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Short Communication

Changes in the immune system in patients with Coronavirus Disease-19 (CoViD-19), Caused by SARS-CoV-2 Virus

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Abstract

Changes in the cellular and humoral links of the immune system of patients with coronavirus disease-19, modifications of laboratory parameters, including biochemical, acute phase, cytokine, interferon systems, etc. are discussed. The problem of the formation of post-infection immunity and the possibility of reinfection of patients recovered is discussed.

The information available in the literature

A new strain of coronavirus Covid-19 has caused a global epidemic. Since it is now in full swing, clear data and statistics on the formation of immunity do not yet exist, but some information is still available.

According to the literature, a coronavirus carrier without symptoms does not develop immunity to infection, but with severe symptoms it can infect three more people. The question of the possible reinfection of ill persons is currently open. However, there are suggestions that in healthy people, before infection with a coronavirus infection, after a disease with a clear clinical picture, immunity to the virus may develop, which can last, as suggested, for 1-3 years. With clinical recovery, the formation of specific IgM and IgG antibodies is observed, however, data on the duration and intensity of immunity against SARS-CoV-2 are not available.

It is very important that at present, the presence of persistent immunity makes it possible to successfully use the blood plasma of those who have been ill, containing specific IgG and IgM antibodies for specific immunotherapy of other infected people, and rescue patients, especially in critical situations. Moreover, on March 24, the US Food and Drug Administration approved the use of plasma from recovered patients to treat some severe cases. In Russia, the Ministry of Health also authorized the use of such a technique.

The same practice suppose the effectiveness of the use of human donor immunoglobulins for the treatment of patients with coronavirus infection. Recall that they contain up to 108 types of anamnestic antibodies, which include antibodies from carriers or who have had an infection caused by other types of coronaviruses, or from persons immunized with cross

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antigens [1]. These immunoglobulins are especially useful for controlling secondary bacterial infection with COVID-19 [2].

There are reports that SARS-CoV-2 does not induce elevated levels of type I, II, or III interferons in infected human lung tissues, and for some messages even suppresses their synthesis.

He causes the development of strong inflammatory processes, increases the levels of IL-2, IL-7, IL-10, GCSF, TNFα which is often referred to as a "cytokine storm". Coronavirus does not change the content of procalcitonin, which increases only when a secondary bacterial infection is attached. In patients, ferritin, C-reactive protein rises; lactate and D-dimer (especially fatal), alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase. In severe cases of infection, deep lymphopenia and neutrophilia are noted. However, the often described eosinopenia is not associated with the severity of the disease. It is important to note that the severity of the disease in the absence of sepsis is determined based on the saturation of arterial blood with oxygen, respiratory rate, detection of virus RNA in the patient's blood.

After infection, the virus spreads through the mucus through the respiratory tract, causing a large release of cytokines and a high immune response in the body. In this case, a decrease in the number of lymphocytes in the blood, in particular T-lymphocytes, can be observed. One might think that too many lymphocytes are spent on fighting the virus and their deficiency reduces the protective abilities of the immune system, causing an exacerbation of the disease.

And one more message is of great interest since one of the mysteries of COVID-19 is the variability of the severity from asymptomatic to life-threatening. A study by German scientists shows that this variability can depend on the differences in the T-cell immune response, because of past cold diseases caused by other types of coronaviruses [3]. So, of 18 patients with COVID-19, 12 showed T-cells that respond to peptides from the N-terminus of the S-protein, and 15 (83%) - to peptides from the C-terminus. Patients with the absence of such T-cells in blood had a much more severe course of the disease. S-reactive CD4+ T-cells were found in 24 of 68 healthy donors (34%), and to peptides from the N-terminal of the protein in only 6 people (8.8%). Thus, T-cells of healthy people that respond to the protein of the new Coronavirus clearly "prefer" its C-end, which is more similar to the proteins of seasonal coronaviruses. Significantly, S-reactive CD4+ T-cells from patients with COVID-19 differed from healthy donor cells by co-expressing higher levels of CD38 and HLA-DR proteins, which indicates their recent in vivo activation. According to the authors, this indicates the potential for cross-reactive cellular immunity to a new coronavirus infection, which is an immune response in those who have previously been ill with seasonal coronaviruses. The authors' point is that the protective antibodies may decrease, but cellular immunity remains, and this cross-reactivity contributes to the easier courses of COVID-19 in children and youth. Of course, this idea is constructive.

