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Pathogenetic Role of Violation in the Cytokine System in Non-Specific Interstitial Pneumonia

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Abstract **PURPOSE:** study of the role of production of pro- (TNFα) and anti-inflammatory (IL10) cytokines in the prognosis of the course of non-specific interstitial pneumonia. **MATERIAL AND METHODS:** Blood serum of 78 patients with NSIP and COPD. The control group consisted of 25 practically healthy people of the same age. The concentration of TNFα and IL-10 in the blood serum is determined by the method of solid-phase enzyme immunoassay using the AO-Vector-Best test (Novosibirsk, Russia). **RESULTS:** Characteristic features of the level of secretion of cytokines TNFα and IL-10 in the blood serum of patients with NSIP in comparison with COPD were established, which indicates a significant role of these cytokines in the pathogenesis of fibrosis.

Keywords Pneumonia, Cytokines, Serum, Imbalance

1. Introduction

In recent decades, the discovery of cytokines and their regulatory role in the immune response has determined the priorities of research in this area in various pathological processes. [4]. It has been shown that cytokine deficiency contributes to the development of a number of diseases, and their normal content increases the body's resistance to infections [6].

There is quite a lot of evidence of the pathogenetic role of cytokines and imbalance in their system in respiratory diseases [2]. But despite intensive research into the process of lung damage in pneumonia [3], Until now, the role of various cytokines has not been determined, the issues of identifying integral markers of the development of the pathological process in the lungs in pneumonia associated with different etiological agents, as well as the role of the etiological factor in the development of pneumonia have not been resolved [1].

Pulmonary fibrosis is a chronic and progressive tissue repair response that results in irreversible scarring and remodeling of the lung, characterized by high mortality and limited treatment options [13].

Non-specific interstitial pneumonia (NSIP) is the most devastating progressive interstitial lung disease that remains refractory to treatment. The pathogenesis of NSIP is based on aberrant crosstalk, which also damaged alveolar cells and myofibroblasts, ultimately leading to an aberrant fibrotic reaction. Recent evidence suggests that both innate and adaptive immune responses may be involved in the fibrotic process. The contribution of the immune system to the development of NSIP remains poorly understood [11].

In connection with the above, the aim of this study was to investigate the role of production of pro- (TNFα) and anti-inflammatory (IL10) cytokines in assessing the prognosis of the course of nonspecific interstitial pneumonia.

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2. Material and Methods

The present study involved 103 women and men. All examined individuals were divided into 3 groups: Group 1 consisted of 14 men and 34 women with an established diagnosis of NSIP (48), Group 2 for comparison consisted of 13 men and 17 women with COPD (30), and the control group included 25 practically healthy individuals. Immunological studies of the examined patients were conducted in the laboratory of immunoregulation of the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan. The concentration of tumor necrosis factor alpha (TNFα) and interleukin-10 (IL10) in the peripheral blood serum was determined by solid-phase enzyme-linked immunosorbent assay using test systems from JSC VECTOR-BEST (Russia, Novosibirsk). The quantitative evaluation of the results was carried out by constructing a calibration curve reflecting the dependence of optical density on concentration for a standard antigen and allowing comparison of the studied samples with it.

Statistical processing of the obtained data was performed using the Statistica 6.0 computer program. The reliability of differences in the mean values (p) of the compared indicators was assessed using the Student's criterion (t).

3. Results and Discussion

A decisive role in immune surveillance of the lungs, connecting innate and adaptive immunity, is played by many immunocompetent cells (ICC), which are producers of immune response mediators (cytokines). Resident alveolar macrophages and monocytes recruited to the lungs play an important role in enhancing the inflammatory response in the lower respiratory tract [10]. Any inflammatory process begins with the formation of a focus of inflammation and the synthesis of key mediators of the immune response, which is tumor necrosis factor alpha (TNFα).

TNFα – occupies a special place among cytokines. The main producers are monocytes and macrophages. It is also secreted by neutrophils, endothelial and epithelial cells, eosinophils, mast cells, B and T lymphocytes when they are involved in the inflammatory process. The biological properties of TNFα are extremely diverse and depend on the predominance of one or another cytokine from its family [8]. TNFα enhances the expression of adhesion molecules, the synthesis of proinflammatory cytokines and chemokines, acute phase proteins, phagocytic cell enzymes, etc. TNFα is involved in the formation of all major local, as well as some systemic manifestations of inflammation [7].

