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PECULIARITIES OF INFLAMMATORY MARKERS IN PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA ASSOCIATED WITH CORONAVIRUS INFECTION

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Introduction. The global spread of COVID-19 and the development of its complications remain important research topics for the scientific community. The mutation of the virus has led to several waves of the pandemic, so some universal aspects, such as the inflammatory process, remain relevant for study. Viral pathogens affect the respiratory tract and stimulate the production of various proinflammatory factors, including histamine, interleukin-6 (IL), etc. that are involved in the implementation of inflammatory reactions of the lung tissue and systemic inflammatory reactions (Zhou F., 2020; Lipsitch M., 2020).

Pathogenicity of microorganisms. The acute inflammatory process that characterises pneumonia occurs in the most vulnerable parts of the bronchoalveolar tree - the distal lungs. Increased functional activity of T cells leads to a sharp activation of all components of the immune system. During the immune phase of inflammation, cytotoxic T lymphocytes, T helper cells, and various types of antibodies are involved in the focus of lung tissue damage (Lamers M. M., 2022; Zanforlin A., 2021)

Pneumonia is accompanied by changes in the peripheral blood system and bronchial lymphoid tissue. Serum concentrations of cytokines, such as tumour necrosis factor-α (TNF-α), IL-1β, IL-4, IL-6 and IL-10, increase. The production of IL-1β, TNF-α and IL-6 increases from the first day of the disease. The degree of inflammation depends on the increase in their level. The intensity of changes in

cytokine status also depends on the pneumonia pathogen (Chen R., 2020; Rosolowski M., 2020).

Cytokines activate the production of acute phase proteins, such as C-reactive protein (C-RP), fibrinogen, and also affect the production of chemokines by endothelial cells, thereby enhancing leukocyte adhesion and mobilisation. A 'cytokine storm' can occur during COVID-19 pneumonia, which is associated with high mortality. The above immunological parameters are important in the pathogenesis of pneumonia and determine the course of the disease and higher mortality. According to X. Luo et al. high levels of C-RP are associated with more severe forms of COVID-19, so controlling its level is important (Pasrija R., 2021; Luo X., 2020).

Cytokines trigger a series of reactions in a certain order, characteristic of pneumonia, which is manifested by damage to the microcirculatory system, tissue hypoxia, alveolar edema, and impaired lung metabolic functions The importance of the status and ratio of pro- and anti-inflammatory cytokines in the diagnosis of the severity of pneumonia and its impact on the course and outcome remains unclear. Therefore, the determination of cytokines is important for understanding their impact on the pathological process of community-acquired pneumonia associated with coronavirus infection, which determined the purpose of this study.

Objective. To determine the characteristics of inflammatory markers in patients with community-acquired pneumonia associated with coronavirus infection.

Material and methods: An open, prospective, observational study was conducted to achieve the goal and solve the tasks. In the period from January 2021 to February 2022, 256 patients with community-acquired pneumonia aged 40 to 65 years were examined at the outpatient clinic of the Kherson City Clinical Hospital named after Athanasius and Olga Tropin of the Kherson City Council, of whom 177 were associated with SARS-CoV-2 and 79 were negative for coronavirus infection. In addition, 35 healthy volunteers were examined on an outpatient basis. To participate in the study, patients signed the Voluntary Informed Consent to Participate in the Study form.

Study inclusion criteria: male and female patients aged 40 to 65 years; community-acquired pneumonia; informed consent to participate in the study.

Exclusion criteria for the study: Pregnant women; uncontrolled hypertension; hypertension of the third stage; decompensated diabetes mellitus; congenital and acquired haemodynamically significant heart defects; chronic heart failure of the second and third stages; oncological diseases; lung damage of more than 75% according to CT scan; contraindications to the administration of drugs and their components; alcohol dependence, drug addiction, mental disorders; patient's refusal to participate in the study.

All patients were carefully screened for inclusion/exclusion criteria. The diagnosis of community-acquired pneumonia was verified on the basis of the adapted evidence-based clinical practice guideline Community-Acquired Pneumonia in Adults, 2019. COVID-19 was detected in accordance with Order No. 722 of the Ministry of Health of Ukraine dated 28.03.2020 as amended by Order No. 2122 of the Ministry of Health of Ukraine dated 17.09.2020.

