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ОСОБЕННОСТИ ИММУННОГО СТАТУСА БОЛЬНЫХ С ОСТРЫМ КОРОНАРНЫМ СИНДРОМОМ, ПЕРЕНЕСШИХ COVID-19, В ЗАВИСИМОСТИ ОТ ЧИСЛА ЦИТОТОКСИЧЕСКИХ Т-ЛИМФОЦИТОВ (CD8+)

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Резюме. Пандемия коронавирусной болезни 2019 года (COVID-19) оказала беспрецедентное воздействие на здоровье и экономику во всем мире. Прямое повреждение миокарда и цитокиновый шторм, приводящий к дестабилизации ранее существовавших бляшек и ускоренному образованию новых бляшек, являются двумя механизмами, провоцирующими острый коронарный синдром при COVID-19. Недостаточно данных об иммунном статусе пациентов с острым коронарным синдромом, перенесшим COVID-19. Целью работы явилось исследование Т- и В-клеточного, гуморального звеньев иммунитета в зависимости от числа цитотоксических Т-лимфоцитов (CD8+) у больных с острым коронарным синдромом (ОКС), перенесших COVID-19.

Обследовано 65 мужчин с нестабильной стенокардией и острым инфарктом миокарда (острым коронарным синдромом) от 40 до 65 лет, которые ранее болели COVID-19. Проведено исследование периферической крови: общий анализ крови (прибор Medonic — Швеция), общие и специфические IgM, IgG, IgA, фрагменты комплимента («Вектор Бест», Россия). Субпопуляции Т- и В-лимфоцитов определены методом проточной цитометрии. У лиц с острым коронарным синдромом, перенесших COVID-19 преимущественно с нормальным и повышенным уровнями цитотоксических Т-клеток наблюдалось более тяжелое течение заболевания — превалировали больные с острым инфарктом миокарда, у них была больше смертность, продолжительность лечения, отмечались чаще тромбозы стентов. У больных с повышенными цитотоксическими Т-клетками наблюдалось максимальное увеличение эритроцитов, гемоглобина, гематокрита, лимфоцитов как общего числа, так и субпопуляций — Т-хелперов, Т-NK-лифоцитов, NK-лимфоцитов, Т-лимфоцитов ранней и поздней активации,

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В1- и В2-лимфоцитов, индекса НСТ-индуцированного теста. У пациентов с нормальным уровнем NK-клеток в сравнении с другими группами наблюдалось повышение НСТ спонтанной активности и индекса, значимое снижение С3а и С5а фрагментов комплемента. Превалирование тромбоза стентов и смертности в группе больных с нормальным уровнем цитотоксических Т-клеток может свидетельствовать о торпидности иммунной системы у этих пациентов с неблагоприятными исходами. Полученные данные свидетельствуют о значительной вариабельности ответов клеток иммунной системы у постковидных пациентов ОКС с различным уровнем цитотоксических клеток. Все это следует в дальнейшем рассмотреть подходы и к иммунокоррекции выявленных нарушений.

Ключевые слова: цитотоксические Т-лимфоциты, COVID-19, острый коронарный синдром, лимфоциты, иммунная система, комплемент

FEATURES OF THE IMMUNE STATUS OF PATIENTS WITH ACUTE CORONARY SYNDROME WHO UNDERWENT COVID-19, DEPENDING ON THE NUMBER OF CYTOTOXIC T LYMPHOCYTES (CD8+)