The results we obtained are presented in Table 1.

Table 1. Serum levels of the studied cytokines in the examined patients

Indicator	M±m, pg/ml	Me [Q1; Q3]	Min, pg/ml	Max, pg/ml
Control group, n=25				
TNF-α	20,36±1,02	21,84 [17,15;24,74]	10,63	27,38
IL-10	11,23±0,45	10,80 [9,7; 13,10]	7,4	15,7
NSIP, n=48				
TNF-α	69,70±2,24***	71,54 [63,27; 78,24]	32,32	95,03
IL-10	4,85±0,32***	4,02 [3,20; 6,03]	2,12	9,94
COPD, n=30				
TNF-α	41,12±2,01***	44,13 [31,31; 49,67]	18,77	61,58
IL-10	6,25±0,43***	6,11 [4,67; 7,77]	2,1	9,91

Note: * - reliable compared to control group data (* - P<0,05, ** - P<0,01, *** - P<0,001). Me – median, Q1(percentile) –25%, Q3 (percentile) – 75%.

TNFα-mediated inflammation is thought to play a key role in both respiratory and systemic manifestations. Analysis of the serum TNFα level before treatment revealed that the cachexin level in the group of patients with NSIP was increased by 3.4 times with an average value of 69.70±2.24 pg/ml (P<0.001) with an individual range from 32.32 to 95.03 pg/ml, in the group of patients with COPD by 2 times 41.12±2.01 (P<0.001) in the range from 18.77 to 61.58 pg/ml, compared with the values of the group of healthy women and men 20.36±1.02 pg/ml (Table 1).

Interleukin-10 (IL-10 or IL-10) is a pleiomorphic cytokine with diverse phenotypic effects. Originally discovered as a product of Th2 inhibiting Th1 activation, it is now known to be produced by nearly all types of activated immune cells, including B cells, mast cells, granulocytes (e.g., neutrophils, basophils, eosinophils), macrophages, dendritic cells, and multiple T cell subsets. Its primary actions are thought to be primarily anti-inflammatory, inhibitory, and IL-10 is considered a general T-suppressor cytokine [12].

Increased production of IL-10 causes a decrease in the antigen-specific immune response and has a suppressive effect on macrophages, although its mechanism has not been sufficiently studied [9].

Analysis of IL-10 content revealed a significantly reduced level in all groups of individuals examined. As shown in Table 1, IL-10 synthesis in the group of patients with NSIP was reduced by 56.8%, with an average NSIP value of 4.85± 0.32 pg/ml (P<0.001), while the normal values averaged 11.23±0.45 pg/ml. Also, in the group of patients with COPD, the content was reduced by 44.3%, which averaged 6.25± 0.43 pg/ml (P<0.001) versus the control - 11.23±0.45 pg/ml.

We assume that the obtained results indicate a profound disturbance of the regulatory system of cytokines responsible for the regulation of humoral, cellular and non-specific immunity in both NSIP and COPD. Being a suppressive cytokine, IL-10 has the ability to suppress immune inflammation, in particular inhibition of the synthesis of such pro-inflammatory cytokines as TNF-α, which is a product of alveolar macrophages (M2), and is the most important regulator of cytokines, largely determining the direction of immune reactions.

Thus, the study allowed us to establish characteristic features of the level of secretion of cytokines TNFα and IL-10 in the blood serum of patients with NSIP compared to COPD, which indicates a significant role of these cytokines in the pathogenesis of fibrosis. The data obtained indicate that the inflammatory process in patients with pneumonia and broncho-obstructive syndrome is accompanied by a significant increase in the level of TNFα and a decrease in the synthesis of IL-10. The results of the study confirm the leading role of the cytokine system in the pathogenesis of various disorders of the immune response, including leading to fibrosis of the pulmonary tissue.

4. Conclusions

1. Analysis of serum TNFα levels showed that in the group of patients with NSIP, the cachexin content was increased by 3.4 times.
2. It was revealed that IL-10 synthesis in the group of patients with NSIP was reduced by 56.8%.
3. The results obtained indicate a profound disruption of the regulatory system of cytokines responsible for the regulation of humoral, cellular and nonspecific immunity.

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