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ORIGINAL RESEARCH

Evaluation of Interleukin-1α, Interleukin-10, Tumor Necrosis Factor-α and transforming Growth Factor-β in the Serum of Patients with Pemphigus Vulgaris

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ABSTRACT

Pemphigus is an autoimmune blistering disease characterized by a loss of cell adhesion result in acantholysis. Genetic factors and immunologic factors such as cytokines particularly IL-1α, IL-10, TNF-α, and TGF-β may counterpart to developing of Pemphigus. The aim of this study was to evaluate. The concentration of IL-1α, IL-10, TNF-α, TGF-β in serum of pemphigus vulgaris (PV) patients and normal individuals.

Material and methods: In this analytic and descriptive study 25 patients with pemphigus vulgaris (in active phase) and 25 healthy persons were examined. Serum samples of two groups were obtained and the level of IL-1α, IL-10, TNF-α and TGF-β were measured by ELISA technique. The data were analyzed statistically by independent T test (α = 0/05).

Results: All cytokines tested, showed higher concentration in patient's sera comparing to healthy control individuals. The level of IL-1α (p = 0.004), TNF-α (p = 0.008) and TGF-β (p = 0.009) were statistically different in two experimental groups, There was no significant difference in IL-10 level (p = 0.605).

Conclusion: Cytokines such as IL-1α, IL-10, TNF-α and TGF-β probably have a role in pathogenesis of PV. Further comprehensive studies are suggested to confirm these findings.

Keyword: IL-1α, IL-10, pemphigus vulgaris, TNF-α, TGF-β.

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INTRODUCTION

Pemphigus is an autoimmune disease in which auto antibodies against the epidermal cell surface glycoproteins, desmoglein (Dsg) 3 and desmoglein 1 causes a loss of cell adhesion and results in acantholysis and blister forming. The most common form of pemphigus is pemphigus vulgaris (PV). The oral lesions are often the first sign of the disease and they are the most difficult to resolve and treat.[1]

It has been suggested that pro-inflammatory cytokines i.e. interleukin-1α (IL-1α), interleukin-10 (IL-10), Tumor necrosis factor (TNF)-α and transforming growth (TGF)-β have an important role in acantholysis.[2-4] Desmoglein-specific T-cells produce cytokines that induce the activation and differentiation of autoreactive B-cells. Cytokines, such as interleukin-4 (IL- 4), IL-5 and IL-10 act at various stages of B-cell growth and differentiation.[5] Antigen-presenting cells (APCs) play an important role in the induction of auto antibodies. Several cytokines are involved in emigration of APCs from peripheral tissues to secondary lymphoid organs. The homeostatic balance between pro and anti-inflammatory cytokines produced during skin inflammation controls APC motility tightly. This balance affects the resulting adaptive immune response quantitatively and qualitatively.[6,7] Langerhans cells are the professional antigen presenting cells in the skin, which capture, process and carry antigens from the epithelium to the lymph nodes. In this process, cytokines such as IL-10, TGF-β and TNF-α play different roles.[7,8] Certain polymorphisms in the IL-10, TGF-β and TNF-α genes have been associated with a variety of human diseases.[9-14] Feliciani et al[3] reported that TNF-α and IL-1α might play a role in the pathogenesis of PV.

The aim of this study was to evaluate and compare the levels of IL-1α, IL-10, TNF-α and TGF-β in serum of PV patients and normal individuals.

The four cytokines tested in this study have different Pro-inflammatory and pro-angiogenic activities and their roles in the regulation of immune and inflammation responses have not been fully disclosed.

Table 1: Mean (SD) serum levels of IL-1 in PV patients and control group

Groups	*N*	*Mean (pg/ml) (SD)*	*p-value*
PV patients	25	3.00 (1.58)	0.004
Controls	25	1.62(0.73)	

IL-1: Interleukin 1; PV: Pemphigus vulgaris; SD: Standard deviation

Table 2: Mean (SD) serum levels of TNF-α in PV patients and control group

Groups	*N*	*Mean (pg/ml) (SD)*	*p-value*
PV patients	25	4.00 (1.37)	0.008
Controls	25	2.81(0.50)	

PV: Pemphigus vulgaris; SD: Standard deviation; TNF-α: Tumor necrosis factor α

Table 3: The mean serum levels of TGF-β in PV patients and control group

Groups	*N*	*Mean (pg/ml) (SD)*	*p-value*
PV patients	25	31.00 (106.94)	0.009
Controls	25	0.80 (1.22)	

PV: Pemphigus vulgaris; SD: Standard deviation; TGF-β: Transforming growth factor β

Table 4: The mean serum levels of IL-10 in PV patients and control group

Groups	*N*	*Mean (pg/ml) (SD)*	*p-value*
PV patients	25	2.00(0.48)	0.605
Controls	25	1.80(0.45)	

IL-10: Interleukin-10; PV: Pemphigus vulgaris; SD: Standard deviation

Table 5: Mean serum levels of four cytokines in PV patients and control group

Cytokines	*Controls*	*PV patients*	*p-value*
IL-1α	1.62	3.00	0.004
IL-10	1.80	2.00	0.605
TNF-α	2.81	4.00	0.008
TGF-β	0.80	31.00	0.009

PV: Pemphigus vulgaris; IL: Interleukin; TNF-α: Tumor necrosis factor α; TGF-β: Tumor growth factor β

MATERIALS AND METHODS

Serum samples were collected from 25 PV patients (13 men and 12 women, age range of 28 to 45 years) with active disease and 25 healthy controls (15 men and 10 women with age range of 20 to 42 years). All the patients and controls were recruited from Alzahra hospital, Isfahan University of Medical Sciences. The requirements of Helsinki declaration were observed and the patients gave informed consent. The ethical board of Isfahan University of Medical Sciences has reviewed and approved the study design (Grant# 38811).

