ПОСТКОВИДНЫЙ СИНДРОМ ИММУНОПАТОЛОГИИ. ХАРАКТЕРИСТИКА ФЕНОТИПИЧЕСКИХ ИЗМЕНЕНИЙ ИММУННОЙ СИСТЕМЫ У ПОСТКОВИДНЫХ ПАЦИЕНТОВ

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Резюме. В данном исследовании рассматриваются долгосрочные последствия инфекции SARS-CoV-2 в отношении иммунного статуса. Учитывая длительную и глубокую иммунную дисрегуляцию, наблюдаемую во время острой инфекции SARS-CoV-2, необходимо определить, переходят ли эти изменения в последующую дисфункцию иммунной системы у выздоравливающих людей. В связи с этим целью исследования явилось изучение параметров иммунной системы у пациентов, перенесших SARS-CoV-2-инфекцию.

Было проведено обследование 150 пациентов, перенесших SARS-CoV-2 инфекцию по 96 параметрам методом проточной цитометрии. Общий анализ крови проводился на приборе Medonic (Швеция); методом иммуноферментного анализа определены уровни общих и специфических IgM, IgG, IgA, фрагменты комплимента (АО «Вектор-Бест», Россия); согласно общепринятой методике исследована активность фагоцитов.

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В ходе исследования установлено, что у пациентов выявляется минимум 4 фенотипа нарушений иммунной системы. Первые два фенотипа относятся к нарушению врожденных факторов иммунной системы и связаны со снижением количества $CD46^+$ и NK-клеток. Отмечено, что снижение $CD46^+$ сохраняется у значительного числа переболевших пациентов на протяжении длительного времени, что подчеркивается нарушениями экспрессии этого маркера на различных субпопуляциях лимфоцитов. Снижение уровня натуральных киллеров сопровождалось компенсаторным повышением количества Т-лимфоцитов, преимущественно за счет Т-хелперов и TNK-лимфоцитов и роста общих В-клеток памяти. Два других выявленных фенотипа характеризуются повреждением факторов приобретенного иммунного ответа и связаны с повреждением В-клеток и Т-цитотоксических клеток. Показана связь таких нарушений с повреждением эритроцитарного и тромбоцитарного ростков кроветворения, способствующих появлению гипоксии и возможному нарушению системы свертывания крови.

Таким образом, полученные результаты свидетельствуют о длительном выраженном повреждении иммунной системы постковидных пациентов, требующих иммунокоррекции данных нарушений. При этом нарушения врожденных и приобретенных параметров иммунной системы (4 новых фенотипа постковидной иммунопатологии) сопровождаются повреждениями эритроидного и тромбоцитарного ростков кроветворения. Данные изменения могут способствовать формированию как нарушений, связанных с гипоксэмическими процессами, так и способствовать тромбообразованию у постковидных пациентов. Длительное сохранение таких повреждений всех ростков кроветворения может приводить к нарушениям и других систем организма (сердечно-сосудистой, нервной и эндокринной), что требует дополнительных исследований в этих направлениях.

Ключевые слова: SARS-CoV-2, постковидные пациенты, CD-типирование, иммунная система, иммуноглобулины, комплемент, фагоциты

POST-COVID IMMUNOPATOLOGY SYNDROME: CHARACTERISTICS OF PHENOTYPICAL CHANGES IN THE IMMUNE SYSTEM IN POST-COVID PATIENTS

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Abstract. This study examines the long-term effects of SARS-CoV-2 infection on immune status. Given the prolonged and profound immune dysregulation observed during acute SARS-CoV-2 infection, it remains to be determined whether these changes translate into subsequent immune system dysfunction in recovering individuals. In this sense, the aim of the study was to study the parameters of the immune system in patients who had undergone SARS-CoV-2 infection.

150 patients who underwent SARS-CoV-2 infection were examined according to 96 parameters using flow cytometry. A complete blood count was performed using a Medonic device (Sweden); ELISA method determined the levels of general and specific IgM, IgG, IgA, compliment fragments (JSC Vector-Best, Russia). The activity of the phagocytes was studied according to the generally accepted method.

