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PATHOGENESIS AND PATHOMORPHOLOGY OF CORONOVIRAL INFECTION

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✓ ***Resume***

Analyzing the latest scientific research on COVID - 19, the authors concluded that the course of coronavirus infection caused by various types of pathogens has similar pathological features of certain changes. Data on the dysregulation of the lymphocytic link together with the violation of the formation of germinal centers is limited due to the small number of cases described. For a full understanding of possible specific changes, further study of the pathomorphological changes occurring in the regional lymph nodes is required.

Key words: coronavirus infection, COVID-19, pathomorphology, lymphopenia, lymph nodes.

ПАТОГЕНЕЗ И ПАТОМОРФОЛОГИЯ КОРОНОВИРУСНОЙ ИНФЕКЦИИ

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✓ ***Резюме***

Авторами анализируя последные научные исследовании по COVID – 19 заключено что, течение коронавирусной инфекции, вызываемой различными типами возбудителей имеет сходные черты патоморфологчисеких изменений. Данные о дисрегуляции лимфоцитарного звена совместно с нарушением формирование зародышевых центров имеет ограниченный характер ввиду малого количества описываемых случаев. Для полноценного понимания о возможных специфических изменениях требуется дальнейшее изучение патоморфологических изменений, протекающих в регионарных лимфатических узлах.

Ключевые слова: коронавирусная инфекция, COVID-19, патоморфология, лимфопения, лимфатические узлы.

KORONOVIRAL INFEKTSION PATOGENEZI VA PATOMORFOLOGIYASI

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COVID - 19 bo'yicha so'nggi ilmiy tadqiqotlarni tahlil qilib, mualliflar har xil turdagi patogenlar tomonidan kelib chiqqan koronavirus infektsiyasi kursi ma'lum o'zgarishlarning o'xshash patologik xususiyatlariga ega degan xulosaga kelishdi. Germinal markazlarning shakllanishini buzish bilan birga limfotsitik bog'lanishning regulyatsiyasi to'g'risidagi ma'lumotlar tasvirlangan holatlarning kamligi sababli cheklangan. Mumkin bo'lgan o'ziga xos o'zgarishlarni to'liq tushunish uchun mintaqaviy limfa tugunlarida yuzaga keladigan patomorfologik o'zgarishlarni yanada o'rganish talab etiladi.

Kalit so'zlar: koronavirus infektsiyasi, COVID-19, patomorfologiya, limfopeniya, limfa tugunlari.

Relevance

Information on specific changes in the organs of the immune system is very limited. A wide range of changes was revealed - from the devastation of the B-dependent and T-dependent zones of the lymphoid tissue, to hyperplasia of the tissue of the lymph nodes and spleen of varying degrees. There is no doubt about the relevance of further identification of apoptosis of cells of the immune system as one of the causes of lymphopenia and immune dysfunction in COVID-19, which has prospects for searching for means of pharmacological influence on the process of lymphocytic apoptosis.

On February 11, 2020, the International Committee on Virus Taxonomy assigned the official name to the infectious agent - SARS-CoV-2. The advent of COVID-19 has posed challenges for healthcare professionals to quickly diagnose and

provide medical care to patients. At present, an intensive study of the clinical and epidemiological features of the disease continues, the development of new means of its prevention and treatment. The most common clinical manifestation of a new variant of coronavirus infection is bilateral pneumonia (viral diffuse alveolar injury with microangiopathy); acute respiratory distress syndrome (ARDS) was recorded in 3-4% of patients. In some patients, hypercoagulable syndrome with thrombosis and thromboembolism develops, other organs and systems are also affected (central nervous system, myocardium, kidneys, liver, gastrointestinal tract, endocrine and immune systems), sepsis and septic shock may develop. Coronaviruses (Coronaviridae) are a large family of RNA viruses capable of infecting both animals (their natural hosts) and humans [4.8].

Until 2002, coronaviruses were considered to cause mild upper respiratory tract infections (with extremely rare deaths). In the period from 2002 to 2004. SARS-CoV coronavirus from the genus Betacoronavirus (reservoir - bats, intermediate reservoir - civets) for the first time caused the development of the epidemic of the so-called atypical pneumonia (SARS) and the confirmed cause of death of 774 people in 37 countries of the world. Since 2004, there have been no new cases of SARS-CoV SARS. The appearance of mutations is typical for RNA viruses. Analysis of various lines of circulating strains of SARS-CoV-2 in early May 2020 showed that their diversity within individual countries is gradually decreasing, probably due to the disappearance of some viral lines and the rapid spread of other (dominant) lines. The original strain, isolated from samples from patients hospitalized in Wuhan in December 2019, was assigned to genetic clade L and is the reference genome for all subsequent sequences obtained by sequencing.