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Abstract. The 2019 coronavirus disease (COVID-19) pandemic has had an unprecedented impact on health and economies around the world. Direct myocardial injury and cytokine storm, leading to destabilization of pre-existing plaques and accelerated formation of new plaques, are two mechanisms that trigger the acute coronary syndrome in COVID-19. There is insufficient data on the immune status of patients with acute coronary syndrome who have undergone COVID-19. The aim of the study was to study T and B cell, humoral immunity depending on the number of cytotoxic T lymphocytes (CD8+) in patients with acute coronary syndrome who underwent COVID-19. Materials and methods of research: 65 men with unstable angina pectoris and acute myocardial infarction (acute coronary syndrome) from 40 to 65 years old, who had previously had COVID-19, were examined. A study of peripheral blood was carried out: complete blood count (Medonic device, Sweden), general and specific IgM, IgG, IgA, compliment fragments (Vector Best, Russia). Subpopulations of T and B lymphocytes were determined by flow cytometry. In persons with acute coronary syndrome who underwent COVID-19 with predominantly normal and elevated levels of cytotoxic T cells, a more severe course of the disease was observed: patients with acute myocardial infarction prevailed, they had longer mortality, longer treatment duration, and stent thrombosis was more common. In patients with elevated cytotoxic T cells, there was a maximum increase in erythrocytes, hemoglobin, hematocrit, lymphocytes of both the total number and subpopulations — T helpers, T-NK lymphocytes, NK lymphocytes, T lymphocytes of early and late activation, B1 and B2 lymphocytes, index of NBT-induced test. In patients with normal levels of NK cells, compared with other groups, there was an increase in spontaneous NBT activity and index, a significant decrease in C3a and C5a complement fragments. Prevalence of stent thrombosis and mortality in the group of patients with normal levels of cytotoxic T cells may indicate torpidity of the immune system in these patients with poor outcomes.

Keywords: cytotoxic T lymphocytes, COVID-19, acute coronary syndrome, lymphocytes, immune system, complement

Introduction

The 2019 coronavirus disease pandemic (COVID-19) has had an unprecedented impact on health and the economy around the world. In patients with a new coronavirus infection (COVID-19), ma-nifestations of lymphopenia occur early and are prognostic, most often potentially associated with a decrease in the number of T helpers and some cytotoxic T lymphocytes. This leads to an imbalance of the innate and acquired immune response, delayed

viral clearance and hyperstimulation of macrophages and neutrophils [1]. Inflammation in the vascular system can lead to diffuse microangiopathy with thrombosis. Inflammation in the myocardium can cause myocarditis, acute coronary syndrome, as well as rapid deterioration and sudden death [6]. The influx of T helpers into the cardiac vascular system leads to an increase in the production of cytokines, which stimulate the migration of smooth muscle cells into intima and the production of collagen and other fibrous products, which causes pronounced atherosclerotic damage. Direct myocardial injury and cytokine storm leading to destabilization of pre-existing plaques and accelerated formation of new plaques are two mechanisms provoking acute coronary syndrome in COVID-19 [10].

In the work of Khusainova L.N. et al. [4] it was shown that in patients with acute coronary syndrome (ACS), the number of T lymphocytes decreased, the number of lymphocytes affecting apoptosis increased (CD25+, CD95+).

According to Lebedeva O.K. et al. [5] the development of acute heart failure in patients with acute myocardial infarction (AMI) is associated with an increase in CD16(-) monocytes and a decrease in the number of CD16(+) T-NK cells (natural killers).

According to other data [8], in patients with ACS, in comparison with the control, the relative indices of subpopulations of T helper cells, T lymphocytes of early and late activation, as well as B lymphocytes are statistically higher. At the same time, there is a tendency to increase the absolute values of these parameters. There was a statistically significant increase in the T-NK lymphocyte subpopulation in relative and absolute terms, and total T lymphocytes ($p < 0.01$), as well as T cytotoxic lymphocytes ($p < 0.001$) decreased. As a result of an increase in T helper cells and a decrease in cytotoxic T lymphocytes, the CD4/CD8 lymphocyte index increased by more than 2 times ($p < 0.001$).

There is insufficient data in the available literature on the immune status of patients with ACS who have undergone COVID-19, which determines the relevance of the study.

The aim of the study was to study the T and B cell, humoral links of immunity depending on the number of cytotoxic T lymphocytes (CD8+) in patients with acute coronary syndrome who underwent COVID-19.

Research objectives:

1. To identify clinical differences in the course of the disease in patients with ACS who underwent COVID-19, depending on the number of T cytotoxic lymphocytes.

