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INTERRELATIONS OF CYTOKINE PRODUCTION LEVELS IN THE MECHANISMS OF INFLAMMATORY PROCESS REGULATION IN PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

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The aim of study was to study of cytokine production levels and their relationship in the mechanisms of regulation of the inflammatory process in community-acquired pneumonia.

Materials and methods. The study was carried out in the period 2017–2020 based on the therapeutic department of the Municipal non-profit enterprise “City Clinical Multidisciplinary Hospital No. 25” of Kharkiv City Council. The study involved 34 adult patients with CAP aged 18 to 80 years (mean age 36.5 ± 10.3). The control group consisted of 20 apparently healthy individuals (mean age 39.5 ± 12.5). Levels of IL-17, IL-1Ra, TGF β 1, visfatin, adiponectin were determined by enzyme-linked immunosorbent assay.

Results. Levels of IL-1 Ra and IL-17 in the group of patients with CAP were 3.77 ± 0.24 and 33.08 ± 0.10 pg/ml, respectively. In the PPI group, the level of these indicators was probably higher ($p < 0.05$) and was 2.53 ± 0.13 and 28.17 ± 0.53 pg/ml. The level of TGF β 1 in the group of patients with CAP was 24.54 ± 0.55 ng/ml and was slightly higher than in the group of AHI (26.33 ± 0.62 ng/ml). No differences were found between adiponectin levels in the AHI group and patients with CAP, as in the case of visfatin levels. The disappearance of relationships in the system of normal regulation of the inflammatory process between one pair of cytokines and their appearance between other pairs indicates a violation of regulatory mechanisms in patients with community-acquired pneumonia.

Conclusions. The identified characteristics of the cytokine profile reflect the end of the phase of active inflammation in the lungs and the beginning of the phase of compensatory reactions. The findings suggest the importance of studying the cytokine profile in patients with community-acquired pneumonia, which will help to develop new approaches to predict the course of pneumonia, ways to correct metabolic disorders that develop in this condition, and will help identify risk groups for this pathology

Keywords: community-acquired pneumonia, pathogenesis, cytokines, inflammation, diagnosis

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1. Introduction

Community-acquired pneumonia (CAP) remains one of the most pressing problems of modern medicine, primarily due to the consistently high incidence. According to the WHO in recent years, lower respiratory tract infections are the third leading cause of death on the planet [1]. The mortality rate in hospitalized patients with severe disease varies from 14 to 40 % and increases significantly among patients older than 60 years [2, 3].

An important place in the study of molecular mechanisms of pathogenesis of CAP is occupied by intercellular mediators, which play a key role in this process [1, 2].

Interleukin 1 receptor antagonist (IL-1Ra) is one of the most important anti-inflammatory factors. It is part of a biological multisystem – a cytokine network that performs intercellular interactions that maintain cellular homeostasis at a certain level. IL-1Ra blocks the cellular receptor specific for IL-1 α and IL-1 β [4].

TGF β is a multifunctional cytokine, a modulator of cell growth, inflammation, proliferation and differentiation. It is thought that the local enhancement of TGF β production in the site of inflammation and at the same time its systemic inhibition [5]. That is, the effect of TGF β could be both pro-inflammatory and anti-inflammatory. The latter usually prevails, which protects the body from excess production by inflammatory cells of cytotoxic compounds. TGF β 1 plays an important role in bone marrow metabolism, is involved in the regulation of osteoblast-osteoblast interaction, stimulates the proliferation and differentiation of osteoblasts [6].

Adipokines are also involved in the regulation of the inflammatory process, the main function of which is to regulate energy metabolism at various levels. Adiponectin stimulates osteoblastogenesis in *in vivo* and *in vitro* experiments [7]. Thus, the effect of adiponectin is ambiguous and requires further study. Less is known about the effects on the metabolism of visfatin in the body, which requires further research.

In addition to the above cytokines in the pathogenesis of inflammation involved IL-17, a product of Th17 cells – CD4 + T-lymphocytes. Factors such as depletion, decreased activity of physiological processes, lack of physical activity, pro-inflammatory cytokines also contribute [8].

