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Immunohistochemical research of CADM 1 in mycosis fungoides

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Abstract
Background: Mycosis fungoides (MF) is the most prevalent form of cutaneous lymphoma, characterised by clonal proliferation of atypical CD4+ T-lymphocytes.
Objectives: The goal of this research is to investigate CADM1 antibody expression in skin lesions of MFby immunohistochemistry, to throw a light on its possible role in etiology and worsening of this type of cutaneous lymphoma.
Patients and methods: This research was carried out on 20 cases with various stages of mycosis fungoides, specimens were selected from the Outpatient Clinic of Dermatology and Venereology Department, Tanta University Hospitals. 4mm punch skin biopsies were taken and were examined by H&E and CADM1 antibodies.
Results: There was statistically significant upregulation of CADM1 expression in MF specimens with statically significant positive correlation between CADM1 expression and progression of mycosis fungoides.
Conclusion: CADM1 may be useful as a potential diagnostic marker for mycosis fungoides. Moreover, CADM1 may be of value in assessment of mycosis fungoides progression.

Keywords: CADM1, mycosis fungoides

Introduction
The term mycosis fungoides (MF) was first suggested in 1806 by the French dermatologist Alibert [1, 2]. The overall incidence of MF which had been reported in the United States is approximately 4.0 cases per million persons per year [3]. The eitology of MF is complicated and still unclear but it can be explained by a chronic antigenic stimulation with underlying genetic susceptibility that leads to monoclonal proliferation of skin–homing, post-thymic malignant T-lymphocytes manifesting as MF [4]. Mycosis fungoides is characterized by benign course and is manifested by patch stage which slowly progresses into plaque stage and then tumor stage [5].
Cell adhesion molecules (CAMs) are cell surface molecules which regulate the intercellular and cell-matrix communications. They play also a significant role in cell differentiation, proliferation and migration. They include cadherins, selectins, integrins and immunoglobulin super family [6]. Cell adhesion molecule (CADM1) is a single transmembrane molecule of 442 amino acids, composed of three domains, extacellular domain which contains three extracellular immunoglobulin (Ig)-like domains and a signal peptide (at the N-terminal), these immunoglobulin domains involve five *N*-glycosylation sites [7]. CADM1 is involved in forming and maintaining the epithelial and synaptic structures between cells through tanshemophilic or transheterophilic interactions with other CAMs of adjacent cells to allow intercellular adhesions, signaling and communications, CADM1 helps also in organization of the actin cytoskeleton to control epithelial cell polarity and motility [8].

Patients and Methods
This research included 20 patients with mycosis fungoides selected from the Outpatient Clinic of Dermatology and Venereology, Tanta University Hospitals after approval from the Research Ethics Committee, Faculty of Medicine, Tanta University. They were subjected to the following: Complete history taking, full general and dermatological examination, and

routine laboratory investigations. Punch skin biopsy was obtained from each patient, under complete aseptic technique and local anastheia. Biopsies were fixed in neutral formalin 10% and processed for paraffin blocks and 2 sections were cut from each block and stained by Hematoxyline and Eosin (H&E) stain, and immunohistochemical stain for CADM1 (Clone 3E1, Biogenex, USA). Sections were deparaffinized in xylein for 20 minutes. Sections were transferred to 100% alcohol for 5minutes then hydrated through graded alcohol; each for 5 minutes then distilled water for another 5 minutes. CADM1 immunohistochemical expression was detected as a homogenous brown stain in T-lymphocytes, the intensity of expression was defined as: negative, mild, moderate, and strong.

Statistical analysis

Data were entered into the computer and analysed using version 20.0 of the IBM SPSS software (Armonk, New York: IBM Corporation). Quantitative and percentage descriptions were provided for qualitative data. The Kolmogorov-Smirnov test was performed to determine the distribution's normality. Range (minimum and maximum), mean standard deviation were used to represent quantitative data. At the 5% significance level, the acquired findings were deemed significant.

Results

I) Clinical Results

This research included 20 patients with mycosis fungoides (MF)**.** They were 12 males and 8 females, with age mean 42.10 ± 11.52 (15.0 – 72.0) years, 5 patients presented with patch lesions (Figure 1A), 5 patients with plaque lesions (Figure 2A), 3 patients with tumor lesions (Figure 3A). Some patients were asymptomatic, while others had experienced variable degree of itching. None of the MF patients included in the research had lymphadenopathy or organomegaly by clinical examination or ultrasonography.

Histopathological results

- **Patch stage mycosis fungoides** showed perivascular infiltrate of atypical mononuclear cells; it was mild in 9 specimens (75%) and moderate in 3 specimens (25%). Some of these atypical cells infiltrate the epidermis which is called epidermotropism**,** which was mild in 8 specimens (66.67%) and moderate in 4 specimens (33.33%) (Figure 1B & Table 1).
- **Plaque stage mycosis fungoides** showed lichenoid infiltration with atypical mononuclear cells; it was moderate in 4 specimens (80%) and severe in 1 specimen (20%)), Epidermotropism was mild in 1 specimen (20%), moderate in 2 specimens (40%) and severe in 2 specimens (40%). Collection of these cells in epidermis was observed in 2 specimens (40%), which is called Pautrier microabcess (Figure 2B & Table 1).
- **Tumor stage mycosis fungoides** showed dense atypical lymphocytic infiltrate in dermis; it was moderate in 1 specimen (33.33%) and severe in 2 specimens (66.67%). Epidemotropism was mild in 1 specimen (33.33%) and negative (zero) in 2 specimens (66.67%). (Figure 3B & Table 1).

