

Role of toll-like receptor 6 in pathogenesis of mycosis fungoides

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ABSTRACT

Toll-like receptors (TLRs) are transmembrane proteins that function as pattern-recognition receptors for the detection and response to microbial ligands. Toll-like receptors (TLRs) have been implicated in various dermatological diseases including cutaneous T-cell lymphoma (CTCL). The aim of work is to measure the tissue and serum expression of TLR6 in mycosis fungoides (MF) patients in comparison to age and sex matched healthy controls to investigate its role in pathogenesis in MF. This case-control study was carried out on 48 subjects. These included 33 MF patients and 15 age and sex matched healthy volunteers served as controls. Tissue TLR6 expression was decreased in MF patients than in controls in highly statistically significant manner with $p < 0.001$ denoting the strong correlation between TLR6 and MF.

KEY WORDS: Toll-like receptors, Mycosis fungoides, Toll-like receptor 6

INTRODUCTION

Toll like receptors (TLRs) have been established to play an important role in activation of innate immune response by recognizing various microbial-derived molecules. They act as receptors for bacteria and fungi, and mediate the production of cytokines in response to a variety of viruses and viral ligands [1]. To date, 10 TLR family members have been identified in humans, and at least 13 are present in mice [2].

Cutaneous T-cell lymphoma (CTCL); is a lymphoproliferative disorder characterized by clonal expansion of malignant CD4+ T cell in the skin [3]. Mycosis fungoides represents

the most common form of primary cutaneous T-cell lymphoma (CTCL) [4].

TLRs and their pathways have been implicated in various dermatologic diseases including acne, atopic dermatitis, psoriasis, infectious diseases and CTCL [5].

Some studies revealed lower expression of TLR in MF as the study conducted by (*Tawdy et al., 2017*) which revealed lower TLR7 expression in MF patients in comparison to healthy controls. On the other side, there are studies that revealed increased expression of TLR in MF as the study conducted by (*Jarrousse et al., 2006*) in which MF skin showed a strong intensity of labelling with TLR2, TLR4, TLR9 in the epidermis.

The aim of this work is to study expression of TLR6 in tissue and serum of patients with MF in comparison with controls, in an attempt to elucidate its role in the pathogenesis of MF.

PATIENTS AND METHODS

Permission to conduct the study was obtained from the Ethical Committee of Fayoum University. An informed consent was obtained from participants who accept to participate in the study.

This was a case-control study which included 48 participants, 33 patients with MF and 15 healthy controls who were collected from Dermatology, STDs and Andrology Department of Fayoum University Hospital (Fayoum, Egypt) and Al-Haud Al-Marsoud hospital (Cairo, Egypt).

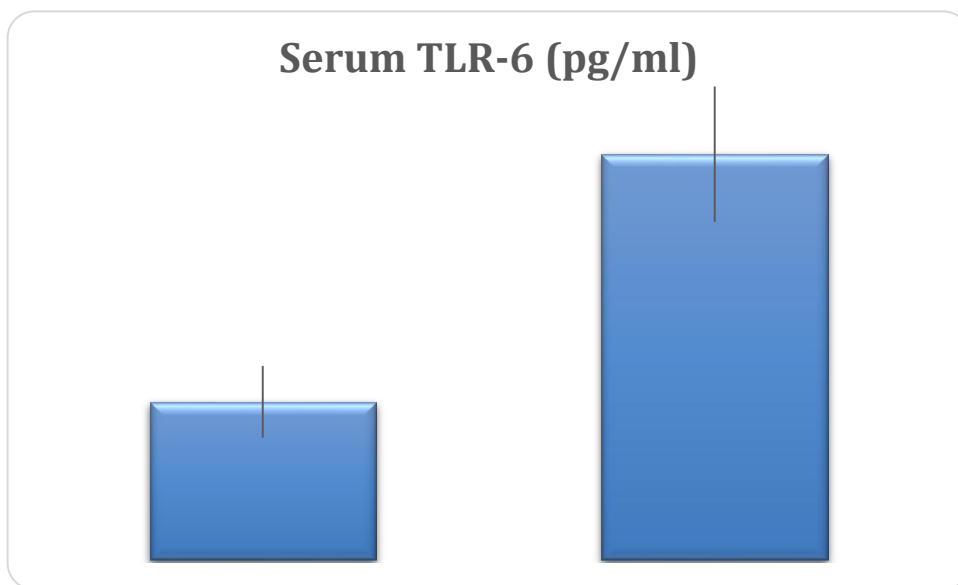
Diagnosis was made clinically and confirmed by skin biopsy. Any patient presented by any stage of MF was included. Patients presented by chronic inflammatory diseases, coexistent cutaneous or internal malignancy, infectious skin diseases, MF patients on continuous treatment for an uninterrupted duration by a minimum of 6 months or history of previously treated malignant tumors were excluded.

All patients underwent detailed history taking and clinical assessment of the type of lesions (patch, plaque, and tumor), and extent of lesions according to their anatomical distribution. Serum and tissue samples were collected from both groups to assess level of TLR6.

