fifties. Patients that are Caucasian are the majority. Although the cause is unknown, it could be brought on by long-term antigenic stimulation that causes T cell clonal growth and infiltration of the skin **(1).**

The three clinical stages of mycosis fungoides are patch, plaque, and tumor, and the clinical course is generally protracted across decades. The patch stage is characterized by reddish patches that are flat, varying in size, and may even appear wrinkled. Plaque stage of mycosis fungoides occurs after patch stage. reddish-brown, raised lesions are its defining feature; in those with darker skin tones, plaques might appear grey or silver. Patch and plaque stages of mycosis fungoides are both regarded as early stages. Large, irregular lumps are frequently present at the tumor stage. Any area of the body, such as the head and face, might develop tumors from plaques or normal skin **(2).**

Histopathologically, MF is distinguished by proliferation of small to medium-sized pleomorphic lymphocytes in the epidermis creating intraepidermal aggregates known as “Pautrier’s microabscesses”. These microabscesses, early lesions and cancers may not have it. an infiltration that resembles a band in a fibrotic papillary dermis is visible in early MF lesions. It is typical to find epidermotropism of single lymphocytes. Useful hints can be found in the arrangement of lymphocytes with somewhat larger nuclei and a tiny halo along the epidermis's basal layer **(3).**

Early-stage MF (patch & plaque) remains a significant diagnostic challenge because it frequently resembles BIDs such eczema, lichenoid dermatoses, psoriasis, and psoriasiform dermatoses. Progressive diseases typically have a high death rate, even though the majority of patients survive for decades following diagnosis in the early stages. Therefore, making a distinction between early MF and BIDs is crucial. Although molecular diagnostics and immunohistochemistry having false-positive, false-negative and inconclusive diagnoses are still frequent. So, the clinical, pathological & immunophenotypic correlation must be considered carefully to diagnose or exclude MF by differentiating it from other inflammatory and reactive processes **(4).**

A glycoprotein known as CD4 is found on the surface of immune cells including T helper cells, monocytes, macrophages, and dendritic cells. The human immune system relies heavily on white blood cells, sometimes referred to as CD4 cells, T-helper cells, or T4 cells. Helper cells are what they are called because one of their primary functions is to communicate with other immune cell types, such as CD8 killer cells, in order to instruct them to attack the infectious particle **(5).**

In the majority of T helper cell-related neoplasms, CD4 is still expressed. On tissue biopsy samples, CD4

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immunohistochemistry can be used to detect the majority of peripheral T cell lymphoma types. MF tumor cells are typically CD4-positive. Other inflammatory dermatoses are positive for CD4, as it is also expressed on Langerhans cells and histiocytes. There aren't many tumor cells in the dermis in early MF [(1)].

Thymocyte selection-associated high mobility group box factor (TOX), a DNA-binding protein that regulates the double dull to $CD4^{+}CD8^{low}$ transformation during the process of T cell positive selection. Before CD4+ T cells leave the thymus, TOX expression decrease after positive selection. Early investigations claimed that TOX was a CTCL- early MF particular marker of tumor cells. based on findings from immunohistochemistry showing that TOX was hardly expressed in inflammatory infiltrates of BIDs compared to tumor cells of CTCLs. However, more recent studies discovered that TOX was expressed, albeit at a low frequency, in invading lymphocytes in BIDs. 32% of BIDs patients and 74% of MF cases were found to have positive TOX expression. Sadly, Although TOX expression may be included to the diagnostic algorithm [(1)].

