

# Serum interleukin-6 concentration in patients with pemphigus

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## Abstract

Pemphigus is a rare blistering autoimmune disease that damages the integumentary system and lowers the quality of life of patients. Interleukin-6 (IL-6) has been linked to the immunopathogenesis of pemphigus, according to recent research. Thus, the investigation purpose was to assess the function of IL-6 in the development and intensity of pemphigus disease. Between January 2022 and August 2022, a case-series study involving 26 patients with pemphigus vulgaris (PV), four patients with pemphigus foliaceus (PF), and 20 healthy volunteers was carried out

at the Ho Chi Minh City Hospital of Dermato-Venereology. Patients with PV and PF had significantly higher serum IL-6 concentrations than healthy volunteers ( $p < 0.001$ ). Patients with a positive Nikolsky sign had significantly higher serum IL-6 concentrations than those with a negative sign ( $p < 0.001$ ). The serum IL-6 concentration and the pemphigus disease area index were found to significantly correlate ( $r = 0.8$ ,  $p < 0.001$ ). According to our findings, IL-6 might be a significant factor in pemphigus development and severity. Thus, novel treatments that specifically target IL-6 could be a good option for managing pemphigus, particularly in its more severe forms.

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## Introduction

Pemphigus is a potentially life-threatening autoimmune blistering disease characterized by the autoantibody-induced breakage of adhesion molecules (desmogleins) between epidermal keratinocytes, resulting in acantholysis.<sup>1</sup> Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are two major variants of this disease, with different clinical presentations and pathogeneses.<sup>2</sup> The role of autoantibody-producing B lymphocytes in pemphigus has been determined, but the exact function of other immunocytes in the pathogenic pathway remains unclear.<sup>3</sup> Compared with PF, PV is more likely to recur and has a worse prognosis. Mouth ulcers in patients with PV are often resistant to treatment, and skin lesions in patients with PF can lead to erythroderma.<sup>4</sup> Since corticosteroids began to be used for the treatment of pemphigus, the mortality rate has been reduced to 1.6-12.0%. Nevertheless, the mortality rate remains two-fold higher in patients with pemphigus than in the general population.<sup>5-7</sup>

Despite the performance of numerous investigations worldwide, the exact mechanism of acantholysis in pemphigus has not been fully elucidated. Recent studies have shown that interleukin 6 (IL-6) is closely involved in the immunopathogenesis of pemphigus. The first study of IL-6 in patients with pemphigus was conducted in 1997, paving the way for other investigations of the IL-6 concentrations in serum and skin lesions. Most of these studies revealed increased IL-6 concentrations in both serum and skin lesions, suggesting that IL-6 plays a role in the immunological disturbances of patients with pemphigus.<sup>8-13</sup>

Given this background, the present study was performed to compare the serum IL-6 concentration in patients with PV and PF with that in healthy individuals. We also assessed the correlation between the serum IL-6 concentration and clinical severity using the pemphigus disease area index (PDAI).

## Materials and Methods

### Study subjects

This case series was conducted at Ho Chi Minh City Hospital of Dermato-Venereology from January 2022 to August 2022. 30

patients with PV and PF were recruited. The diagnosis of pemphigus was based on clinical symptoms, histopathology, and direct immunofluorescence tests. All patients were  $\geq 18$  years of age. Patients with autoimmune diseases, acute or chronic infections, pregnancy, or any malignancies were excluded because of evidence that IL-6 is involved in such conditions.<sup>14-18</sup> All patients underwent a thorough physical examination and laboratory tests by dermatologists. The control group comprised 20 age- and sex-matched healthy volunteers.

### Collection of biological samples

Venous blood specimens (3 mL) were collected from each patient and control subject into dipotassium ethylenediaminetetraacetic acid anticoagulant tubes and stored at  $-80^{\circ}\text{C}$  until analysis. IL-6 quantification was then performed with an Elecsys IL-6 Kit (Roche, Basel, Switzerland) and enhanced chemiluminescence immunoassay according to the manufacturer's protocol.

### Statistical analysis

All data were analyzed using Stata software version 14.2 (StataCorp, College Station, TX, USA). Because the laboratory data did not fit a Gaussian distribution according to the Shapiro-Wilk test, all results are expressed as median (50%) and interquartile range (25-75%), and nonparametric tests were used to test for statistical significance (Mann-Whitney U test and Kruskal-Wallis test). For correlation studies, Spearman's rank correlation was used. In all calculations,  $p < 0.05$  was regarded as statistically significant.