When analyzing the results of studies of the sectional material of 11 patients who died in the Primorsky Territory, it was confirmed [9] that COVID-19 is a systemic disease with extensive involvement not only of the lungs and heart, but also other organs. At the same time, all patients had a lesion of the blood vessels. I. Reva et al. [12] consider the possible mechanism of the pathogenesis of COVID-19 associated with damage to erythrocytes, which are attributed to the main key target that triggers a cascade of reactions leading to multiple organ failure. In the blood vessels and parenchyma of damaged lungs in patients with COVID-19, pathological forms of erythrocytes (anisocytosis and poikilocytosis, hypochromic and hyperchromic erythrocytes) characteristic of various anemias were identified. According to the authors of [2], the presence of macrophages with hemosiderin in the cytoplasm, as well as the presence of free hemosiderin in the vascular lumen, indicate that the death of erythrocytes begins not in the lung parenchyma, but at the stage of circulation and oxygen delivery to tissues, which leads to cell ischemia. and anemia due to the inability to transfer hemoglobin by damaged erythrocytes. Previously, the possibility of attachment of influenza and encephalomyocarditis viruses to human erythrocytes was established at the expense of the glycophorin A receptor, followed by hemagglutination of cells [2]. To date, many works have been published on the pathomorphological study of the sectional material of patients who died from COVID-19, but there is still not enough information about the changes that occur in the organs of the lymphatic system, in particular in the lymph nodes. According to the literature, the prevalence of hilar lymphadenopathy is approximately 6% among all cases of COVID-19 [3,4]. SARS-CoV-2 RNA was detected in hilar and subcarinal lymph nodes using both immunohistochemistry (monoclonal antibodies to the spike protein) and polymerase chain reaction (PCR) [5,6]. Morphologically, the lymph nodes had a normal follicular structure with a pattern of hemophagocytosis in about half of the cases described [3,5]. Coronavirus RNA was also identified in the trachea, spleen, and renal tubular epithelium, which confirmed the disseminated nature of the course of the new coronavirus infection.

The nucleocapsid protein of the virus was found in the cytoplasm of the epithelial cells of the salivary glands, stomach, duodenum and rectum, urinary tract, and also in the lacrimal fluid. However, the main and rapidly achievable target of SARS-CoV-2 is the alveolar cells of type II (AT2) of the lungs, which determines the development of diffuse alveolar damage. It is believed that with COVID-19, catarrhal gastroenterocolitis can develop, since the virus infects epithelial cells of the stomach, small and large intestine that have ACE2 receptors. However, its morphological features have not been sufficiently studied. There is evidence of specific damage to the vessels (endothelium), as well as the myocardium, kidneys and other organs. Changes in immunocompetent organs have not been sufficiently studied, the possibility of a specific lesion of lymphocytes with their apoptosis and pyroptosis (underlying characteristic and prognostically unfavorable lymphopenia), macrophage hyperactivity syndrome and hemophagocytic syndrome, neutrophilic leukocyte netosis (as one of the causes of disseminated intravascular coagulation syndrome) is being discussed. 1-3].

In the organs of the immune system, a wide range of changes was revealed, which, like the damage to other organs, apparently depends on infectious agents, the duration of the disease, comorbid diseases, the characteristics of therapy, etc. - from pronounced devastation, reminiscent of changes in HIV infection at the AIDS stage. , to varying degrees of hyperplasia, mainly T-dependent, and, less often, B-dependent zones of lymphoid tissue. As well as in the lungs, in the marginal sinuses of the lymph nodes, the phenomenon of autocytophagy was found, from hemocytophagy to phagocytosis by macrophages of fragments and whole lymphocytes [2].

Virus pathogenicity and risk assessment

It is now known that human angiotensin-converting enzyme 2 (ACE2) is a receptor and "entry point" into the cell of some coronaviruses. It is expressed in most tissues, including in a number of organs of the endocrine system, such as the pancreas, thyroid gland, testes, ovaries, adrenal glands, and pituitary gland [1.7].