A well-known tumor suppressor gene in several human cancers, such as non-small cell lung cancer carcinoma, is cell adhesion molecule 1 (CADM1), one of the adhesion molecules. CADM1 is crucial for establishing connections between cells, making contact with them to communicate, and serving as a scaffolding molecule for the development of immunological responses by other immune cells. normal T lymphocytes are negative for CADM1, although some B cells, monocytes, and neutrophils are positive. Few studies have looked at the part that CADM1 plays arole in the development of cutaneous malignancies [(6)]. Tumor cells from Adult T-cell Leukemia/Lymphoma (ATLL) overexpress CADM1, which contributes to oncogenesis. Considering that CADM1 is not expressed, it can be used as a diagnostic marker for ATLL on healthy T cells. In a recent investigation, 94.8% of MF patients were positive, however no reactive dermatitides had immunohistochemical evidence of CADM1 positivity so it may serve as a helpful diagnostic indicator for MF. Further investigation is needed to prove the validity of immunohistochemical expression of CADM1 in diagnosis of early stage MF [(6)].

MATERIALS AND METHODS

This retrospective, controlled, selective cross-sectional analysis was done on 75 paraffin blocks of skin tissue that were gathered from the pathology department of the faculty of medicine at Zagazig University between 2021 to 2023.Thirty five blocks with early Mycosis fungoides(patch & plaques) and forty blocks with other benign dermatoses (15 cases of psoriasis, 15 lichen planus, 10 chronic dermatitis) were enrolled in this study Following receiving endorsement from the regional institutional review board (IRB), approval number 9060.
Tumor stage MF, other cutaneous malignancies, Sezary syndrome, patients who have second malignancies, patients who have chronic morbidity (e.g. systemic diseases) were excluded from the study.
Age, sex, and clinical presentation of all patients were evaluated clinically, and these data were taken from pathology reports that were accessible with the tissue specimens.

Histopathological evaluation:
3-4 µm sections from the paraffin blocks were cut for histopathological evaluation using Hematoxylin and eosin stain (H&E) to revise, record all histopathologic data evaluate and confirm the diagnosis.

Immunohistochemical examination:
Representative blocks from all the studied cases were immunostained with CD4 , TOX and CADM1 and the results were analysed and recorded.

Primary antibody
-CD4: mouse monoclonal antibody, clone 4A4 of the lab vision business, Santa Cruz, California, USA, diluted 1:100.
-TOX: rabbit polyclonal antibody (dilution 1:50)
(Clone TOX, lab vision corporations).
-CADM1: (antihuman CADM1 antibody (clone 3E1, 1:400 dilution, MBL, Nagoya, Japan)

Technique
-To confirm the diagnosis, paraffin blocks were sectioned at a thickness of 3 microns, dyed, and Following that, charged slides were sectioned using representative blocks. Dako Autostainer link 48 (Dako) was used for staining in line with the guidelines provided by the manufacturer.
- Sections were dried, deparaffinized, and rehydrated prior to staining, and then Epitope retrieval was carried out at a high pH (Dako PT Link machine, Dako).
- The automated staining procedure included 5 minutes of Envision Flex Peroxidase-Blocking Reagent (Dako) application, 20 minutes of anti-CADM1 incubation, 20 minutes of a peroxidase-labelled polymer (Envision Flex /HRP; Dako), and 10 minutes of substrate chromogen incubation (Substrate Working Solution, Dako).
-The pieces were rinsed in buffer (Envision Flex Wash buffer, Dako) after each process.
- The slides were dehydrated, cleaned, counterstained with hematoxylin, and mounted after the last wash stage.
-Tonsil tissue (strong membranous) served as positive controls for CD 4.
- The interfollicular zone and the germinal center served as (strong nuclear) positive controls for TOX.

- The liver tissue served as a membranous positive control for CADM1.
- Primary antibodies were swapped out with non-immune serum to provide negative controls.

Immunohistochemistry Assessment:

1.**The CD4 expression**: Semi-quantitative evaluation of immunohistochemically positive cells in the epidermis (0 = 0 cells, 1 = 1–10 cells, 2 = 11–20 cells, and 3 >20 cells) and superficial peri-vascular, deep perivascular, and interstitial dermis (0 = 0 cells, 1 = 1–20 cells, 2 = 21–100 cells, and 3 >100 cells) [(7)].