II) Immunohistochemical results of CADM 1 expression

- CADM1 showed variable degree of expression in various stages of mycosis fungoides. CADM1 expression in patch stage was negative (zero) in 2 specimens, mildly expressed (+1) in 9 specimens and moderately expressed (+2) in 1 specimen (Figure 1C & Table 2). While, CADM1 expression in plaque stage was mild (+1) in 3 specimens and moderate (+2) in 2 specimens (Figure 2C-3C & Table 2). While, CADM1 expression in tumor stage was moderate (+2) in 2 specimens and strong (+3) in 1 specimen, (Figure 3C & Table 2). There was statically significant difference between CADM1 expression and MFstaging with $^{MC}p=$ 0.029*, (Table 2).

Table 1: Comparison between mycosis fungoides stages (patch, plaque and tumor) according to atypical lymphocytic infiltrate in epidermis (epidermotropism) and dermis.

Atypical lymphocytic infiltrate	Patch (n=12)		Plaque (n=5)		Tumor (n=3)	
***In epidermis* (epidermotropism)**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Zero	-	-	-	-	2	66.67
Mild	8	66.67	1	20	1	33.33
Moderate	4	33.33	2	40	-	-
Severe	-	-	2	40	-	-
In dermis						
Zero	-	-	-	-	-	-
Mild	9	75	-	-	-	-
Moderate	3	25	4	80	1	33.33
Severe	-	-	1	20	2	66.67

Table 2: Cell adhesion molecule 1 expression in mycosis fungoides

CADM1 expression	Type of skin lesion						$\chi^2=$	p
	Patch (12)		Plaque (5)		Tumor (3)			
	No.	%	No.	%	No.	%		
Negative	2	16.7	0	0.0	0	0.0	10.721*	$^{MC}p=$ 0.029*
Mild	9	75.0	3	60.0	0	0.0		
Moderate	1	8.3	2	40.0	2	66.7		
Strong	0	0.0	0	0.0	1	33.3		

*: Statistically significant at $p \leq 0.05$

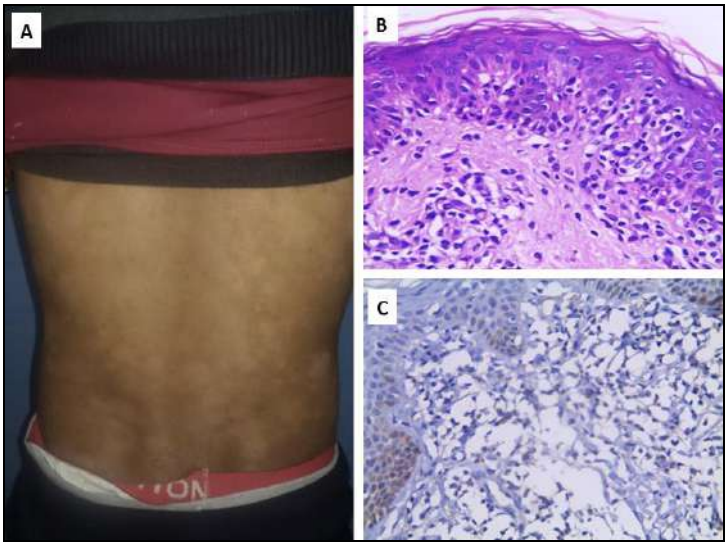

Fig 1: Patch stage mycosis fungoides. (A) Male patient aged 36 years presented with multiple hypopigmented patches on the back since 4 years (Stage IB), (B) H&E stained section showing upper dermal atypical lymphocytic infiltrate and epidermotropism (H&E x400), (C) Immunohistochemical stained section showing mild CADM1 expression (+1) in neoplastic lymphocytes (x400).

