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Cytokine Profiles of Patients with Psoriasis Vulgaris who Experienced Acute Respiratory Infection with COVID-19

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Abstract

BACKGROUND: COVID-19, developing hyper-inflammatory reactions, can be a trigger factor for the manifestation or exacerbation of psoriasis in people who have undergone this infection. According to the scientific literature, patients with psoriasis are more likely to be infected with a coronavirus infection than the healthy population. However, they tolerate it in a milder form. At the same time, there have been reported exacerbation cases of the psoriatic process during the active phase of the disease and after experiencing COVID-19.

AIM: The purpose of the study is to analyze the profiles of cytokines interleukin (IL)-17, IL-10, IL-8. IL-6, IL-4, and IL-1β in patients with psoriasis vulgaris and patients with psoriasis who contracted COVID-19.

METHODS: We examined two groups of patients: The first group – 46 patients with psoriasis vulgaris in the period of exacerbation of the disease; the second group – 15 patients with exacerbation of psoriasis who contracted a mild or moderately severe coronavirus infection. The control group consisted of 15 conditionally healthy donors. The levels of cytokines IL-1β, IL-6, IL-8, IL-17a, IL-4, and IL-10 in the blood of patients and practically healthy individuals were determined by the enzyme immunoenzymatic method, using the "Human ELISE Kit" reagent sets (Fine Biotech., China), according to the manufacturer's instructions. The difference between the study groups was assessed using the Mann–Whitney U-test. The results were considered significant at $p < 0.01$. All calculations were carried out using Microsoft Excel (Office 365).

RESULTS: Psoriasis patients who have contracted COVID-19 had higher levels of IL-1β, IL-6, and IL-8 in their blood than patients with psoriasis vulgaris.

CONCLUSION: Increased levels of IL-1β, IL-6, and IL-8 in the blood of patients with psoriasis may be a trigger factor for acute psoriasis in patients who have suffered from COVID-19.

Introduction

Psoriasis is a widespread chronic papulosquamous skin disease that occurs at any age worldwide it is also a complicated problem for patients and society. Psoriasis has a multifactorial etiology caused by dysregulation of innate and acquired immunity with activation of T-helpers Th-1 and Th-17 as well as an increase in the production of pro-inflammatory cytokines interleukins (IL)-1, IL-6, IL-22, IL-17, IL-23, IL-33, tumor necrosis factor (TNF-α), and interferon (IFN-γ) [1], [2]. Its most common form, chronic plaque or psoriasis vulgaris, is the result of genetic predisposition, especially in the presence of the HLA-C*06:02 risk allele, and environmental triggers such as streptococcal infection, stress, smoking, obesity, and alcohol [3].

Pathogenesis of COVID-19 is associated with the development of a "cytokine storm" — a sharp increase in the concentration of pro-inflammatory cytokines TNF-α, IL-6, IL-33, granulocyte colony-stimulating factor, IFN. -γ-induced protein 10 (IP10), and others. Thus, during the critical course of COVID-19, pathological activation of hereditary and acquired (Th1- and Th17-type) immunity develops [2].

There is dysregulation of the synthesis of pro-inflammatory, immunoregulatory, anti-inflammatory cytokines, and chemokines (IL, TNF-α, IP10, IFN-α, and IFN -β, as well as markers of inflammation, including C-reactive protein [CRP] and ferritin) [4]. Recently, severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) has been discovered to activate the nuclear factor kappa B (NF-κB) signaling pathway through the ORF7 (a protein signaling pathway), leading to the expression of pro-inflammatory cytokines. In addition to NF-κB-dependent inflammatory cytokines (IL-1α, IL-1β, IL-6, IL-8, IL-10, TNF-α, and IFNβ), ORF7a also induces other interleukins (IL-3, IL-4, IL-7, and IL-23) and chemokines [5].

The resulting hyper-inflammatory reactions of the developing COVID-19 can be a trigger factor for the manifestation or exacerbation of psoriasis in people who have suffered this infection [6]. According to the scientific literature, patients with psoriasis are more likely to be infected with a coronavirus infection than the healthy population, although they bear it in a milder form. At the same time, cases of exacerbation of the psoriatic

process during the active phase of the disease and after recovering from COVID-19 have been described in the literature, too [7], [8], [9], [10], [11], [12], [13].