2. The TOX: The TOX stain is nuclear IHC stain, and semi-quantitatively graded as follow, negative: Nothing of immunoreactive cells is stained, weak positive <10% of immunoreactive cells are stained , moderate positive 10%-30% of immunoreactive cells are stained and strong > 30% of immunoreactive cells are stained [(8)].

3. CADM1 assessment: postive cases presented with brown membranous staining for CADM1 were evaluated quantitatively via 4 score system based on the proportion of positive cells: 0, less than 5%; 1+; 5% to 25%, 2+; 25% to 50%,3+ ;more than 50% [(4)].

Ethical Approval:

All participants in the study provided their informed permission. Approval from Zagazig University's department of medicine's institutional review board (IRB).

Statistical analysis:

All data were collected, tabulated and statistically analyzed using SPSS 26.0 for windows (SPSS Inc., Chicago, IL, USA). The used tests were Chi-square (X2) test and Mann-whitney test.

Results: all results are summarized in tables.

Table 1: Demographic data among mycosis fungoides and benign inflammatory dermatoses.

		Benign inflammatory dermatoses (n=40)	Mycosis fungoides (n=35)	Test	P-value
Age	*Median (range) Mean±SD*	45.5 (21-70) 44.1±11.9	49 (3-67) 44.8±17.1	U	0.3
Sex	Male Female	21 (52.5%) 19 (47.5%)	22 (62.9%) 13 (37.1%)	X^2	0.4

*U: Mann-whitney test

*X^2: Chi square test

There was no statistically significant difference between the studied groups as regards age or sex distribution (Table 1).

Table 2: CD4 dermal score among mycosis fungoides and benign inflammatory dermatoses.

	Benign inflammatory dermatoses (n=40)	Mycosis fungoides (n=35)	X^{2*}	P-value
Score 1	6 (15%)	6 (17.1%)	0.09	0.95
Score 2	18 (45%)	16 (45.7%)		
Score 3	16 (40%)	13 (37.1%)		

*Chi square test

There was no statistically significant difference between benign inflammatory dermatoses and mycosis fungoides as regards CD4 dermal score (Table 2).

Table 3: CD4 epidermal score among mycosis fungoides and benign inflammatory dermatoses.

	Benign inflammatory dermatoses (n=40)	Mycosis fungoides (n=35)	X^{2*}	P-value
Score 0	30 (75%)	0 (0%)	54.9	**<0.001**
Score 1	10 (25%)	10 (28.6%)		
Score 2	0 (0%)	15 (42.9%)		
Score 3	0 (0%)	10 (28.6%)		

*Chi square test

There was a highly statistically significant difference between the 2 groups as regards CD4 epidermal score, as most of mycosis fungoides patients had score 2 and 3 (Table 3).

Table 4: TOX expression among mycosis fungoides and benign inflammatory dermatoses.

	Benign inflammatory dermatoses (n=40)	Mycosis fungoides (n=35)	X^{2*}	P-value
Negative	35 (87.5%)	3 (8.6%)	55	**<0.001**
Weak positive	5 (12.5%)	4 (11.4%)		
Moderate positive	0 (0%)	13 (37.1%)		
Strong positive	0 (0%)	15 (42.9%)		

*Chi square test

There was a highly statistically significant difference between MF and BIDs as regards TOX expression, as it was higher among mycosis fungoides patients (Table 4).

Table 5: CADM1 expression among studied groups

	Benign inflammatory dermatoses (n=40)	Mycosis fungoides (n=35)	X^{2*}	P-value
Score 0	37 (92.5%)	2 (5.7%)	52.8	**<0.001**
Score 1	3 (7.5%)	17 (48.6%)		
Score 2	0 (0%)	12 (34.2%)		
Score 3	0 (0%)	4 (11.4%)		

*Chi square test

There was a highly statistically significant difference between the 2 studied groups as regards CDAM1 expression as it was higher among mycosis fungoides group (Table 5).