## Results

30 patients (26 with PV, 4 with PF) and 20 healthy controls were enrolled in the study. Among all patients with pemphigus, the male:female ratio was 1:1 and the mean age was  $52.5 \pm 14.25$  years (range, 32-81 years) (Table 1). The mean PDAI score was  $55.9 \pm 33.77$  (range, 12-154). Stratification of patients using the PDAI led to 17 patients in the extensive subgroup, 10 in the severe subgroup, and 3 in the moderate subgroup. The serum IL-6 con-

centrations were significantly different among these groups ( $p = 0.005$ ) (Table 2).

The serum IL-6 concentrations were significantly higher in the 30 patients with pemphigus than in the controls ( $p < 0.001$ ) (Figure 1). The serum IL-6 concentrations were also significantly higher in patients with a positive than a negative direct Nikolsky test ( $p < 0.001$ ). The difference in the serum IL-6 concentration between the PV and PF groups did not reach statistical significance. A significant correlation was found between the serum IL-6 concentration and the PDAI score ( $r = 0.8$ ,  $p < 0.001$ ) (Figure 2). There were no significant correlations between the serum IL-6 concentration and patient age or medications.

**Table 1.** Distribution of age and sex in patients and controls.

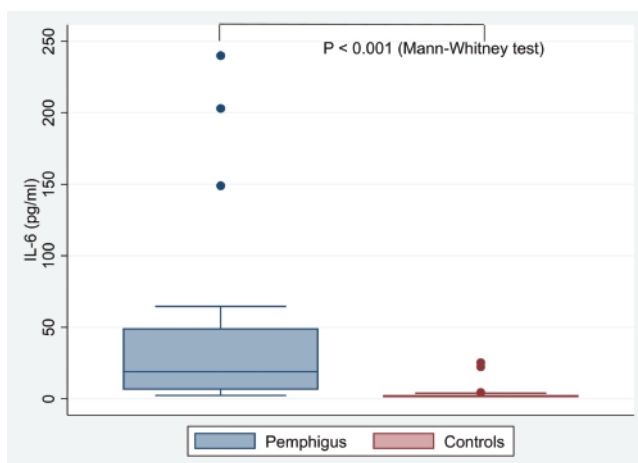
Characteristics	Patients	Controls	p
Age, years	$52.5 \pm 14.25$	$52.6 \pm 14.35$	0.95 <sup>a</sup>
Age group			0.95 <sup>a</sup>
<40 years	8 (26.67)	5 (25.0)	
40-59 years	12 (40.0)	8 (40.0)	
$\geq 60$ years	10 (33.33)	7 (35.0)	
Sex			
Male	15 (50.0)	10 (50.0)	1 <sup>a</sup>
Female	15 (50.0)	10 (50.0)	
Total	30	20	

Data are presented as mean  $\pm$  standard deviation or n (%). <sup>a</sup>Mann-Whitney test.

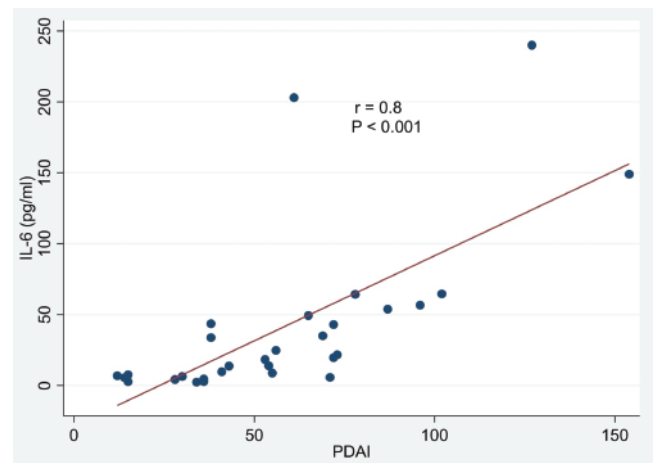
**Table 2.** Distribution of age and sex in patients and controls.

Severity	Frequency, n	Serum IL-6 concentration, pg/mL	p
Moderate	3	6.17 (4.85-7.25)	0.005 <sup>a</sup>
Severe	10	8 (4.54-33.8)	
Extended	17	46.15 (16.75-64.45)	

IL-6, interleukin 6; IL-6 concentration is presented as median (interquartile range). <sup>a</sup>Kruskal-Wallis test.



**Figure 1.** Comparison of serum interleukin 6 concentrations. The box plot shows the median and percentiles (25, 75) of the serum interleukin 6 concentrations between patients with pemphigus and controls. IL-6, interleukin 6.