The study found that at least four phenotypes of immune system disorders are detected in patients. The first two phenotypes are related to the impairment of innate immune system factors and are associated with a

decrease in the number of $CD46^+$ and NK cells. It has been observed that a decrease in $CD46^+$ persists for a long time in a significant number of recovered patients, highlighted by the impaired expression of this marker in various subpopulations of lymphocytes. The decrease in the level of natural killers was accompanied by a compensatory increase in the number of T lymphocytes, mainly due to T helpers and TNK lymphocytes, and the growth of total memory B cells. Two other identified phenotypes are characterized by damage to acquired immune response factors and are associated with damage to B cells and T cytotoxic cells. The relationship of such disorders with damage to hematopoiesis erythrocyte and platelet sprouts, which contribute to the appearance of hypoxia and possible violation of the blood coagulation system, has been shown.

Therefore, the results obtained indicate a long-term pronounced damage to the immune system in post-COVID patients that requires immunocorrection of these disorders.

Keywords: SARS-CoV-2, post-COVID patients, CD typing, immune system, immunoglobulins, complement, phagocytes

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Introduction

Recent studies have significantly improved our understanding of SARS-CoV-2 infection by highlighting profound and disease-specific changes in the innate and adaptive immune compartments [2, 3, 4]. Lymphopenia and altered lymphocyte function in COVID-19 patients are correlated with disease severity, indicating the key role of T and B cells in pathology [2, 3, 4].

Given the profound and long-term immune dysregulation observed during acute SARS-CoV-2 infection, it is necessary to determine whether these changes translate into long-term immune changes and subsequent dysfunction in recovering individuals. However, the long-term consequences of SARS-CoV-2 infection are still poorly understood. The literature suggests significant and long-term changes in T cell populations and key events associated with the pathogenesis of COVID-19 in affected patients [6]. Furthermore, specific neutralizing antibodies against SARS-CoV-2 and T cell responses have been found to persist even 12 months after initial infection, according to the literature [7]. Some patients may also experience a variety of mental and somatic symptoms, including chronic fatigue, myalgia, altered memory, and emotional state, as well as signs of fibrotic lesions of the lungs and diseases of the pulmonary vessels [8].

Therefore, this study aims to investigate the parameters of the immune system in patients who have undergone SARS-CoV-2 infection.

Materials and methods

A survey was carried out in 150 patients 6-12 months after being diagnosed with COVID-19 in Chelyabinsk, Russian Federation, on 1 May 2021 to 30 December 2022. The sample size was determined based on previous work [1, 5, 12]. The inclusion criteria for the study groups were a confirmed diagnosis of SARS-CoV-2 infection by polymerase chain reaction (PCR), the presence of IgM, IgG, and IgA in the SARS-CoV-2 virus, and data from the computed tomography from previous pneumonia. The study was carried out no earlier than 6 months after pneumonia caused by SARS-CoV-2 infection.

All patients were previously examined by a general practitioner and an immunologist-allergist to identify concomitant diseases. The groups were randomly assigned by sex, age, and comorbidities according to the χ^2 test. Depending on the examination, the patients were divided into groups with altered immune system parameters and normal immune parameters. The data presented in the monograph by Zurochka et al. (2018) [9] were used. All studies were approved by the Independent Local Ethics Committee at the City Clinical Hospital No. 1, Chelyabinsk, Protocol No. 8 dated April 11, 2022.

Flow cytometry was used to determine $CD45^+$ and $CD46^+$ (panleukocyte markers for gating lymphocytes), $CD45^+$ and $CD46^+$, $CD3^+$ (T lymphocytes), $CD45^+$ and $CD46^+$, $CD3^+$, $CD4^+$ (helper inducers), $CD45^+$ and $CD46^+$, $CD3^+$, $CD8^+$ (cytotoxic T lymphocytes), $CD45^+$ and $CD46^+$, $CD3^+$, $CD56^+$ (TNK cells), $CD45^+$ and $CD46^+$, $CD3^-$, $CD56^+$ (natural killers), $CD45^+$ and $CD46^+$, $CD3^-$, $CD19^+$ (B lymphocytes), $CD45^+$ and $CD46^+$, $CD3^+$, $CD4^+$, $CD25^+$ (activated helpers, early activation of lymphocytes), $CD45^+$ and $CD46^+$, $CD3^+$, HLA-DR (activated T lymphocytes, late activation of lymphocytes). A general blood test was also carried out on Medonic Device (Sweden), and the levels of general and specific IgM, IgG, IgA, complement fragments ("Vector-Best", Russia) were determined by the enzyme immunoassay method. The activity of phagocytes was studied according to the generally accepted method.