Table 6: CD4 epidermal expression and Clinical presentation among MF group.

CD4 epidermal expression	Clinical presentation		X^2 test*	P-value
	Patch stage (n=14)	Plaque stage (n=21)		
Score 1	4 (28.6%)	6 (28.6%)	2.78	0.25
Score 2	8 (57.1%)	7 (33.3%)		
Score 3	2 (14.3%)	8 (38.1%)		

*Chi square test

There was no significant difference in CD4 epidermal expression between patch and plaque stage among mycosis fungoides group (Table 6).

Table 7: TOX expression and Clinical presentation among MF group.

TOX	Clinical presentation		X^2 test*	P-value
	Patch stage n=14 (40%)	Plaque stage n=21(60%)		
Negative	**2 (14.3%)**	**1 (4.8%)**	**8.01**	**0.046**
Weak positive	**2 (14.3%)**	**2 (9.5%)**		
Moderate positive	**8 (57.1%)**	**5 (23.8%)**		
Strong positive	**2 (14.3%)**	**13 (61.9%)**		

***Chi square test**

There was a statistically significant difference in TOX expression between patch and plaque stage (P<0.05), as patients with strong positive TOX expression were higher in plaque stage in comparison to patch stage (61.9% vs 14.3%) (Table 7).

Table 8: CADM1 expression and clinical presentation among MF group.

CADM1	Clinical presentation		X^2 test*	P-value
	Patch stage (n=14)	Plaque stage (n=21)		
Score 0	2 (14.3%)	0 (0%)	4.04	0.08
Score 1	8(57.1%)	7 (33.3%)		
Score 2	3 (21.4%)	11 (52.3%)		
Score 3	1 (14.2%)	3 (14.3%)		

*Chi square test.

There was no statistically significant difference in CADM1 expression between patch and plaque stages (Table 8).

Table 9: Correlation between CADM1 and other biomarkers.

Variable	CADM1	
	r *	P
CD4 dermal score	-0.23	0.97
CD4 epidermal score	0.74	**<0.001**
TOX	0.75	**<0.001**

*Spearman rank correlation coefficient

CADM1 expression shows a strong positive correlation with CD4 epidermal and TOX expression (r=0.7, P<0.01) and (r=0.7, P<0.01) respectively (Table 9).

Table 10: Validity data of TOX and CADM1 as diagnostic markers to discriminate between MF and benign dermatoses.

	Cut-point	Sensitivity (%)	Specificity (%)	PPV (%)	NPP (%)	AUC
TOX	**10**	88.57%	95%	93.9 %	90.5 %	0.95
CADM1	**5**	94.3%	92.5%	91.67%	94.87%	0.96

For CADM1, AUC was (0.96), sensitivity was (94.3%) and specificity was (92.5%). So CADM1 was an excellent biomarker to discriminate between benign inflammatory conditions and mycosis fungoides with the highest sensitivity in comparison TOX expression (Table 10).

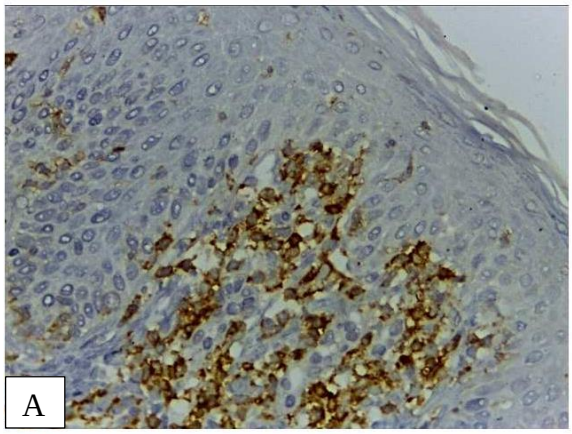

Figure 1A) CD4 immunostaining showing score 2 positive expression of CD4+ T-cells in the upper dermis and along the basal layer of the epidermis in acase of plaque stage MF.(X400, H&E).

