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IMMUNE DISORDERS IN COMMUNITY-ACQUIRED PNEUMONIA AND THEIR INFLUENCE ON THE SEVERITY OF THE DISEASE

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Annotation. Humoral and cellular immunity factors: blood content of T-lymphocytes and their subpopulations, B-lymphocytes, circulating immune complexes, determination of neutrophilic phagocytosis activity, cytokine system - IL-2, -4, -6, -8; TNFα in the dynamics of the disease provide information on the state of the immune system. Disorders in the immune system that determine the severity of pneumonia and the volume of inflammatory damage to the lung tissue have been identified. Insufficiency of phagocytic protection and impaired elimination of immune complexes, decreased activity of T-effector cells against the background of an increased reaction of natural killers, deficiency of humoral factors in the form of a decrease in the level of B-lymphocytes and a tendency to decrease in immunoglobulins M and G cause severe course of community-acquired pneumonia and lobar lung damage. The indicated disturbances in the immune system are reliably associated with an imbalance of cytokines, with the predominance of their proinflammatory activity and a decrease in regulatory functions, and require the development of immunomodulatory therapy.

Keywords: community-acquired pneumonia, pathogenesis, immune system, cytokines, immunocorrective system.

RELEVANCE OF THE TOPIC

Community-acquired pneumonia (CAP) remains one of the most pressing problems of modern medicine due to its stable high incidence, which tends to increase. Mortality in hospitalized patients with severe forms of the disease ranges from 14% to 40% and increases among patients over 60 years of age.

Currently, changes in the body's immunological reactivity are one of the leading causes of complicated and protracted pneumonia.

At the same time, the nature of immune disorders at individual stages of the inflammatory process, factors of intercellular interaction have not been studied fully enough and are interpreted ambiguously. In this regard, it is of interest to study cytokines that perform the functions of mediators of the immune system. They regulate the strength, duration of the immune response and the nature of the inflammatory process, providing positive and negative immunoregulation.

In lung diseases, cytokines are involved in the infectious-inflammatory process and the allergic response at the level of the immune mechanisms themselves and the effector link, largely determining the direction, severity and outcome of the pathological process.

PURPOSE OF THE STUDY

Identification of clinical and immunological disorders and changes in the cytokine system in patients with community-acquired pneumonia, assessment of their impact on the severity of the disease and justification of the appropriateness of using immunocorrective therapy.

MATERIALS AND METHODS OF RESEARCH

A total of 120 patients with community-acquired pneumonia (61 men and 59 women) aged 17 to 60 years who were undergoing inpatient treatment at the Andijan City Clinical Hospital were examined. The patients had no history of chronic diseases. The control group consisted of 20 practically healthy individuals comparable to the patients in age and gender.

To carry out statistical calculations, patients with mild and moderate forms of CAP, having a low risk of mortality (according to the Pneumonia PORT scale, Fine M., 1997) - less than 5% - were combined into the first group of 83 (69.2%) people, and patients with a severe form of the disease, having a higher risk of mortality, up to 30%, into the second group - 37 (30.8%) people.

Based on the results of chest X-ray, patients with varying degrees of severity were divided into 3 subgroups depending on the volume of lung tissue damage. The first subgroup (with focal changes) included 65 patients (54.2%), the second (with segmental lesions) - 26 (21.7%), the third (with lobar pneumonia) - 29 (24.2%) people.

Upon hospitalization, all patients examined were prescribed antibacterial therapy, according to the standards of the International Society of Pulmonologists, including aminopenicillins, second- and fourth-generation cephalosporins, macrolides, and alternative groups of antibiotics (fluoroquinolones).

The examination of patients was carried out in accordance with the republican medical and economic standards. Verification of the causative agents of pneumonia was carried out by generally accepted microscopic and bacteriological methods. Etiological diagnostics of atypical pneumonia pathogens included an enzyme immunoassay in dynamics with the determination of specific immunoglobulins IgM and IgG to Mycoplasma and Chlamydia pneumoniae in the blood serum.

The complex of standardized immunological studies included: analysis of capillary blood leukogram data; study of phagocytosis with determination of bactericidal activity in the nitroblue tetrazolium reduction test (NBT test) by neutrophils, spontaneous and induced by latex particles with calculation of the percentage of activated cells and the activation index; specific cellular link with determination of the population and subpopulation composition of peripheral blood lymphocytes in dynamics by the method of indirect immunofluorescence using monoclonal antibodies (MAB) from Coulter with characterization of activation markers; determination of the concentration of circulating immune complexes (CIC) was performed by the precipitation method with a 3.75% polyethylene glycol solution.