Thus, the systemic phenotype associated with the inflammatory response caused by SARSCoV-2 infection is very broad and may resemble that of some autoimmune or inflammatory diseases [14].

The purpose of the study is to analyze the profiles of cytokines IL-17, IL-10, and IL-8. IL-6, IL-4, and IL-1β in patients with psoriasis vulgaris and patients with psoriasis who had recovered from COVID-19 before treatment.

Patients and Methods

The authors studied cytokines content in the blood of two groups of patients: The first group included 46 patients with psoriasis vulgaris during the exacerbation of the disease; the second group consisted of 15 patients with exacerbation of psoriasis who suffered from mild or moderate coronavirus infection. The patients received inpatient treatment in the Dermatology department of the "Institute of Dermatology and Venereology, National Academy of Medical Sciences of Ukraine." Among the 15 patients with psoriasis who developed a coronavirus infection, there were 11 men aged 20–68 years (average age — 42.9 ± 5.8) and four women aged 38–62 years (average age — 46.0 ± 3.0). The duration of the disease with COVID-19 in the patients was from 3 to 6 months. The group of patients with psoriasis vulgaris consisted of 46 patients: 25 men aged from 20 to 60 years (average age — 41.6 ± 3.5) and 21 women aged from 25 to 62 years (average age— 43.0 ± 3.0). The duration of the illness until the moment when the patients applied to the "IDV NAMSU" varied from several months to 35 years (in 12 persons (26.7%), the duration of the illness was up to 5 years; in 9 persons (20.9%) — from 6 to 10 years; 8 people (17.5%)—from 11 to 20 years; 12 people (26.4%)—from 21 to 30 years; 22 people (9.4%) — over 30 years).

The control group consisted of 15 conditionally healthy donors, including five men aged 24–46 (39.2 ± 4.2) years and 10 women aged 32–61 (41.4 ± 2.7) years.

The Institute of Dermatology and Venereology, National Academy of Medical Sciences of Ukraine approved the research protocol. The patients informed about their consent for the research.

Analysis of cytokines

Venous blood samples (5–10 mL) from patients and conditionally healthy donors were collected in vacuum tubes in the morning on an empty stomach. Blood serum was centrifuged and immediately frozen at −70°C and stored until processing.

The levels of cytokines IL-1β, IL-6, IL-8, IL-17a, IL-4, and IL-10 in the blood of patients and practically healthy individuals were determined by the enzyme immunoenzymatic method, using the "Human ELISE Kit" reagent sets (Fine Biotech., China), according to the manufacturer's instructions. Units of measurement: pg/mL.

Statistical analysis

The obtained results were statistically processed using non-parametric evaluation methods. We used median (Me), lower (LQ), and upper (UQ) quartiles of the distribution for descriptive statistics of central tendencies and the amount of variation. The correctness of the features distribution according to each of the obtained variation series was evaluated during the study. We calculated a significance level of $\alpha = 0.05$, taking into account the Bonferroni correction. Using the Mann–Whitney U-test, we assessed the difference between groups (a group of conditionally healthy donors compared to patients with psoriasis, patients with psoriasis compared to patients with psoriasis who developed a coronavirus infection, patients with psoriasis who developed a coronavirus infection as compared to healthy controls). The results were considered reliable at $p < 0.01$. All calculations were made using Microsoft Excel (Office 365).

Results

The results in Table 1 show that indicators of cytokine content are characterized by unidirectional manifestations in patients with psoriasis vulgaris during the exacerbation of the disease. Patients with psoriasis in both groups showed a significant increase in the level of all studied cytokines compared to the group of conditionally healthy donors, indicating a systemic inflammatory process (Table 1).