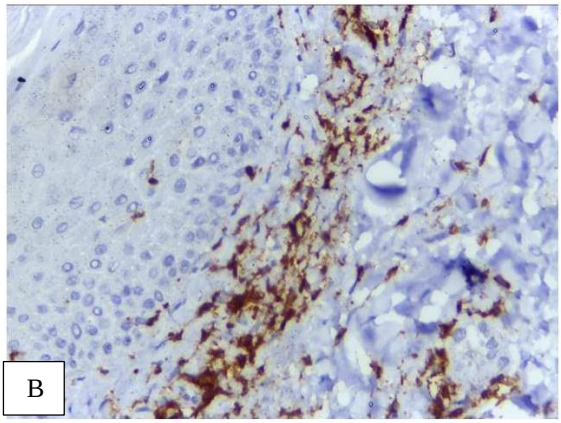

Figure 1B) CD4 immunostaining showing score 3 positive expression of CD4 in the upper dermis in acase of lichen planus .(X400,H&E).

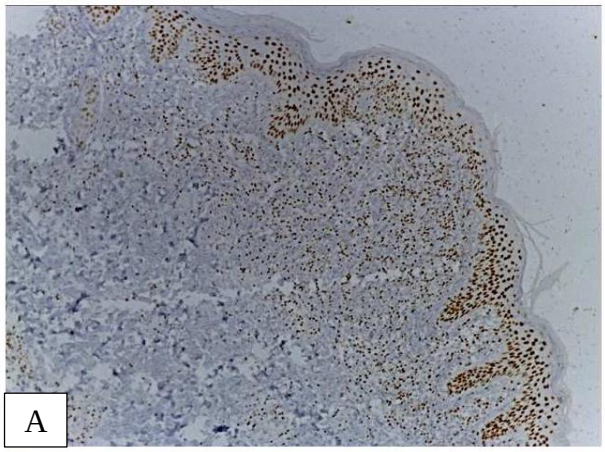

Figure 2A) TOX immunostaining showing score 3 positive TOX expression in the upper dermis and in the epidermis in case of plaque stage of MF (X100,H&E).

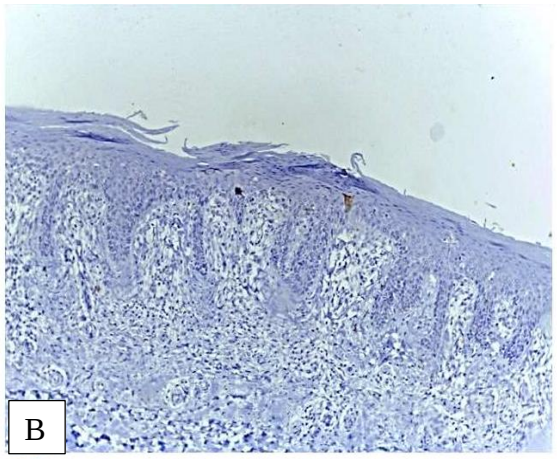

Figure 2B) Negative TOX expression in the epidermis and dermis in case of psoriasis. (X200,H&E).

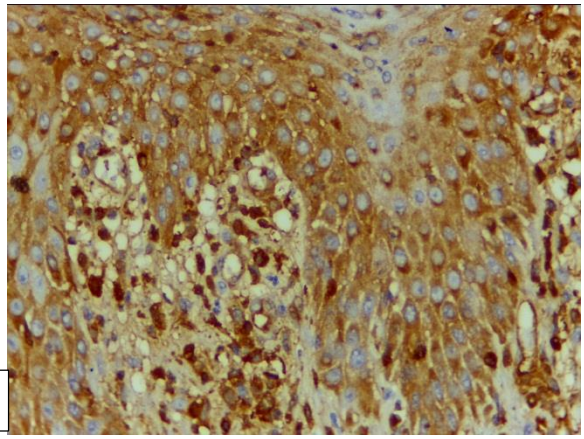

Figure 3A1) CADM1 immunostaining showing Score 2 positive expression in case of plaque stage MF. (X400,H&E)