R. Pal and M. Banerjee (2020) [6] emphasize that today there is not enough knowledge about possible endocrine system lesions in patients with COVID-19. For example, it is known that ACE2 acts as a receptor for coronavirus in a pneumocyte, but in turn, the virus RNA is detected in plasma, which confirms the fact that the virus can interact with ACE2 in other tissues as well [9]. There are no clinical or preclinical data to suggest that the endocrine system will recover without consequences after interacting with SARS-CoV-2 via ACE2 receptors expressed on its cells.

The accumulation of data on polymorphic variants of the gene encoding ACE2, its methylation or overexpression on the surface of T cells, demethylation / methylation of genes that regulate the exchange of cytokines and interferon, as well as genes regulating the immune response (for example, suspected of developing autoimmune thyropathies) could become the subject of research.

By analogy with SARS [7], it is possible that SARS-CoV-2 causes hypophysitis or affects the hypothalamus due to edema and neuronal degeneration, especially since cases of encephalitis in COVID-19 have already been described. Probably, in the near future, studies on patients who have undergone COVID-19 will become promising to assess the risk of damage to the hypothalamus and pituitary gland, which may result in the development of secondary (central) hypothyroidism [3, 4].

A typical neurological manifestation - a violation of the sense of smell - can be explained by the expression of ACE2 on olfactory epithelial cells [5]. The tissues of the hypothalamus and pituitary gland also express ACE2 and theoretically can become a target for the virus. At autopsy, edema and degeneration of neurons and identification of the SARS genome in them were demonstrated in the hypothalamus. Biochemical evidence for the involvement of the hypothalamic-pituitary system in SARS was found by Leow et al. in 2005 [2]. SARS survivors (61 participants) were examined by this group 3 months after recovery and then followed up periodically. Central hypocorticism was detected in 40%, and in 62.5% of them, the function of the pituitary-adrenal axis returned to normal. Of these, 87.5% presented typical complaints of weakness and postural dizziness. 5% also had central hypothyroidism.

It is hypothesized that some amino acid sequences of SARS-CoV viruses, like the influenza virus, have molecular similarities to ACTH, and the so-called "immunoinvasive strategy" of the virus is implemented due to this similarity in reducing the release of cortisol in response to stress in the body of an infected person. In addition, antibodies to the virus acquire the ability to cross-inactivate adrenocorticotropic hormone (ACTH) [2-6]. Most of the SARS-CoV-2 proteins have 95-100% homology with the proteins of the SARS-CoV molecule, which allows us to assume the ability of SARS-CoV-2 to include the same mechanisms of molecular mimicry [7], and a patient with a severe form of COVID-19 may be in the risk group of the so-called "glucocorticoid insufficiency of a critically ill patient."

The situation is aggravated for clinicians by the fact that, firstly, the diagnostic criteria for this syndrome themselves are not sufficiently developed, and secondly, the appointment of pharmacological doses of glucocorticoids in severe COVID-19 in the first recommendations was rejected and welcomed in subsequent [8], therefore, it is difficult to evaluate the contribution of the disease itself and the suppression of high doses of adrenal corticosteroids. So far, the assessment of the results of short-term administration of high doses of glucocorticoids in severe SARS has raised questions, and it was not recommended to transfer this technique to all patients with COVID-19 [11].

It is known that IL-1 and IL-6, produced by inflammatory cells, are stimulators of the endocrine system through the synthesis of ACTH. This impulse, apparently, passes through the hypothalamic receptors, as a result of which the central nervous system interacts with the endocrine and immune systems in response to pathogens. Moreover, this relationship suggests that the regulation of the hypothalamic-pituitary-adrenal axis by cytokines during inflammation depends on