During the inflammatory process in the lung tissue there is a transformation of the microcirculatory tract, which is manifested in dystonia, thinning of the capillary network until the appearance of avascular areas. As a result of disorders of the microcirculatory tract develops ischemia and hypoxia of lung tissue of varying severity, including inhibition of osteoblast activity, exudation predominates [3, 5].

The aim of the research was to study the levels of cytokine production and their relationship in the mechanisms of regulation of the inflammatory process in CAP.

2. Materials and methods

The study was conducted in the period 2017–2020 based on the therapeutic department of the Municipal Non-Profit Enterprise “City Multidisciplinary Hospital No. 25” of the Kharkiv City Council. The study involved 34 adult patients with CAP aged 18 to 80 years (mean age 36.5 ± 10.3 years). The diagnosis of CAP was established based on epidemiological, clinical, laboratory, radiological data. Patients with such pathologies as tuberculosis, bronchial asthma, hepatitis B, C and D, HIV, blood diseases and oncological diseases were excluded from the examination.

The control group was formed of 20 almost healthy individuals (AHI), which is comparable to patients by age (mean age 39.5 ± 12.5 years) and sex.

Patients were examined in accordance with Medical Standards (F. G. Yanovsky National Institute of Tuberculosis and Pulmonology of the National Academy NAMS of Ukraine).

The study was conducted in accordance with the requirements of the Helsinki Declaration of the World Medical Association, the Council of Europe Convention on Human Rights and Biomedicine, Good Clinical Practice (GCP) and approved by the Commission on Bioethics of Kharkiv Medical Academy of Postgraduate Education (Minutes No. 4 of 20.04.2017). Patients who participated were included in the study after signing an informed consent.

Verification of CAP pathogens was performed using microscopic and bacteriological methods. Etiological diagnosis of atypical CAP pathogens included enzyme-

linked immunosorbent assay (Vector-Best-Ukraine reagent kit) using latex agglutination to detect bacterial antigen and / or antibody antibodies.

At hospitalization, all subjects were prescribed standard antibacterial therapy in accordance with the standards of the International Society of Pulmonologists and the Recommendations of the “F. G. Yanovsky National Institute of Tuberculosis and Pulmonology of the National Academy” of Medical Sciences of Ukraine (Kyiv, 2019).

Blood for the study was taken from the ulnar vein (10 ml). Levels of IL-17 and IL-1Ra were determined in the serum by enzyme-linked immunosorbent assay using Vector-Best reagent kits (Novosibirsk). TGFβ1 levels were determined by the DRG kit (Germany), visfatin by the RayBio kit (USA), and adiponectin by the BioVendor kit (Czech Republic).

Statistical processing of the obtained data was performed using the software package Statistica for Windows 8.0, the results were considered reliable at $p < 0.05$. Correlation analysis was performed in the same package Statistica 8.0, using the Spearman rank correlation coefficient [9].

3. Research results

It was found that patients with CAP have significant differences in cytokine profile from the AHI group (Table 1).

Levels of IL-1 Ra and IL-17 in the group of patients with CAP were 3.77 ± 0.24 and 33.08 ± 0.10 pg/ml, respectively. In the AHI group, the level of these indicators was significantly higher ($p < 0.05$) and was 2.53 ± 0.13 and 28.17 ± 0.53 pg/ml.

The level of TGFβ1 in the group of patients with CAP was 24.54 ± 0.55 ng/ml and was slightly higher than in the group AHI (26.33 ± 0.62 ng/ml). No differences were found between adiponectin levels in the AHI group and patients with CAP, as in the case of visfatin levels (Table 1).

In the AHI group, a positive correlation was found between adiponectin and IL-17 levels and between IL-1Ra and IL-17 levels. Also in this group there was a negative correlation between the levels of visfatin and IL-17, as well as IL-1Ra and visfatin (Table 2).

A correlation between the levels of IL-1Ra and visfatin, IL-17 and visfatin was observed in a correlation analysis in a group of patients with CAP. There was also a negative correlation between the levels of TGFβ1 and IL-1Ra, TGFβ1 and visfatin, IL-17 and adiponectin (Table 3).