Results and discussion

The present study selected patients with a violation of natural killers among those who underwent COVID-19, as described in published works [9, 10]. Among the 150 patients examined, 50.9% had a

markedly reduced level of natural killers when gated with the CD45 panleukocyte marker, and an even lower level of natural killers when gated with the CD46 panleukocyte marker. Additionally, an increase in T lymphocytes, T helper cells and TNK lymphocytes (likely compensatory), as well as memory B cells, was observed against the background of disturbances in the natural level of killers, accompanied by a decrease in the level of total IgM. Platelet levels, thrombocrit, and erythroidhemotopoietic germs also showed decreased levels of blood cortisol. These data indicate that patients with post-COVID syndrome exhibit a phenotype associated with impaired innate immunity systems.

Furthermore, the study found a pronounced decrease in $CD46^+$ expression (the receptor for the complement fragment) in T lymphocytes in 57.9% of patients with post-COVID syndrome. This indicates the involvement of CD46 in the immunopathogenesis of the disease. According to the literature, CD46 controls at least three key metabolic events, including the translocation of the γ-secretase-treated intracellular domain of CYT-1 CD46 to the nucleus, where it induces the expression of carrier proteins (GLUT1, LAT1 and CAT1) and the assembly of mTORC1. Activation of CD46 also induces increased expression of metabolic enzymes, such as fatty acid synthases and GAPD, as well as activation of intracellular C5 pools with intracellularly generated C5a, which stimulates mitochondrial C5aR1 and drives ROS production and activation of the NLRP3 inflammasome in $CD4^+$T cells.

These changes contribute to increased glycolysis and OXPHOS and ROS production, which are necessary for induction of IFNγ production and granzyme B expression, and ultimately lead to the implementation of protective effector responses of Th1 and T killers [11]. However, more research is needed to determine whether the observed changes are caused by the direct interaction of the virus and CD46. In particular, the identified complex of changes persists for a long time in a significant number of recovered patients, as highlighted by the impaired expression of this marker in various subpopulations of lymphocytes.

Additionally, the study detected two types of phenotypic changes in the immune status of patients with post-COVID syndrome that are related to acquired immune defense mechanisms. One of the most common disorders in patients with acute COVID-19 is the violation of the formation of cytotoxic T cells. This disorder was detected in 29.9% of patients with post-COVID syndrome, consistent with data from the literature [13]. In addition to a decrease in cytotoxic lymphocyte levels, these patients also showed lower levels of total T lymphocytes, TNK lymphocytes, and late activated T lymphocytes bearing HLA-DR.

The study found that in patients with COVID-19 with impaired natural killer cell function, the majority of patients had reduced levels of natural killer cells. This was accompanied by an increase in T lymphocytes, particularly T helpers and TNK lymphocytes, as well as an increase in memory B cells, but a decrease in total IgM. Platelet and erythroidhemotopoietic germ levels were also reduced, and blood cortisol levels were lower. These changes suggest that patients with post-COVID syndrome have an immune phenotype associated with impaired innate immune systems.

Furthermore, the study found that almost all changes in immune system parameters were found in the acquired immune system and did not depend on the CD45 or CD46 gated immune system. However, a subset of patients (17%) had a special type of immune system disorder characterized by a disorganized switch of B lymphocytes from IgM to IgG and IgA synthesis, leading to a marked decrease in the subpopulations of B2 lymphocytes. These patients also had a decrease in hemoglobin and platelet parameters, which may contribute to hypoxia and blood coagulation problems. This phenotype of immune system disorders is difficult to determine and requires non-standard approaches to assess immune status.

Conclusion

In general, the study identified four phenotypic immune system disorders associated with damage to $CD46^+$, NK cells as innate immunity factors, and B lymphocytes and cytotoxic cells as acquired defense factors in COVID-19 survivors. These findings suggest pronounced long-term immune system damage and the need for immunocorrection in patients with post-COVID syndrome.

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