The study of the level of cytokines (IL-2, -4, -6, -8; TNFα) in the blood serum of patients with CAP in dynamics (upon admission to hospital and after 10 days) was carried out quantitatively using the enzyme immunoassay method.

Statistical processing of digital data was carried out using descriptive, parametric and nonparametric statistics methods on a personal computer using the program “Statistica 6” Statsoft USA.

RESULTS OBTAINED

An analysis of the clinical manifestations of CAP depending on the severity revealed more pronounced syndromes of intoxication and general inflammatory changes, a clinical and radiological predominance of lobar damage to the lung tissue with pleural effusion syndrome, and

in the auscultatory picture - moist fine bubbling rales and crepitations in patients with severe pneumonia.

The etiologic structure of CAP according to the results of microbiological research was as follows: pneumonia in patients with mild and moderate course was caused in most cases by intracellular pathogens, in particular Mycoplasma pneumoniae, gram-positive microflora - Streptococcus pneumoniae; in 25% of patients the pathogen was not identified. The leading pathogens of severe pneumonia were Streptococcus pneumoniae and mixed bacterial cultures, with an increase in the proportion of Staphylococcus aureus, in addition, gram-negative pathogens were detected.

Analysis of capillary blood leukogram data in patients with CAP revealed such nonspecific changes as leukocytosis with neutrophilia, left shift in the leukocyte formula, monocytosis, and increased ESR, which reflected different intensity of the inflammatory process. Relative lymphopenia was noted in both groups of patients and absolute lymphocytosis was noted in patients of the first group. A tendency toward a decrease in the absolute lymphocyte content was noted in the second group (severe forms), indicating insufficient response of the lymphocyte link in severe patients.

The results of the study of neutrophil phagocytic activity in patients with CAP of varying severity showed that the percentage of active phagocytes in both groups was significantly ($p < 0.001$) lower than in the control group. In addition, a decrease in the phagocytic number was found in both groups ($p < 0.001$). The dynamics showed an increase in the values of these indicators, but they did not reach the level of the control group. Similar data were obtained during immunological monitoring depending on the volume of lung tissue damage.

According to the NBT test, the relative content of cells capable of reducing nitroblue tetrazolium in the peripheral blood in both groups of patients was higher than in the control. This may characterize the activation of neutrophils in response to antigen stimulation and (or) bacterial sensitization.

The index of the functional reserve of microbiocidal activity of peripheral blood neutrophils (NSTst.-NSTsp.) was reduced in both groups, which can be assessed as a criterion for the insufficiency of reserve functions.

In our opinion, dysphagocytosis is evidenced by the disruption of the elimination of CIC from the body. Thus, the content of circulating immune complexes was statistically significantly increased in patients of both groups.

Thus, the first non-specific line of defense in CAP is accompanied by an increase in the absolute number of neutrophils with reduced phagocytic activity, hyperactivation of cells with depletion of reserve capabilities. Analysis of changes in cellular and humoral links of immunity in CAP was carried out taking into account the severity.

It was found that in patients of the first group (mild and moderate CAP) it was accompanied by an increase in the relative number of mature T-lymphocytes (CD3+) with a decrease in their absolute value, a decrease in the number of T-helper inducers (CD4+), an increase in the number of cytotoxic (CD8+) and natural killer cells (CD56+), and a decrease in the number of HLA-DR.

In patients of the second group (with severe CAP), a decrease in the relative number of mature T-lymphocytes (CD3+) and T-helpers (CD4') was determined, relative and absolute B-lymphopenia (CD19+) and a significant increase in the relative indicator of natural killer cells (CD56') were detected.

When studying immunoglobulins in patients with community-acquired pneumonia of varying severity, the following data were obtained: the IgA level tended to increase, and the IgM level to decrease in patients of both groups, but the indicators did not statistically significantly differ from the level of those in the control group. The IgG level was significantly ($p < 0.05$) reduced in patients of both groups.

Similar to the study of cellular and humoral immunity indicators, the study of cytokines in blood serum was conducted taking into account the severity of the disease.

Common to patients with varying degrees of severity of CAP was an initial increase in the blood level of the inflammatory cytokine IL-2 ($p < 0.01$), a tendency towards an increase in the value of TNFα.

In patients of the first group (with mild and moderate CAP), the level of IL-4, the values of the regulatory cytokine IL-6 and the proinflammatory chemokine IL-8 increased slightly. On the contrary, in severe patients (in the second group), the level of the lymphokine IL-4 was significantly lower than the control ($p < 0.01$), the value of IL-8 was higher ($p < 0.05$), and the IL-6 indicator exceeded the control value by tens of times.