Table 1

Serum cytokine composition of patients with community-acquired pneumonia ($\bar{X} \pm S_x$, $n=34$)

The composition of cytokines	Unit of measurement	Groups	
		AHI (n=20)	Patients with CAP (n=34)
IL-1Ra	pg/ml	2.53 ± 0.13	$3.77 \pm 0.24^*$
TGFβ1	ng/ml	26.33 ± 0.62	$24.54 \pm 0.55^*$
Adiponectin	μg/ml	0.66 ± 0.01	0.66 ± 0.02
Visfatin	ng/ml	141.61 ± 8.70	134.08 ± 8.77
IL-17	pg/ml	28.17 ± 0.53	$33.08 \pm 0.10^*$

Note: * – $p < 0.05$

Table 2

Correlation of cytokine levels in the AHI group (n=20)

The composition of cytokines	IL-17	Adiponectin	Visfatin	IL-1Ra
Adiponectin	0.35*			
Visfatin	-0.34*	-0.11		
IL-1Ra	0.41*	0.17	-0.46*	
TGFβ1	0.06	-0.17	0.00	0.42*

Note: * – correlation coefficients are probable at $p < 0.05$

Table 3

Correlation of cytokine levels in the group of patients with community-acquired pneumonia (n=34)

The composition of cytokines	IL-17	Adiponectin	Visfatin	IL-1Ra
Adiponectin	-0.30*			
Visfatin	0.58*	-0.04		
IL-1Ra	-0.09	-0.20	0.33*	
TGFβ1	0.12	-0.16	-0.30*	-0.30*

Note: * – correlation coefficients are probable at $p < 0.05$

4. Discussion

It could be assumed that changes in the cytokine profile in patients with CAP are associated with the beginning of the transition of the already started process, initiated by inflammation, in the phase of compensatory reactions. Perhaps alteration, causing the first stage of inflammation, allows the body's adaptive mechanisms to move to the next stage - the stage of limited exudation. Increasing the level of IL-1Ra also contributes to the processes of counteracting the effects of anti-inflammatory cytokines. The decrease in TGFβ levels due to its modulatory functions in the cytokine system could be interpreted ambiguously. The increase in the level of IL-17 confirms the development of inflammation, which was induced by alteration [5, 8].

There is no consensus in the literature on the relationship between adiponectin levels and other proinflammatory cytokines. For example, according to some authors [10] adiponectin inhibits induced osteoclastogenesis; globular adiponectin strongly inhibits TNFα / RANKL-induced osteoclast differentiation. Adiponectin acts as a potent regulator in diseases associated with cytokine activation, and PP is no exception in this case [7].

In addition, it was found that with the development of inflammation, the level of adiponectin reactively increases due to the stimulation of its synthesis and secretion. This probably protects the tissues from further damage.

Thus, adiponectin is likely to have a modulating effect on inflammation, changing the depth of the processes triggered by IL-1 and IL-17. The observed correlations between the levels of different cytokines may reflect the points of their inclusion in the system of functioning of cellular and molecular mechanisms of the inflammatory process.

Study limitations. The article considers the relationship between cytokine production levels in the mech-

anisms of regulation of the inflammatory process in patients with CAP, correlates between these indicators, but does not study the relationship between cytokine and immunoglobulin levels in patients with CAP.

Prospects for further research. The next step in our study will be to study the oxidative metabolism of erythrocytes in patients with CAP, in order to expand current ideas about the pathogenesis of CAP, its diagnosis and prognosis.

5. Conclusions

The disappearance of relationships in the system of normal regulation of the inflammatory process between one pair of cytokines and their appearance between other pairs indicates a violation of regulatory mechanisms in patients with community-acquired pneumonia.

The identified characteristics of the cytokine profile reflect the end of the phase of active inflammation in the lungs and the beginning of the phase of compensatory reactions.

The findings suggest the importance of studying the cytokine profile in patients with community-acquired pneumonia, which will help develop new approaches to predicting the course of pneumonia, ways to correct metabolic disorders that develop in this condition and will help identify risk groups for this pathology.

Conflict of interests

The authors declare that they have no conflicts of interest.

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