Table 1: Cytokine profiles in the blood of patients with psoriasis vulgaris (Group I) and patients with psoriasis who fell ill with COVID-19 (Group II), Me (LQ–UQ)

Index	Study group		
	Group I	Group II	Control group
IL-1β	43.25 (15.65–88.27) <0.00001*	100.6 (60.0–138.825) <0.00001* 0.0002**	4.0 (1.7–6.6)
IL-4	17.51 (9.11–39.07) <0.00001*	11.94 (9.49–30.04) <0.001*	3.8 (1.4–6.3)
IL-6	12.7 (9.8–15.6) <0.00001*	46.9 (18.78–49.30) <0.00001* <0.00001**	2.7 (1.62–4.475)
IL-8	10.9 (7.9–17.2) <0.00001*	22.5 (18.05–28.8) <0.00001* <0.00001**	2.7 (1.5–4.925)
IL-10	17.62 (8.80–24.97) <0.00001*	19.405 (6.99–251.44) <0.00001*	4.7 (2.9–6.7)
IL-17α	98.05 (54.6–145.92) <0.00001*	80.90 (67.65–348.40) <0.0001*	10.5 (7.87–19.3)

*Compared to a control group, **Compared to the first group of patients. IL: Interleukin, Me: Median, LQ: Lower quartile. UQ: Upper quartile.

The difference in laboratory parameters

between patient groups showed significantly higher levels of IL-1β (Me = 100.6 pg/mL vs. Me = 43.25 pg/mL, p = 0.0002), IL-6 (Me = 46.9 pg/mL vs. Me = 12.7 pg/mL, p < 0.00001), and IL-8 (Me = 22.5 pg/mL vs. Me = 10.9 pg/mL, p < 0.00001) in Group II compared to Group I.

Psoriasis patients who suffered from COVID-19 (Group II) had relatively implicit reactions on the part of IL-10, IL-17α, and IL-4: No significant difference was found between the groups of patients in terms of these indicators (Table 1).

Discussion

Persistent inflammation is common to both diseases, both psoriasis and COVID-19. An essential place in the pathogenesis of psoriasis belongs to the imbalance of pro-inflammatory and anti-inflammatory cytokines. The activity of the pathological process in psoriasis after COVID-19 is confirmed by a significantly high level of key pro-inflammatory cytokines IL-1β, IL-6, IL-8, and IL-17a. IL-1β is known to play a critical role in the development of psoriasis. Recently, a number of publications have proven that an increase in IL-1β production can not only stimulate the development or recurrence of skin inflammation but also increase the likelihood of autoimmunization. IL-1β induces the proliferation of T cells and enhances the production of IL-17, thereby fueling the inflammatory processes in psoriasis. That is, higher levels of IL-17a and IL-1β in patients with psoriasis, who suffered from COVID-19, indicate their importance in the pathogenesis of this dermatosis. Mature Th17 produce pro-inflammatory cytokines, of which IL-17 and IL-22 are important. IL-17, consisting of the monomers IL-17a and IL-17f, is able to bind to the IL-17 receptor, which is expressed on keratinocytes, endothelial cells, T lymphocytes, monocytes, and fibroblasts. The result of this interaction is increased production of the cytokines IL-6 and IL-8.

IL-6 is a pro-inflammatory cytokine, being an important mediator of the acute inflammatory response in acute respiratory distress syndrome and cytokine storm. It probably affects the severe course of COVID-19 as well, contributing to an increase in the concentration of CRP, hypercoagulation, and hyperferritinemia [14]. IL-6 at the beginning of acute inflammation mediates acute phase reactions [15]. The observed increase in the level of IL-6 in the blood serum in patients of Group II may be the basis of the increased stage of chronic inflammatory proliferation.

Given that IL-8 induces chemotaxis in neutrophils and that neutrophils can synthesize IL-8 after activation, it is likely that IL-8 also acts in an autocrine manner, supporting neutrophil infiltration in psoriatic tissue, thus contributing to inflammation [16]. It is likely that the significantly increased content of IL-6 and IL-8 in the blood of patients with psoriasis, who suffered from COVID-19, indicates an important role of these cytokines as factors ensuring the prolongation of immunoinflammatory reactions.

Coronavirus infection stimulates the release of IL-17, which can provoke an exacerbation of psoriasis [17]. Probably, the relatively low expression of anti-inflammatory cytokines IL-4 and IL-10 in patients with psoriasis who suffered from COVID-19 indicates insufficient anti-regulatory properties of the immune system in these patients.

Conclusion

The conducted study revealed a difference in cytokine profiles in patients with psoriasis vulgaris and psoriasis patients who experienced COVID-19. The authors have found that patients with psoriasis who contracted COVID-19 had higher levels of IL-1β, IL-6, and IL-8 in their blood than patients with psoriasis vulgaris.

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