During immunological monitoring it was revealed that the IL-2 level remained significantly elevated in both groups, and even increased in severe patients, while the IL-4 value slightly increased in the group with mild and moderate forms of the disease, and significantly ($p < 0.001$) decreased in severe cases. In both groups, after 10 days of treatment, the inflammatory activity index IL-8 was normalized. However, in patients with severe forms of the disease, the regulatory IL-6 value remained significantly high. The level of TNFα, a lymphokine with pronounced proinflammatory activity, which tended to increase in both groups at the onset of the disease, decreased during treatment in mild cases of CAP and increased in severe patients.

Changes in cytokine levels characteristic of varying degrees of severity also corresponded to the extent of lung tissue damage.

Thus, activation of chemokine IL-8 increased with the increase in the volume of the inflammatory process in the lungs. The IL-8 indicator was 1.9 times higher in segmental and 2.7 times higher in lobar lesions than in focal lesions, while the level of the anti-inflammatory cytokine IL-4 was significantly reduced. Its level was lower, the greater the volume of lung tissue damage - 2 times lower than the control in segmental lesions and 3.2 times lower in lobar lesions. The value of the regulatory cytokine IL-6 was 1.5 times higher in segmental and 4 times higher in lobar processes than in focal ones.

When studying the correlation between cytokine levels and other indicators of the immune system, the inducing role of these most important factors of intercellular interaction on various links of immunity was revealed.

DISCUSSION

The results of the analysis of the clinical course and etiological characteristics of community-acquired pneumonia in the patients we examined reflect the general trends in the course of the disease, consistent with literary data.

At the same time, the nature of the immune response of patients with CAP has features of reactivity that determine the severity of the disease. At the onset and peak of pneumonia, relative lymphopenia was detected in both groups of patients, more pronounced in severe cases of the disease, which, in our opinion, indicates an insufficient response of lymphocyte cells. This trend is clearly seen in the analysis of lymphocyte subpopulations in various categories of patients with pneumonia. Thus, in patients with mild and moderate cases, an increase in the number of mature T-lymphocytes (CD3+), cytotoxic (CD8+) and natural killer cells (CD56+) was noted. On the contrary, severe CAP is accompanied by a decrease in the number of mature T-lymphocytes (CD3+), T-helpers (CD4+), the CD4/CD8 index, with a simultaneous decrease in the level of B-lymphocytes (CD19+), against the background of an increase in the number of natural killer cells (CD56+). Such changes in the group of patients with severe CAP are characteristic of systemic inflammatory processes, but at the same time may indicate an inadequate immune response.

The indices of the main classes of immunoglobulins in the initial period of CAP were also characterized by lower values than in the control group, with the exception of IgA disimmunoglobulinemia against the background of the detected enhancement of immune complex mechanisms and functional insufficiency of the phagocytic link suggests the presence of immune complex and autoimmune components in the pathogenesis of complicated pneumonia. Of greatest interest are the results of the studies of the cytokine system.

In patients with mild and focal disease, equivalent activation of opposing cytokine pools is observed at the onset of the disease (IL-2, -4, -6, -8, TNFα) with an increase in IL-2, -4 and a decrease in IL-6, -8 and TNFα over time. On the contrary, severe disease and lobar lung tissue damage are accompanied by an imbalance in the cytokine link in the form of an increase in IL-6 by 10.5 times, IL-8 by 1.4 times, TNFα by 1.3 times and a decrease in IL-2 by 1.6 times, IL-4 by 2.7 times (in comparison with the indicators of patients with mild disease).

Considering the most important regulatory role of lymphokines IL-2, IL-4 (synthesized by Th1, Th2 lymphocytes, respectively), one can assume insufficient intercellular activation of specific factors of the cellular link of immunity (indirectly confirmed by low indicators of T- and B-lymphocytes, the level of immunoglobulins) in patients with a severe course, leading to an aggravation of the infectious process.

CONCLUSION

Thus, in patients with severe forms of community-acquired pneumonia and a large volume of lung tissue damage, an imbalance in the cytokine link is observed, which, in our opinion, determines the pathogenetic features of the course of the disease.

Insufficiency of cellular and humoral immunity mechanisms and imbalance of the cytokine link in patients with community-acquired pneumonia determines the severity of the disease.

The data of immunological monitoring allow us to conclude that standard therapy of patients with community-acquired pneumonia leads to its clinical and radiological resolution, but is not accompanied by normalization of immunity indicators in the group of patients with a severe form of the disease and lobar lung damage. This justifies the need for further development of pathogenetic, including immunocorrective therapy in severe cases of the disease.

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