We also have our own little experience in monitoring patients with confirmed severe coronavirus infection. In two patients with confirmed coronavirus total and subtotal pneumonia, there were unambiguous changes - a sharp increase in the content of total and segmented neutrophils, severe endogenous intoxication in the decompensation phase, deficiency of total monocytes and cytotoxic/suppressor T-lymphocytes (CD8+), B-cells (CD21+), monocytes with the expression of endotoxin and polysaccharide receptors (CD14+) and 5 member analogs of α-TNF receptors (CD40+). A sharp imbalance and deficiency of natural killers (lymphocytes CD16+, CD56+, CD56+16-), killer K-cells monocytes (CD16+), lymphocytes with the expression of integrin LFA-1 (CD11b+) and monocytes with expression intercellular adhesion molecules NCAM-1 (CD56+), as well as HLA-DR+ lymphocytes, was noted, which reflected a deficiency of antiviral immunity, hyperactivation of innate immunity, the development of an intense inflammatory process and viral infection.

Detailed immune information about one clinical case is of interest and concerning of a 47-year-old woman from Wuhan, presented by the emergency department in Melbourne [4]. During the period of clinical symptoms, she was characterized by febrile temperature, tachycardia, and tachypnea, 98% oxygen saturation during breathing, wheezing in the lungs, and SARS-CoV-2 in a nasopharyngeal swab for 4 days. It was very interesting that an increased number of AT-forming cells, follicular T-helpers, activated CD4+ T-cells and CD8+ T-cells and IgM and IgG specific antibodies were detected in the blood even before the onset of symptoms and persisted for at least 7 days after full resolution of symptoms. The virus was detected on days 5–6 in the nasopharynx, sputum, and fecal samples, but not on day 7. The patient had a high level of CRP, but the content of total lymphocytes and neutrophils remained unchanged. On days 7–9, the percentage of CD38+HLA-DR+CD8+ T cells increased (coexpression of CD38 and HLA-DR on activated CD8+ T cells increases with viral infections), which preceded the resolution of the symptoms of the disease. CD16+CD14+ monocytes (a marker of immunopathology) were reduced by 7–9 days of the disease, which was possibly due to their migration to the lesion foci.

At the same time, the content of activated HLA-DR+CD3−CD56+ natural killer effectors did not change while simultaneously registering low levels of the chemokine MCP-1 (CCL2), as well as pro-inflammatory cytokines in the patient's plasma, even during the period of severe symptoms on days 7-9. Symptoms of the disease disappeared completely by day 13, and the patient's clinical condition remained good even on day 20 with a parallel increase in plasma specific IgM and IgG antibodies for 7 to 20 days. It is significant to note that the patient did not experience complications in the form of respiratory failure or acute respiratory distress syndrome, did not require additional oxygenation, and was discharged within a week after hospitalization. However, we must not forget that she noted a mild, but symptomatically severe disease.

Thus, immune changes depend significantly on the severity of coronavirus infection, but it is too early to draw conclusions about the laws of immunopathology.

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Regarding the treatment of coronavirus infection, there is an opinion that in most cases (approximately 80%) some specific treatment is not required, and recovery takes place by itself. Severe forms of the disease are more likely to develop in older people and people with certain concomitant diseases, including asthma, diabetes, heart disease, and other diseases. In severe cases, funds are used to maintain the functions of vital organs.

It is very important today there is no unconditional evidence of the effectiveness of the use of any medications for the prevention and treatment of COVID-19. It is possible to use medications for nonspecific infection prevention, aimed at reducing the likelihood of illness in a potentially susceptible population because evidence of their clinical efficacy or inefficiency is currently insufficient.