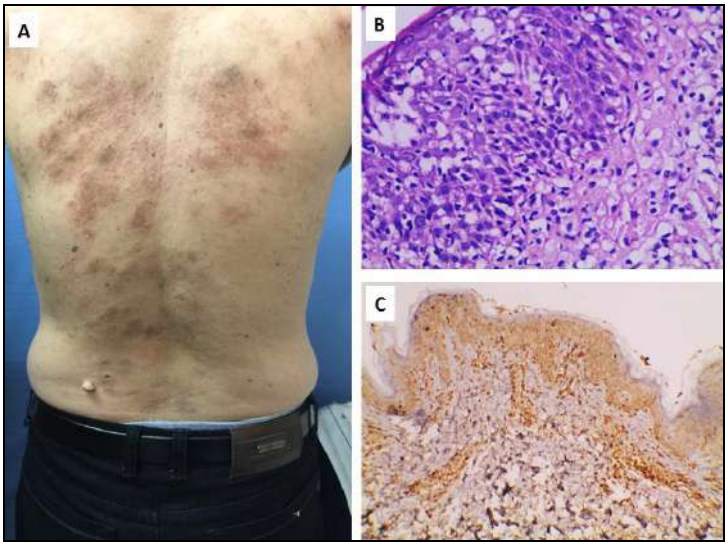

Fig 2: Plaque stage mycosis fungoides. (A) Male patient aged 43 years presented with multiple plaques on the back since 8 years (Stage IA), (B) H&E stained section showing band like atypical lymphocytic infiltrate with epidermotropism and Pautrier microabcess (H&E x400), (C) Immunohistochemical stained section showing moderate CADM1 expression (+2) in neoplastic lymphocytes (x200).

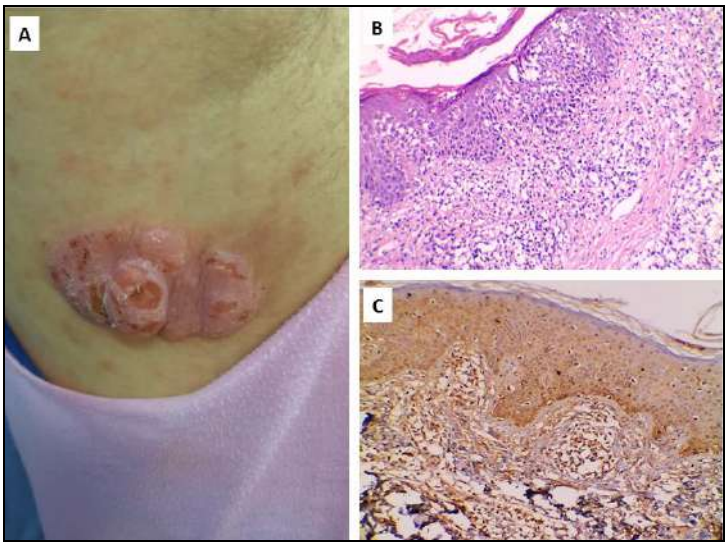

Fig 3: Tumor stage mycosis fungoides. (A) Female patient aged 55 years presented with tumor mass since 13 years (Stage IIB), (B) H&E stained section showing diffuse dermal infiltrate by neoplastic cells (H&E x200), (C) Immunohistochemical stained section showing strong CADM1 expression (+3) in neoplastic lymphocytes (x200).

Discussion

In the current research, the incidence of mycosis fungoides (MF) was higher in males (60%) (40%) with a male to female ratio equals 3:2 which was matching with Sidiropoulou *et al*., 2020 [9], Ocampo *et al*., 2020 [10], Amorim *et al*., 2018 [11] and Boulos *et al*., 2014 [12], they had demonstrated that the incidence of MF was higher in males. On the other hand, Neinaa *et al*., 2018 [13] had demonstrated that MF incidence was higher in females.

The age of MF patients in this research ranged from 15 to 72 years with a mean age of 42.10 ± 11.52. The higher incidence of MF in our research was among adults which was in the same line with Alghamdi *et al*., 2012 [14], who had concluded that the mean age of their MF patients was 33.5. However, Jung *et al*., 2021 [15], Ocampo *et al*., 2020 [10], Castano *et al*., 2013 [16] had observed that the incidence of mycosis fungoides, especially the hypopigmented variant was more common among children and adolescents. On the other hand, Leinweber *et al*., 2009 [17], Kuen-kong *et al*., 2005 [18] had observed that the higher incidence of MF was in older patients, mainly in the fifties.

In the current research, histopathological examination of MF specimens showed that epidermotropism was higher in patchy and plaque stages compared to tumor stage. By contrast, the dermal infiltrate with the atypical lymphocytes was higher in tumor stage than patch and plaque stages. These histopathological findings were in agreement with Amorim *et al*., 2020 [19] and Fatima *et al*., 2020 [20] and who had observed a higher incidence of epidermotropism in early than advanced MF and higher dermal neoplastic infiltrate in advanced than early mycosis fungoides.

In the present research, CADM1 immunohistochemical expression was positive in MF specimens which is in agreement with this research, Yuki, *et al*. [21] had observed that CADM1 immunohistochemical expression was positive in MF specimens. In addition, we had observed that CADM1 expression increased with the progression of MF disease, the mean value of CADM1 expression in tumor stage is 2.33 compared to plaque and patch stages which were 1.40, 0.92, respectively, which means that CADM1 could be used as a potential prognostic marker in mycosis fungoides. In agreement with this result, Mashima, *et al*. [22] had reported that high CADM1 expression in MF is associated with a worse prognosis.

In conclusion, the results of the present research revealed statistically significant increase of CADM1 immunohistochemical expression in mycosis fungoides specimens with disease worsening allowing us to recommend it as a prognostic marker for mycosis fungoides.

Conflict of Interest

Not available

Financial Support

Not available

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