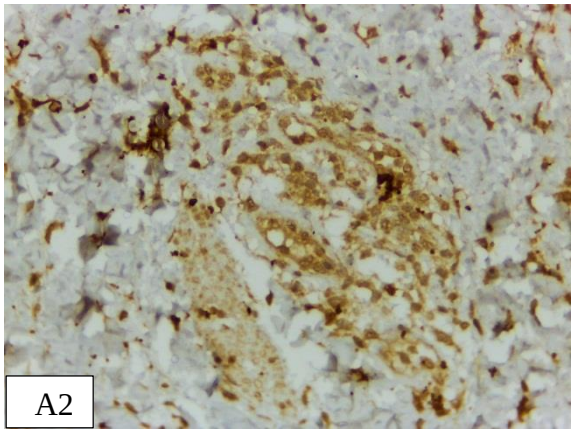

Figure 3A2) Dermal CADM1 expression of the previous case (X400,H&E).

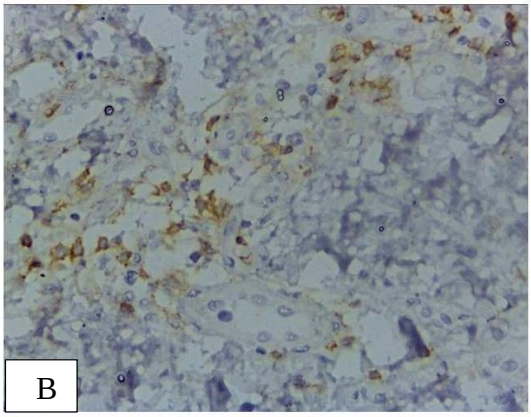

Figure 3 B) CADM1 immunostaining showing Score 1 positive dermal expression. in case of lichen planus. (X400,H&E).

DISCUSSION

In the present study, Using CD4,TOX and CADM1 immunohistochemistry ,we made acomparative analysis of mycosis fungoides in its early stages versus benign inflammatory dermatoses Thirty five blocks with MF and forty blocks with benign inflammatory dermatoses were included. MF and BIDs were common in males than in females being in MF 62.9% :37.1% male to female ratio and 52.5%: 47.5 % in BIDs (p=0.4). The mean age for MF cases of the present study was 44.8±17.1 (3-67) versus 44.1±11.9 (21-70) for BIDs (p=0.3). These results showed no statistically significant difference due to controlled selection of samples with patch and plaque lesions of early-stage MF.

Ito *et al.* [9] agreed with our results that Older persons are more susceptible to MF (median age at diagnosis: 55–60 years; range at diagnosis: 12–82 years; mean: 47.3 years); ratio of men to women (1.6–2.0). The patients included 14 males and 12 females. Regarding age and sex, there were no discernible differences between the MF and inflammatory groups. **Kaufman *et al.*** [10] also reported that At all times, men had a higher prevalence of MF than women, however the ratio of men to women fell from 1.9 in the 1970s to 1.4 after 1990.From 1973 to 1999 to 2000 to 2016 the median age declined to 62.5 and 60 years, respectively.

In disagreement with our study **Gaber *et al.*** [11] reported that women were slightly more than male patients with 1.2 : 1 as the female-to-male ratio .

Regarding CD4+Tcells expression in MF and BIDs , The statistical significance of the difference between MF and BIDS dermal expression was insignificant (p=0.95) while epidermal expression of CD4+Tlymphocytes showed ahighly significant statistically difference between them with higher epidermal expression of CD4+Tcells in MF versus BIDs (p<0.001) . The distribution of epidermal CD4+ Tcells was higher in MF . We found that 42.9% of MF cases showed score 2 epidermal expression and 28.6% MF displayed score 3 whereas 0% of BID cases displayed scores 2 and 3.