2. To identify differences in the content of the main populations of T and B lymphocytes, humoral immunity, blood cell composition in patients with ACS who underwent COVID-19, depending on the number of T cytotoxic lymphocytes.

Materials and methods

Sixty-five men with unstable angina pectoris and acute myocardial infarction (acute coronary syndrome) aged 40 to 65 years, who had previously had COVID-19, were examined. All persons also have hypertension. All patients required stenting of the coronary arteries in the next 3 days after admission to the hospital, since according to coronary angiography (CAG), they had coronary artery stenosis of 70% or more. CAG was performed on an Innova JE device, stents with a drug coating from the company Xience Alpine were implanted. Before this procedure, all patients signed an informed consent (protocol of the Ethical Committee of the Southern State Medical University of the Ministry of Health of the Russian Federation No. 9 dated 11.09.2006 and protocol of the Ethical Committee of the GAU OTKZ GKB No. 1 of Chelyabinsk No. 12 dated 10.10.2022).

The following examinations were performed: a general blood test (25 parameters were examined): leukocyte, erythrocyte and platelet sprouts of hematopoiesis, quantitative and qualitative composition of hematopoietic sprouts was carried out by a standardized method on a Medonic M20 hematological analyzer (Sweden).

From immunological indicators, the phagocytic activity of latex particles with a diameter of 1.7 microns was evaluated by neutrophils (phagocytosis activity, phagocytosis intensity, phagocytic number); spontaneous and induced NBT activity of neutrophils was determined by morphological method (light microscopy using Olympus microscopes (Japan). The phagocytic activity of neutrophils was determined by their ability to absorb latex particles [2].

Specific immunoglobulins M and G to COVID-19 and general immunoglobulins A, M, G were determined by VectorBest kits using standard enzyme immunoassay (ELISA) methods.

From immunological parameters, the following were determined by flow cytometry on the Navios cytofluorimeter (Beckman Coulter, USA) using a standardized technology for assessing the lymphocytic link of immunity [14]: CD45+, CD3+ (T lymphocytes), CD45+, CD3+, CD4+ (helper inducers), CD45+, CD3+, CD8+ (cytotoxic T lymphocytes,), CD45+, CD3+CD16+, CD56+ (T-NK cells) CD45+, CD3-, CD16+, CD56+ (natural killers), CD45+, CD3+, CD4+, CD25+, CD127- (T regulatory cells/suppressors), CD45+, CD3+, CD4+, CD25+ (activated helpers, early activation of lymphocytes), CD45+, CD3+, HLA-DR (activated T lymphocytes − late activation of lymphocytes. Phagocytosis and NBT activity of neutrophils were evaluated by standard

methods. C1q, C3a, and C5a complement fragments were also determined by the standard ELISA method.

The patients also underwent a study of the lipid profile and troponin level using a standard technique.

The clinical condition of patients was assessed at the time of examination and during the entire postoperative period in the hospital, and some indicators (such as mortality and thrombosis) in the next 6 months after surgery.

With the help of IBM SPSS Statistics 19, StatPlus 2009 Professional programs, statistical processing of the material was carried out. Calculated: arithmetic mean (M), arithmetic mean error (m), determined the Student's criterion for independent samples.

Results and discussion

All ACS patients who underwent COVID-19 were divided into 3 groups depending on the number of T cytotoxic lymphocytes [14]: with reduced indicators of T cytotoxic lymphocytes (23 people), normal (36 patients) and elevated − 6 patients. In the group with elevated T cytotoxic lymphocytes (group 1), all patients had AMI.

AMI was diagnosed among patients with normal T cytotoxic lymphocytes (group 2) in 58%, and with reduced T cytotoxic lymphocytes (group 3) − in 47%. The rest of the individuals had unstable angina. The maximum number of stents was implanted in patients of group 1; they also had the highest risk of Grace and the longest duration of hospitalization. At the same time, stent thrombosis and mortality were maximal in patients of group 2 − with normal T cytotoxic lymphocytes.

