

LETTER TO THE EDITOR

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Serum Levels of Interleukin 18 and Interleukin 10 in Iranian Patients with Bullous Pemphigoid and Their Correlation with BP180-NC16a and BP230

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TO THE EDITOR

Significance of interleukin (IL)-10 in the pathogenesis of the autoimmune process and bullous pemphigoid (BP) is under investigation.¹ Activation of inflammasomes, an innate immune signaling complex, leads to IL-18 and IL-1 β production. A recent study showed an increased level of IL-18 in blister fluid and serum of BP patients.²

Since in different studies and ethnicities, different cytokine responses have been reported,³ we aimed to evaluate serum levels of IL-10 and IL-18 in first admitted untreated Iranian BP patients versus BP patients who were under treatment and compare it with healthy controls. In addition, we compared the levels of cytokines with BP180 and BP230 levels. Eighty individuals entered the study in three groups, including 39 healthy controls (27 male and 12 female), 16 first admitted untreated BP patients (8 male and 8 female), and 25 BP patients who were under treatment with systemic agents (14 male and 11 female). The control group consisted of healthy volunteers without the established autoimmune disorder. In BP patients who were under treatment, the therapy was started with response, the doses were adjusted.

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prednisolone 0.5 to 1 mg/kg/day and azathioprine 1 to 2 mg/kg/day, and then according to the treatment Cytokine measurement was performed by using the ELISA method. For the measurement of IL-10 and IL-18, the following kits (IBL International GmbH, Flughafenstraße, Hamburg, Germany) were used.

The diagnosis of BP was confirmed by histopathology, direct immunofluorescent, BP180, and BP230 ELISA findings.

For statistical analysis, the Mann Whitney test, Kruskal Wallis test, Bonferroni adjustment, Chi-square test, and Spearman correlation coefficient were used.

The mean age of first admitted untreated BP patients, BP patients under treatment and control group were accordingly 66.13, 65.52 and 58.67 years.

There were significant differences in the level of IL-18 between three groups ($p=0.008$). Based on the pairwise comparison, there were significant differences between healthy controls vs. first admitted untreated BP patients ($p=0.009$), and BP patients who were under treatment vs. first admitted untreated BP patients ($p=0.028$), but there was no significant difference between the control group and BP patients who were under treatment ($p=0.857$).

Regarding IL-10 levels, based on post hoc test, there was only a significant difference between healthy controls and first admitted untreated BP patients ($p=0.015$).

When comparing untreated BP patients with patients being under treatment, non-significant decreased levels

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of IL-18 and increased levels of IL-10 were observed.

With regard to the level of BP180, there were significant differences between the control group vs. BP patients being under treatment and first admitted untreated BP patients ($p < 0.0001$). Regarding the levels of BP230, there was a significant difference between the

control group and first admitted untreated BP patients ($p = 0.026$). A significant weak correlation was found between IL-18 ($\rho = 0.252$, $p = 0.024$), IL-10 ($\rho = 0.37$, $p = 0.001$) levels, and Anti-BP180. Besides, a weak correlation between IL-18 ($\rho = 0.298$, $p = 0.007$) and Anti-BP230 was observed (Table 1).

Table 1. Serum levels of IL-18, IL-10, Anti-BP180 and 230 in three groups including healthy controls (Control), first admitted untreated BP patients (New Case) and BP patients under treatment (Treated)

Cytokine & ELISA	Groups	N	Mean	SD	Median	Minimum	Maximum	p-value*
IL-18 (pg/mL)	Control	39	222.46	255.35	78	78	998	0.008
	New case	16	599.88	519.47	520	78	1684	
	Treated	25	249.20	284.16	78	78	1068	
IL-10 (pg/mL)	Control	39	3.18	1.10	3.00	3.00	9.90	0.015
	New case	16	3.88	1.91	3.00	3.00	9.80	
	Treated	25	4.30	5.27	3.00	3.00	29.10	
Anti-BP180 (U/mL)	Control	39	4.21	6.55	1.40	1.00	33.00	<0.001
	New case	16	170.33	147.88	150.50	3.60	423.00	
	Treated	25	81.09	113.20	25.00	1.00	376.00	
Anti-BP320 (U/mL)	Control	39	4.41	6.76	2.00	1.00	38.00	0.022
	New case	16	72.21	114.52	12.60	1.00	356.00	
	Treated	25	37.98	66.06	5.20	1.00	242.00	

*Kruskal Wallis test

In previous studies, the role of cytokines in the pathogenesis and severity of pemphigus and BP, have been studied.⁴ In our study, the mean serum level of IL-10 in first admitted untreated BP patients was significantly higher than its level in healthy controls ($p = 0.015$). In Ahmed's group study, only 2 of 15 BP patients had detectable serum levels of IL-10, Liu et al showed that in BP patients, the number of IL-10 producing B cells was increased.⁵ Antiga et al demonstrated that there was an insignificant difference between serum level of IL-10 in BP patients and healthy control groups.¹

In the present study, the mean and maximum serum levels of IL-10 in BP patients who were under treatment were higher than their levels in first admitted untreated BP patients and the control group. However, there was no difference between the median and minimum levels of IL-10. In Antiga et al study, serum levels of IL-10 were increased after corticosteroid therapy. Increased number of IL-10 producing cells following corticosteroid therapy may be responsible for increased serum levels of IL-10.^{1,5} In the present study, the higher levels of IL-10 in BP patients who were under treatment might be due to the anti-inflammatory effect of corticosteroid therapy.

IL-18 is a member of the IL-1 family cytokines. Through interferon-gamma production, IL-18

may be involved in autoimmunity and increased levels of IL-18 have been reported in the autoimmune process. In addition, IL-18 contributes to innate immunity.⁶ The important finding of our study is the higher level of IL-18 in first admitted untreated BP patients in comparison with both the control group and BP patients who were under treatment. This finding suggests the important role of IL-18 in the disease activity and the point that IL-18 and innate immunity might be involved in the pathogenesis of BP. The lower level of IL-18 in BP patients being under treatment in comparison with treated patients shows the effect of therapy on IL-18 level. Recently, IL-18 binding protein (IL-18BP) which is an inhibitor of IL-18 is discovered and might be used as an adjuvant therapy.⁷

We also found a weak significant correlation of BP180 with IL-18 levels. This finding is in accordance with previous report and correlation of IL-18 levels with the activity of BP.² Recent studies elucidated the critical role of BP180 in autoimmunity of BP, therefore the correlation of IL-18 with BP180 in our study shows the important role of IL-18 in the pathogenesis of BP.^{8,9}

IL-18, innate immunity¹⁰, and IL-10 might be involved in the pathogenesis of BP. IL-18 binding protein (IL-18BP) could be used as part of BP therapy and for this purpose, further studies are needed.

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