**Figure 2.** Correlation between serum interleukin 6 concentration and pemphigus disease area index score. IL-6, interleukin 6; PDAI, pemphigus disease area index.

## Discussion

Quantifying the serum levels of cytokines is a direct way to obtain valuable information about the role of cytokines in the pathogenesis of pemphigus. In this study, we compared the serum levels of IL-6, a very popular proinflammatory cytokine, between patients with pemphigus and controls.

Human IL-6 is comprised of 212 amino acids, including a 28-amino-acid signal peptide. The IL-6 gene is located on chromosome 7p21.<sup>14</sup> IL-6 is also known as a B-cell differentiation factor, but recent studies have shown that IL-6 is a multifunctional protein involved in immunological regulation, erythrocyte and platelet formation, and acute inflammation.<sup>19</sup> IL-6 can be produced by T cells, B cells, monocytes, fibroblasts, keratinocytes, and adipocytes.<sup>15</sup> Several studies have suggested that IL-6 is involved in autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, dermatomyositis, and Crohn's disease.<sup>14,15,20</sup>

In the present study, the serum IL-6 concentrations were significantly higher in patients with pemphigus than in controls [18.95 (6.34-49.3) and 1.5 (1.5-2.695) pg/mL, respectively] ( $p < 0.001$ ). In 1997, D'Auria *et al.*<sup>9</sup> conducted the first study to assess the serum IL-6 concentrations in 25 patients with PV and 20 controls. They reported that the serum IL-6 concentrations in patients with pemphigus [8.6 (0.3-45.0) pg/mL] were significantly higher than those in controls [1.6 (0.2-4.7) pg/mL] ( $p < 0.001$ ). In 2012, Chrügner *et al.*<sup>13</sup> reported similar results, showing that the serum IL-6 concentrations of 12 patients with PF and 7 patients with PV were significantly higher than those of controls (934.5±66.8 and 501.7±87.9 pg/mL, respectively;  $p < 0.005$ ). Masjedi *et al.*<sup>8</sup> and Keskin *et al.*<sup>12</sup> also found significant differences in the serum IL-6 levels between patients with pemphigus and controls ( $p < 0.05$  and  $p < 0.001$ , respectively).

An important finding in our study is that the serum IL-6 concentrations were significantly higher in patients with a positive than a negative direct Nikolsky sign ( $p < 0.001$ ). Narbutt *et al.*<sup>11</sup> also showed that the serum IL-6 concentration was higher in patients presenting with the active stage of PV than in patients who had achieved remission. However, the difference was not statistically significant. Our results support the role of IL-6 in the pathogenesis of pemphigus, especially in the active stage of the disease.

Consistent with these findings, we also found a positive and significant correlation between the serum IL-6 concentration and the PDAI score ( $r_s = 0.8$ ,  $p < 0.001$ ). D'Auria *et al.*<sup>9</sup> also showed a positive correlation between the serum IL-6 concentration and the number of skin lesions ( $r = 0.9$ ,  $p < 0.001$ ). In 2020, Metwally *et al.*<sup>21</sup> reported a similar correlation between the serum IL-6 concentration and the pemphigus area and activity score ( $p = 0.03$ ).

In the present study, we found no significant differences in the serum IL-6 concentrations between treatment-naïve patients, patients treated with corticosteroids at  $\leq 0.5$  mg/kg/day, patients treated with corticosteroids at  $> 0.5$  mg/kg/day, and patients treated with corticosteroids in combination with immunosuppressants ( $P > 0.05$ ). This result is in line with that of Mortazavi *et al.*<sup>22</sup> who found that the serum IL-6 concentrations in patients with PV after 6 months of treatment with corticosteroids were not significantly different from those in the patients at onset. Chrügner *et al.*<sup>13</sup> also found that IL-6 synthesis in patients with PV was not inhibited even with high doses of dexamethasone.

## Limitations of this study

The sample size was small due to the rarity of pemphigus, and

no sex- or age-matching protocols were used when recruiting participants in the control group. Multicenter studies with larger sample sizes are needed to confirm our results and obtain more data on pemphigus patients.

## Conclusions

In summary, this study provides further support for the role of IL-6 in the pathogenesis of PV and PF. In addition, a strong correlation between serum IL-6 and disease severity was found in our study, similar to other research. It was recently shown that anti-IL-6 therapies could be an effective option for treating autoimmune diseases such as rheumatoid arthritis and Crohn's disease.<sup>23</sup> Therefore, new therapies targeting IL-6 may be a promising choice for treating pemphigus, especially in its severe forms.

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