As for the general clinical blood test, it should be noted that there were no significant differences in the number of leukocytes, but there was a tendency to increase them in group 2. Red blood cells were significantly higher in group 1 compared to group 2 ($p < 0.05$) and group 3 ($p < 0.001$). Erythrocytes were also quantitatively larger in group 2 individuals compared to group 3. The concentration of hemoglobin is maximal in individuals of group 1 in comparison with group 2 ($p < 0.05$) and group 3 ($p < 0.01$). Statistically significant differences in hematocrit were observed in groups 1 and 3 ($p < 0.01$): higher in group 1. The average concentration of corpuscular hemoglobin was higher in patients with reduced T cytotoxic lymphocytes compared to their normal level ($p < 0.05$). In patients with normal T cytotoxic lymphocytes, the percentage of segmented neutrophils was higher than in group 1 ($p < 0.01$). The absolute number of lymphocytes was observed more in group 1 compared with groups 2 and 3 ($p < 0.001$), and in patients with normal T cytotoxic lymphocytes compared with their reduced level ($p < 0.001$). The relative number of lymphocytes was higher in patients with elevated T cytotoxic lymphocytes compared

with normal and reduced T cytotoxic lymphocytes ($p < 0.001$). The relative number of segmented neutrophils was recorded higher in group 3 compared to group 2 ($p < 0.05$) and group 1 ($p < 0.001$).

The width of the distribution of red blood cells was higher in group 3 compared to group 2.

NBT spontaneous activity and index were significantly higher ($p < 0.05$) in patients with normal T cytotoxic cell content compared with reduced. The NBT-induced index was maximal in group 1 and significantly differed ($p < 0.05$) from that in patients of groups 2 and 3. The relative number (%) of T lymphocytes (CD45$^+$CD3$^+$CD19$^-$) was maximal in group 2 and significantly ($p < 0.05$) differed from the same indicator in groups 1 and 3.

The absolute number of T lymphocytes (CD45$^+$CD3$^+$CD19$^-$) was significantly higher in group 1 compared to group 2 ($p < 0.01$) and group 3 ($p < 0.001$). Also, this parameter was higher in individuals with normal T cytotoxic lymphocytes in comparison with the group with a reduced level of T cytotoxic lymphocytes ($p < 0.001$).

As for the absolute values of T helpers, it should be noted that they were minimal in group 3 ($p < 0.001$) in comparison with 2 and 3 groups. The immunoregulatory index (CD4/CD8) was maximal in group 3 and significantly differed from that of group 1 ($p < 0.05$) and group 2 ($p < 0.01$).

T-NK lymphocytes relative values were significantly higher ($p < 0.05$) in individuals with elevated T cytotoxic lymphocytes in comparison with this parameter in patients of groups 2 and 3. The absolute number of T-NK lymphocytes was higher in group 1 compared to groups 2 and 3 ($p < 0.001$). In patients of group 2, this indicator exceeded that of group 3 ($p < 0.01$).

The absolute number of B lymphocytes (CD45$^+$CD3$^+$CD19$^+$) was minimal in group 3 and significantly differed from this parameter in group 1 ($p < 0.001$) and group 2 ($p < 0.01$).

T lymphocytes of early activation (absolute number) were maximal in group 1 and had a statistical difference from 3 groups ($p < 0.001$). At the same time, this indicator was higher in group 2 than in group 3 ($p < 0.01$).

T lymphocytes of late activation were higher in individuals with elevated T cytotoxic lymphocytes compared to group 2 ($p < 0.001$) and group 3 ($p < 0.0001$). In the group with normal T cytotoxic lymphocytes, this parameter was recorded higher than in group 3 ($p < 0.01$).

The content of C5a and C3a complement fragments was higher in group 3 patients compared with that of group 2 individuals ($p < 0.05$).