These finding were concordant with **Tirumalae *et al.*** [12] They claimed that CD4, CD8 cells in the epidermis were measured. Epidermal CD4 elevation favors MF. It is believed that epidermal/dermal discordance in these markers' expression is crucial for diagnosis. Remember that CD4 also stains other cells, particularly Langerhans cells, which increase the quantity. By accentuating the basilar epidermotropism of lymphocytes, CD4 helped with the diagnosis as well. Also keep in mind that not all MF have the CD4 phenotype. **Scarisbrick *et al.*** [13] also mentioned that 284 patients (81.6%) had classical MF, 62 (17.8%) had Folliculotropic MF, and two (0.6%) had syringotropic MF. 307 individuals (88.2 percent) had CD4+ T cells as their phenotype.

Aladily *et al.* [14] found that There was a high CD4:CD8 ratio in 20 (95%) of the MF patients and that three patients with BIDs (two with spongiotic dermatitis and one with keratosis that resembles lichen planus) had a high CD8:CD4 ratio. Patients experienced a membranous reaction that varied in strength. The most frequent changes in MF include an increase in the CD4/CD8 ratio that is more than four. However, an increase in Langerhans cells and histiocytes, both of which are typically CD4 positive, could make the interpretation process difficult.

Regarding TOX positive CD+T cells expression , our study found that the difference between MF and BIDs was highly statistically significant , as it was higher among MF patients (P=0.001).MF had higher TOX expression with positve nuclear staining than BIDs . The percentage of strong positive TOX expression in MF was (42.9%), while in BIDs was (0%).

Also Compared to patch and plaque, TOX expression in plaque stage was very statistically significant (P<0.05), as patients with strong positive TOX expression were higher in plaque stage in comparison with patch stage (61.9%vs14.3%) . Positive predictive value for TOX was 93.9%, while negative predictive value was 90.5%.

In agreement with our results **McGirt *et al.*** [15] examined the expression of TOX in 53 MF skin biopsy samples. 39 of these with positive stain (73.6%) and 14 negative (26.4%). Any TOX expression (Grades 1-3) had a positive predictive value (PPV) of 86.7% and a negative predictive value (NPV) of 48.1%. 33 of 53 MF cases (62.3%) had strong TOX expression (Grade 2-3), which had a PPV of 97.1% and an NPV of 47.4%. On the other hand, only 1 of 19 (5.3%) BID samples showed substantially positive TOX expression, while 6 of 19 (31.6%) BID/normal skin samples showed positive TOX expression.

Schrader *et al.* [16] showed that in (78%) of cases with More than 50% of the neoplastic T cells in early stage MF (stages IA-IB) were stained. the degree of TOX staining + neoplastic T-cells was significant and consistent in each patient.In BIDs, less than 50% of the inflammatory T cells expressed TOX in 59 out of 60 instances (98%) of which 24 out of 59 (41%) were rated as less than 10%. Only one patient (2%), who had drug-induced dermatitis, had inflammatory lymphocytes that were stained in more than 50% of the cells. Often, TOX expression was of a low intensity. While epidermotropic blasts and a few isolated blasts were present, cells that showed significant staining, particularly in people with atopic dermatitis. Using T-cell antigens for further immunophenotyping, it was discovered that the CD4-CD8+ In the TOX + epidermotropic T-cells, phenotype prevailed. Surprisingly, the reactive tonsils and lymph nodes employed as external controls in each area showed TOX expression in both the reactive follicles and scattered T -cells in the interfollicular zones.These findings imply that the presence of TOX + T -cells alone is insufficient for a diagnosis of MF and that further clinical and histological information must always be taken into account. A worse prognosis has been linked to high TOX levels.