RESULTS

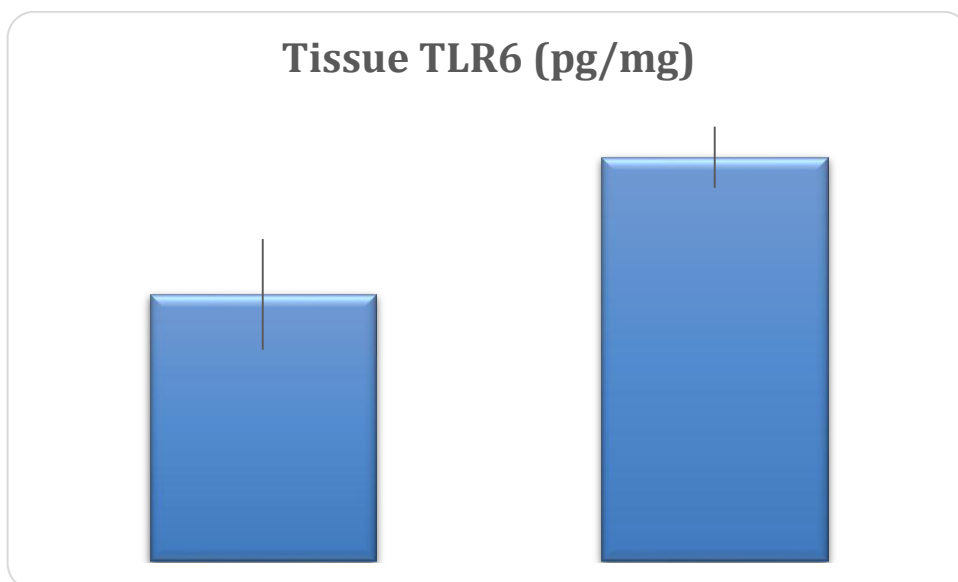
1. This study showed that there is a highly statistically significant difference with p-value < 0.001 between case group and control group regarding serum level of TLR6.

Variable	Groups		t test	p value
	Case	Control		
Serum TLR-6 (pg/ml)	152.33±34.45	390.71±65.27	16.618	0.000 ^{HS}



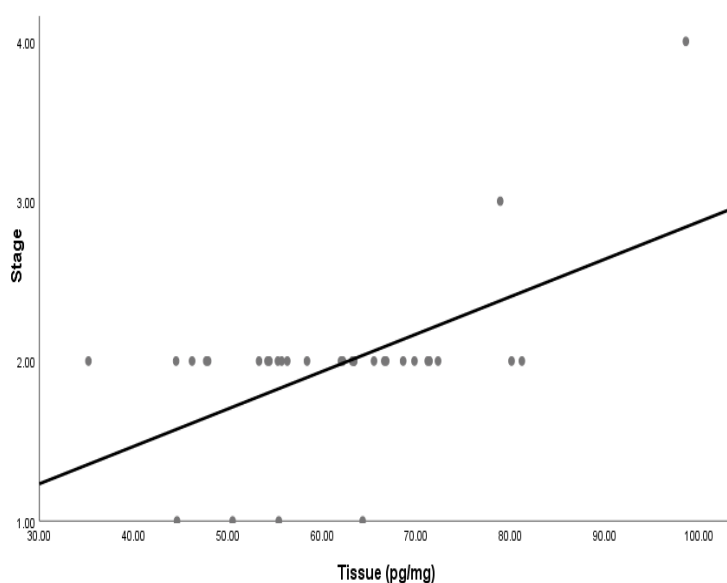
2. This study also revealed that there is a highly statistically significant difference with p-value < 0.001 between case group and control group regarding tissue TLR6.

Variable	Groups		t test	p value
	Case	Control		
Tissue TLR6 (pg/mg)	61.49±12.80	93.16±7.07	8.947	0.001 ^{HS}



2. The present study showed that there is a statistically significant positive correlation between tissue TLR6 and stage with p-value < 0.05 and there is no statistically significant correlation with age, sex, duration and type with p-value >0.05.

Variable	Tissue TLR6		
	Pearson Correlation	p value	Significant
Age	0.003	0.987	Non significant
sex	-0.07	0.699	Non significant
Duration	-0.059	0.742	Non significant
type	-0.144	0.424	Non significant
Stage	0.566	0.001	Significant



Discussion

Skin microenvironment plays a crucial supporting role in MF [6]. Toll like receptors are one of pattern recognition receptors that function as surface transmembrane receptors and permit cells to recognize self from non-self in immune activation. Consequently, in the last two decades mounting evidence has inextricably linked TLR activation with the pathogenesis of immune diseases and cancer [7].

Tissue TLR6 level was lower in MF cases than in controls and the difference was highly statistically significant with p value < 0.001. Comparing the tissue TLR6 levels in relation to MF staging revealed the lowest mean value in stage Ib and highest mean value in stage IIb.

Kado et al., 2012 observed that TLR6 staining was increased in epidermis, endothelial cell lining and tumor infiltrate compared with controls. Similar to our present study independent patient cases with disease progression from patch to plaque or nodular stage did exhibit increased intensity of TLR6 in epidermis, endothelial cell lining and tumor infiltrate. This increased staining of tumor infiltrate is particularly interesting in tumor stage as these lymphocytes are thought to represent primarily malignant cells.

However, the study conducted by *Kado et al., 2012* included only 8 patients but the present study included larger scale of patients including age and sex of the patients and type and duration of MF.

Conclusion

To our knowledge, this is the first study to assess the serum and tissue levels of TLR 6 in MF and to prove that serum and tissue TLR6 is decreased in MF and to prove that tissue TLR6 levels correlated positively with the stage of MF, suggesting that tissue TLR6 level could be a possible prognostic factor in MF.

In conclusion, the current study sheds the light on the possible role of TLR6 as a prognostic factor in MF, and also provides an insight about the possible role of TLR6 in the pathogenesis of MF, which offers better options for MF management.

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