the corticotropin-releasing hormone. However, prolonged stimulation with IL-6 does not guarantee a sustained increase in ACTH levels. In fact, chronic inflammation in patients with AID appears to correlate with altered hypothalamic-pituitary-adrenal axis function, since it has been shown that the ratios between serum cortisol and inflammatory cytokines (IL-6 and tumor necrosis factor (TNF)) can reach a level 10 times the normal value) is much higher in healthy people than in patients with rheumatoid arthritis. It is also assumed that the relative insufficiency of the adrenal glands in such patients may be due to impaired liver function during the metabolism of steroid hormones. Like other circulating regulatory molecules, cortisol levels follow a circadian rhythm, peaking in the early morning and trough in the late evening. Cortisol regulates the levels of several circulating pro-inflammatory cytokines such as IL-2, IL-3, IL-6, TNF-a, and IFN-γ. In addition, it affects the activity and vitality of the cells of the immune system. Glucocorticoids also inhibit phagocytosis of antigens and their subsequent elimination by macrophages. They suppress both cellular and humoral immune responses, maintaining the balance of pro- and anti-inflammatory reactions, and cause involution of lymphoid organs. Cortisol inhibits the phagocytic activity of neutrophils and macrophages, inhibits the activity of lymphocytes, inhibiting their maturation and differentiation, and stimulating apoptosis. Due to the immunosuppressive effect, glucocorticoids reduce the number and activity of inflammatory cells, especially tissue macrophages, and limit their ability to respond to incoming antigens. Suppression of the activity of immune cells disrupts their degranulation and the release of tissue-destroying enzymes (matrix metalloproteinases, proteases, nucleases, etc.), chemoattractants, and adhesive molecules [9].

Monoclonal antibodies - adaptation to new therapy.

Another important part of adapting the endocrine system to a postponed COVID-19 infection can be adaptation to one of the most effective methods of its treatment - the use of monoclonal antibodies.

Fortunately, a monoclonal antibody that effectively blocks the cytokine storm (an important link in a possible fatal prognosis in COVID-19; Tocilizumab is a monoclonal antibody against IL-6 expressed on adipocytes, fibroblasts and macrophages, which leads to the formation of EOP), is already approved for the treatment of ophthalmopathy FDA [3, 11], and, thus, conducting this therapy, we should not consider it from the standpoint of negative effects on the endocrine system.

IL-6 is a pro-inflammatory cytokine produced by various types of cells, including T and B lymphocytes, monocytes, and fibroblasts. It is involved in various physiological processes such as activation of T cells, induction of immunoglobulin secretion, induction of hepatic-phase protein synthesis in the liver, and stimulation of hematopoiesis. IL-6 is present in high concentrations in EOP patients and plays an important role in the pathogenesis of the disease. B- and T-lymphocytes are of particular importance at the early stages of EOP development. Further disease progression is thought to involve recruiting T cells into the orbit to participate in immune response and enhance B cell responses, which in turn leads to inflammatory processes such as the production of cytokines (including IL-6) and prostaglandins. as a result, remodeling of the soft tissues of the orbit occurs, which is characteristic of the image intensifier [12, 14].

If, using the so-called inhibitors of the immune response, we are forced to reckon with the potential negative effects on the endocrine system, then when using Tocilizumab, we are rather struck by the pathophysiological similarity (participation of IL-6) in the development of such clinically dissimilar manifestations as EOP, cytokine storm (essentially a hyperergic response of the immune system), and we have few analogues of such a response and data on its predictors.

Conclusion

To date, there is still not enough information about the changes that occur in the lymphatic organs, in particular in the lymph nodes. Taking into account the fact that one of the pathogenetic mechanisms of the development of the disease and its complications is the excessive activation of various links, the study of pathomorphological changes occurring in the regional lymph nodes is of great interest. An analysis of the literature showed that the coronavirus of all presented types is capable of directly infecting the structures of the lymph node, which is confirmed by its detection by the PCR method. Histological changes are more nonspecific in nature and are a reflection of lymphadenitis with hyperactivation and depletion of lymphocytes due to their increased apopotosis: normal, less often erased follicular structure with an observed pattern of hemophagocytosis, a decrease in the number of lymphocytes, macrophage infiltration, vascular endothelial hyperplasia and necrosis, focal vascular endothelial hyperplasia. It is noteworthy that in a severe course of infection, accompanied by an inadequate immune response of the humoral link, changes are revealed in the form

of a lack of formation of embryonic centers, which is a specific manifestation of dysregulation of the immune link. Thus, the course of coronavirus infection caused by various types of pathogens has similar features of pathomorphological changes. Data on the dysregulation of the lymphocytic link together with the violation of the formation of germinal centers are limited due to the small number of described cases. For a full understanding of possible specific changes, further study of the problem is required.

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