Total B1 lymphocytes (absolute number) prevailed in group 1 patients and significantly ($p < 0.001$) differed from group 3 patients. In individuals with

normal cytotoxic T cells, this indicator was higher (p < 0.01) than in patients with reduced. B2 lymphocytes (absolute values) were significantly increased (p < 0.01) in patients of group 1 relative to group 3. B2 lymphocytes were higher in group 2 individuals compared to group 3 (p < 0.05).

T regulatory cells (absolute values) were the largest in group 2 patients and significantly larger (p < 0.05) than in group 3 individuals (minimum values in this group). T regulatory cells of late activation (absolute values) were minimal in the group with reduced T cytotoxic lymphocytes and significantly differed (p < 0.05) from those in the group with normal T cytotoxic lymphocytes.

According to a study by Lebedeva O.K. et al. [5], lower T and NK cells were recorded in patients with acute myocardial infarction.

Other authors [11] note that 51.5% of ACS patients with implanted stents had higher helper T lymphocytes with CD3$^+$CD4$^+$ phenotype and 45.4% had T cytotoxic lymphocytes with CD3$^+$CD8$^+$ phenotype. This indicates immune activation. 63.6% of patients had an increase in NK lymphocytes, which could be explained by an increase in the activity of antitransplantation immunity. In our patients, high NK cells were observed in the group with an increased content of T cytotoxic lymphocytes.

According to Liu Y. et al. [7], a pathological autoreactive immune response is responsible for plaque rupture and the subsequent onset of acute coronary syndrome (ACS). Naturally occurring regulatory T cells (CD45$^+$CD3$^+$CD4$^+$CD25$^+$CD127-) are necessary to suppress the pathological autoreactive immune response and maintain immune homeostasis. In patients with ACS, a decrease in the number and suppressive function of T regulatory cells was revealed. This is also observed in our patients who underwent COVID-19 and had a reduced level of T cytotoxic cells. According to research, Tian X. et al. [12], in patients with ACS, compared with patients with stable angina pectoris and the control group, a violation of the formation of T regulatory cells is closely associated with hyperreactivity of the sympathetic system.

In Gang H. et al. [3], it was shown that T cytotoxic lymphocytes from patients with AMI showed increa-sed cytotoxicity compared to the control group, which was manifested by increased cytolytic activity against target cells, increased secretion of IFNγ and TNFα. Dysregulation of cytotoxic T lymphocytes in patients with ACS and COVID-19 was noted by Shafeghat M. et al. [9].

In this research analysis, Zidar D.A. et al. [13] it was shown that naive T cytotoxic lymphocytes of patients with ACS demonstrate phenotypic and functional characteristics of immune depletion: impaired IL-2 production and activation of programmed cell death-1. Exposure to oxidized low-density lipoproteins repeats these features *in vitro*. These data suggest that oxidized low-density lipoproteins may play a role in immune depletion, and this immunophenotype may be a biomarker of ACS. It is no coincidence that the most clinically severe patients (all with acute myocardial infarction) were in the group with an increased content of T cytotoxic lymphocytes. In many ways, the studies of these authors confirm the data we have obtained.

Conclusions

1. People with acute coronary syndrome who had COVID-19 mainly with normal and elevated levels of cytotoxic T cells had a more severe course of the disease: patients with acute myocardial infarction prevailed, they had more mortality, duration of treatment, stent thrombosis was more common.

2. In individuals with ACS and COVID-19 with elevated cytotoxic T cells, there was a maximum increase in erythrocytes, hemoglobin, hematocrit, lymphocytes of both the total number and subpopulations − T helper cells, T-NK lymphocytes, NK lymphocytes, T lymphocytes of early and late activation, B1 and B2 lymphocytes, NBT-induced test index.

3. In patients with normal levels of NK cells, compared with other groups, there was an increase in spontaneous activity and index of NBT, a significant decrease in C3a and C5a complement fragments.

4. The prevalence of stent thrombosis and mortality in the group of patients with normal levels of cytotoxic T cells may indicate torpidity of the immune system in these patients with adverse outcomes.

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