According to WHO recommendations, it is possible to prescribe drugs with the supposed etiotropic efficacy of "off-label" (that is, medical use that does not comply with the instructions for medical use), and their use must comply with ethical standards recommended by WHO.

In coronavirus infection, a large number of drugs have been and are being used - analogs of nucleosides, chemotherapy drugs, antiviral agents, various interferons and interferonogens, immunomodulators, combinations of chloroquine and hydroxychloroquine, including antibiotics, neuraminidase inhibitors, monoclonal antibodies against pro-inflammatory cytokines. In some cases, positive effects were noted, but there is no documented evidence of the effectiveness of the use of any means for the prevention and treatment of coronavirus infection -19.

In more detail we would like to consider the advisability of using non-specific immunomodulators. This problem has also not been completely resolved, but some researchers believe that their use in coronavirus infection is useful. We also hold the same opinion in connection with which we will state some general principles of such therapy.

How is it justified? By the fact that according to the literature and our observations, including those obtained in our Vishnevsky Center of Surgery, with various types of pathological processes - burns, purulent-inflammatory, bacterial and various viral infections, surgical complications, and others, the immune system responds with an opposite answer [5]. On the one hand, a pronounced deficiency of the humoral and cellular units develops, and on the other, immune hyperactivation, which affects mainly innate immunity. We have extensive experience in using different immunomodulating drugs and in the vast majority they also have an opposite effect on these reactions: with immunodeficiency they correct it, eliminating the deficiency, and with hyperactivation of immune reactions they often decrease their activity to a normal level [2]. And this happens not only in chronic processes but also in acute infectious and inflammatory conditions. Therefore, one should not be afraid of exacerbation of inflammation, tissue damage, but it is necessary to select such immunomodulators, the mechanism of action of which is well known to us and they have a target effect.

We must also observe the *golden rule* - use only those drugs and methods of their administration that have a moderate or low-intensity effect.

The second rule is the use of combination immunotropic therapy, in which immunomodulators acts on various targets in the body that are involved in the pathological process.

One more interesting observation we made in the course of our long scientific and practical medical activity. It consists in the implementation in the body of various infectious and inflammatory processes and the use of immunomodulating drugs of the "summation" rule when repeated use of microdoses of drugs that are tens and hundreds of times smaller than the optimal pharmacopeia often has the same or even significantly more pronounced therapeutic and prophylactic effect [6-8]. At the same time, another fantastic property is realized - side effects, overdose sharply reduced, or canceled altogether.

We have repeatedly shown this in numerous model experiments and in patients [9].

I recall a recent example. A familiar doctor works in one of the hospitals as a surgeon in the «red zone» for coronavirus infection. He was part of a team of 6 doctors who worked with him for more than 1 month in compliance with all safety precautions. As a result, 3 doctors fell ill with severe coronavirus pneumonia, and one of his colleagues, with whom he had been in close contact for several days, became ill and died of coronavirus infection. He was 31 years old. Another doctor did not get sick and continues to work, but specific antibodies to SARS-CoV-2 were found in his blood. Our doctor is not ill and works in the same department to this day. No antibodies to coronavirus were found in his blood.

However, he applied throughout the entire period (about 1.5 months) sodium nucleinate (Na salt of low molecular weight yeast RNA) locally on the nasal and gum mucosa 2 times a day at an approximate dose of 50-80 μg, which is several hundred times lower than the official pharmacopeia.

As it can see, the example is very instructive, although, of course, many will regard this as a coincidence. Maybe.

Author contributions

V.M.Z., A.M.Z. , V.N. - analyzed available data, including immunological data and wrote the manuscript. A.Sh.R., F.M.S., K.N.P. - provided clinical data, analytic support. All authors edited the manuscript.

Compliance with ethical standards

Conflict of Interest All the collective members provided written informed consent to participate in this study. The authors declare that they have no competing interests.

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