Distribution of the examined persons into groups. After establishing their compliance with the study inclusion/exclusion criteria, the study subjects were divided into groups depending on the presence of COVID-19:

- the first group consisted of 177 patients with NHF with COVID-19 (median age: 58.0 [53.0; 62.0] years);

- the second group consisted of 89 patients with UC without COVID-19 (median age 59.0 [50.0; 63.0] years);

- the third group included 35 practically healthy volunteers (median age 55.0 [48.0; 59.0] years) as a control group.

The levels of interleukin-6, interleukin-10, and hsCRP were measured in blood plasma by enzyme-linked immunosorbent assay using standard kits: ‘HF CRP-ELISA-Best’, “IL-6-ELISA-Best”, “IL-10-ELISA-Best” according to the attached instructions, in the certified laboratory of the Kherson City Clinical Hospital named after Athanasius and Olga Tropin of the Kherson City Council. The amount of extension was determined using a HTI Immunochem-2100 plate reader (High

Technology Inc., USA).

The statistical processing of the data obtained during the study began with descriptive statistics, including the calculation of the median and interquartile range (Me [Q25; Q75]). When testing statistical hypotheses, the null hypothesis was rejected at a statistical significance level of $p < 0.05$, which corresponds to the values accepted in biomedical research.

Results and discussion. The level of hsCRP between the groups of patients was significantly higher by 27.5 % in the group of patients with NHF with COVID-19 than in patients with NHF without COVID-19 - 17.20 [12.60; 19.70] mg/l versus 13.50 [9.70; 19.00] mg/l, respectively ($p < 0.05$). The median values of this indicator were significantly higher in both groups of patients compared to the value of 1.20 [0.70; 1.40] mg/l in the group of healthy volunteers ($p < 0.05$). IL-6 was the highest in the group of patients with UC with COVID-19 - 9.00 [7.78; 9.94] pg/ml and was significantly higher by 9.5% compared to the group of patients with UC without COVID-19 - 8.22 [6.94; 9.27] pg/ml and 3.8 times higher compared to the value of 2.40 [1.30; 3.10] pg/ml in practically healthy volunteers ($p < 0.05$).

There was no significant difference in IL-10 levels between the group of patients with UC with COVID-19 and the group of patients with UC without COVID-19 ($p > 0.05$). The level of this indicator in the group of practically healthy volunteers was 5.60 [4.60; 6.60] pg/ml and was significantly higher by 14.3% and 13.9% compared with the group of patients with UC with COVID-19 and the group of patients with UC without COVID-19, respectively ($p < 0.05$).

The median ratio of IL-6/IL-10 in the group of patients with UC with COVID-19 was 1.86 [1.66; 2.11] and was significantly higher by 12.1% than the value of this indicator in the group of patients with UC without COVID-19 - 1.66 [1.47; 1.84], ($p < 0.05$).

Compared with the group of healthy volunteers, where this indicator was 0.40 [0.28; 0.53], in the group of patients with UC with COVID-19 and in the group of patients with UC without COVID-19, a significant increase in 4.7 times and 4.2 times was noted, respectively ($p < 0.05$).

The course of pneumonia and its consequences determine the body's ability to respond to the pathogen by synthesising interleukins. The search for the most informative indicators of pneumonia caused by SARS-CoV-2 continues. Increased serum levels of C-reactive protein occur in both bacterial and viral infections, and it is a widely available biomarker of inflammation. Our data are in line with the results of other studies showing that C-RP is the biomarker that correlates most strongly with the progression of COVID-19, and is significantly elevated at an early stage of inflammation. According to L. Wang, C-RP is an independent discriminator of disease severity, indicating its diagnostic value for patients with COVID-19 (Ponti G., 2020; Gao Y., 2020; Ali N., 2020; Wang L., 2020).

Thus, the immune system responds to the development of pneumonia, and changes in the cytokine profile depend on the pathogen, as the levels of inflammatory response markers in patients with community-acquired pneumonia associated with COVID-19 are significantly higher. However, the mechanisms underlying the development of cytokine imbalance and their significance for the course of the disease remain poorly understood. It is promising to study the possibility of using inflammatory mediators to determine the course of community-acquired pneumonia associated with coronavirus infection.

Conclusions.

1. The level of hsCRP was significantly higher by 27.5% in the group of patients with NHF with COVID-19 compared with the group of patients with NHF without COVID-19, while the value of interleukin-6 in the group of patients with NHF with COVID-19 exceeded the median value of this indicator in the group of patients with NHF without COVID-19 by only 9.5%.

2. At the first contact with patients with community-acquired pneumonia, interleukin-10 determination does not help to distinguish between the groups of subjects.

3. The ratio of IL-6/IL-10 was significantly higher in the group of patients with CAP with COVID-19.

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