Patients had clinical features of PV confirmed by routine histology and direct immunofluorescence that established the diagnosis of PV by intercellular deposition of IgG in lower layers of the epithelium. Active disease was defined as those patients with clinical lesions on the skin and/or oral mucosa. The sera of the patients were collected prior to initiation of systemic therapy.

For determination of IL-1α, IL-10,TNF-α and TGF-β, enzyme-linked immunosorbent assay (ELISA) was performed using commercially available kits (Bender Med System kits, Germany) statistical analysis was performed using independent T-test and SPSS software (version = 11/5) (α = 0/05).

RESULTS

The mean level of IL-1α in patients group was significantly Higher than control group (p = 0/004) (Table 1).

There was significant difference between the mean level of TNF-α in PV patients and healthy subjects (p = 0/008) (Table 2). Similarly PV patients had mean serum levels of TGF-β statistically significantly higher than levels of controls (p = 0/009) (Table 3).

The difference between the elevated serum of IL-10 in PV patients compared with serum of normal controls showed no statistically significance (p = 0/605) (Table 4).

Comparison of mean levels of four cytokines showed that TGF-β, and IL-10 had the most and the least level in PV patients respectively while in control group TNF-α and TGF-β had the most and the least level (Table 5).

DISCUSSION

According to recent literatures cytokines may be involved in the pathogenesis of various inflammatory and autoimmune diseases. In this study, we investigated the presence of IL-1α , IL-10, TNF-α and TGF-β in the serum of PV patients and normal individuals.

According to the results of this study the mean level of IL-1α and TNF-α In sera of PV patients was significantly higher than controls. Similar results were achieved by Feliciani et al.[15] They demonstrated that keratinocytes synthesiz IL-1α and TNF-α. These cytokines can play a role in PV acantholysis. Feliciani et al[15] suggested that PV IgG induced IL-1α and TNF-α may induce acantholysis through the upregulation of urokinase-type of plasminogen activator (uPA) and c3 synthesis in keratinocytes. In this study the mean level of TGF-β was significantly higher in PV patients than normal individuals. TGF-β play a particularly important role in promoting the expression of the adhesion molecule Ecadherin in both keratinocytes and langerhans cells. This molecule act as a glue, which under normal circumstances retains langerhans cells within the epithelium.[7,16] Arkwright et al[17] have shown that children with atopic dermatitis have the highest frequency of the low-producer TGF-β (codon 25c). Although Eberhard et al[7] could not find an

association between TGF- β1 polymorphisms and PV. The result of this study showed that although the mean level of IL-10 was higher in PV patients than controls but the difference was not significant.

Barioni et al[18] reported that the IL-10 levels in the serum of PV patients are below the detection limits when compared to other skin diseases. On the contrary, Bhol et al[19] and D'Auria et al,[20] reported that increased levels of IL-10 have been detected in PV patients' serum compared to normal individuals and these cytokine levels correlate with severity of disease.

IL-10 is an immune regulatory lymphokine, produced by T-cells, B-cells, macrophages, mast cells, eosinophils, keratinocytes and some tumor cells.[21-23] Though, it could be hypothesized that IL-10 might have a dual role to play in the disease process. At the systemic level, IL-10 may actually enhance, promote or facilitate auto antibody production. Bone marrow, spleen or other site of auto-antibody production are the site that this phenomena may occur. T-cells probably produced IL-10 at these sites in contrast at the cutaneous level. IL-10 with the help of other molecules that mediate inflammation may play an important role in decreasing of local inflammation. In this manner, it may limit the damage and prevent more extension of lesions in the skin and mucous membranes.[18,19]

However, the increased levels of these cytokines in serum of PV patients compared to normal subjects might be according to the proinflammatory or immunoregulatory action of these molecules in this autoimmune and inflammatory disease. In addition, the results of this study may have significant utility in the evaluation of chemointerventional therapy.

Cytokines therapy has been successfully applied to treatment of some cancer and autoimmune diseases, e.g. it was found that TNF-α can induce tumor-cell apoptosis,[24] and an antibody against TNF-α was effective in the treatment of Sjogren's syndrome.[25] Berookhim et al[26] although reported the effective role of TNF-α antagonist in the treatment of PV.

CONCLUSION

The results indicate that :

1. The level of IL-1α, IL- 10, TNF-α and TGF-β in patients with PV is higher than controls.
2. These preliminary data suggest that IL-1α, IL-10, TNF-α and TGF-β may play an important role in the pathogenesis of pemphigus vulgaris.

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