Gaber *et al.* [11] study revealed that MF's TOX level was substantially greater than that of inflammatory mimics as the following: we found that most of the cases (16/20) showed positive TOX compared with only two cases of the inflammatory group. This was an excellent idea in terms of its potential to serve as an MF diagnostic marker. a 0.817 Area under the ROC Curve (AUC) score, an 80% sensitivity, and a 99% specificity 95% showed this to be the case.

As Regarding CADM1 expression , One of the factors that establishes cell structure is the capacity for cell adhesion. Patients with high CADM1-expressed groups have a considerably poorer survival rate from mycosis fungoides. As a result, The expression of CADM1 in mycosis fungoid tumor cells is inversely linked with mycosis fungoides prognosis. Mycosis fungoides patients have lymphocytes that are expressing CADM1 in the dermis, but patients with inflammatory skin diseases did not. This suggests that CADM1 is a unique tool for treating mycosis fungoides at an early stage when compared to inflammatory skin diseases [17].

Our study revealed that the difference between MF and was highly statistically significant BIDs , as it was higher among MF patients (P<0.001).MF had higher CADM1 expression with positve membranous staining than BIDs . The percentage of positive CADM1 expression in MF was (94.3%) vs (7.5%) for BIDs. Between patch and plaque, there was no statistically significant difference in CADM1 expression stage (P>0.05). CADM1 showed astrong positive correlation with CD4 epidermal (r=0.7,P<0.01) and TOX expression(r=0.7,P<0.001).

Positive predictive value for CADM1 was 91.67% while negative predictive value was 94.87%.

CADM1 had higher sensitivity 94.3% than TOX 88.57% . CADM1 was excellent biomarker to diagnose early stage MF .

Mashima *et al.* [18] found out that Seven patients (15.2%) had a tumor type diagnosis, 22 had a plaque type diagnosis (47.8%), and 17 had a patch type diagnosis (40.0%). based on the AJCC staging scheme. Each patient's primary tumors underwent immunohistochemical staining for CADM1, and the strength of its expression was evaluated in accordance with the Experimental design guidelines. The "highexpression" group had 23 patients (RD value, 90) while the "low-expression" group had 23 patients (RD value, b90). There was no statistically significant difference in the clinical characteristics between the CADM1 high and low groups. The overall survival rate was significantly lower in the CADM1 high-expression group when compared to the low-expression group. These findings show that the prognosis of mycosis fungoides patients is inversely linked with CADM1 expression in tumor cells.

Yuki *et al.* [19] also concurred with our findings, and in their investigation, Specifically early-stage samples, 33 of 34 (97.0%) and 55 of 58 MF samples (94.8%) were found to be CADM1-positive. They did not discover a

statistically significant difference between early-stage and advanced MF in the rate of CADM1 positivity. There was a substantial difference in CADM1 expression between MF and BIDs patients, with CADM1 expression found in less than 5.0% of infiltrates in BIDs cases. However, none of the 50 BIDs samples showed a positive reactivity score of one or higher (P <.0001) . Between each BID, there was no statistically significant variation in the rate of CADM1 positivity. Sensitivity, specificity, and area under the curve values were 0.97, 94.8%, and 98.0%, respectively. A cut of value of 5.0% was attained. After CADM1 and CD4 double-staining, CADM1 was expressed on the cell surfaces of the CD4+ T cells of MF sample. Patients with MF have high levels of CADM1, and its expression can help distinguish between MF and BIDs.

CONCLUSION

Early stages of MF and BIDs both have similar skin symptoms. Our research demonstrated the utility of CADM1 as a marker for early MF diagnosis, as it showed positive expression in all MF cases. Considering that CADM1 and TOX Positive expression was significanly higher in early stage MF versus BIDs, so combing bothCADM1& TOX can be fruitful in differentiaitng both conditions. CADM1 had the highest sensitivity (94.3%) & TOX had highest specificity (95%).

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