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ATHEROSCLEROSIS AND AUTOIMMUNE PHENOMENA IN COVID-19

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Abstract: Soon after the outbreak of COVID-19 in Wuhan, China, it became clear that patients with cardiovascular diseases (CVD) had a higher risk of acute complications [1]. The cardiovascular system is one of the main targets of the SARS-CoV-2 virus, resulting in the increased incidence of severe disorders including myocarditis, pericarditis, arrhythmias, heart failure and thromboembolism in COVID-19 cases. The mortality rate of such patients ranges from 11% to 19% [1]. Mortality from COVID-19 among people with CVD is much higher than average. In the presence of CVD accompanied by hypertroponinemia (for example, against the background of severe coronary heart disease), it exceeds 70% in some samples. Up to 25% of COVID-19 cases are accompanied with the development of cardiovascular complications, mainly among older people with pre-existing atherosclerosis and its clinical manifestation. In the very beginning of the COVID-19 pandemic, autopsy studies described fulminant myocarditis with features of direct viral and immunopathologically mediated heart damage [4]. It was assumed that myocarditis is common in COVID-19, but further studies on larger samples with magnetic resonance imaging (MRI) reported a more modest prevalence of severe myocarditis (accompanied by systolic dysfunction, electrocardiogram (ECG) changes and an increase in myocardial cell injury biomarkers in the blood) [5]. Thus, out of more than 168,000 patients hospitalized with COVID-19 in Florida, myocarditis was diagnosed only in 0.4% of cases [6]. Apparently, vascular lesions in COVID-19 are more significant than the cytotoxicity of the virus in cardiomyocytes. Of course, cardiovascular implications of COVID-19 are most dangerous for those who, on the basis of preexisting atherosclerosis, already have chronic lesions of the coronary/cerebral arteries and marginally reduced perfusion reserves of the myocardium and other vital organs [1].

Key words: Atherosclerosis, COVID-19, dyslipidemia, inflammation, cytokines.

Atherosclerosis is a chronic disease of the elastic and muscular-elastic arteries, characterized by the deposition of atherogenic lipoproteins in the vascular wall, phagocytic and proliferative, a synthetic reaction to these deposits from the cells of the vascular wall and mononuclear cells migrating there from the bloodstream and the resulting self-sustaining inflammation [7]. Therefore, a pro-inflammatory and thrombophilic state is an integral feature of atherosclerosis, potentially increasing vulnerability to severe COVID-19 because the underlying endothelial dysfunction might represent the ideal deregulated immunological setting in which SARS-CoV-2 triggers a “cytokine storm”. Even despite thromboprophylaxis, heart attacks, strokes and venous thromboembolic complications in the Milan cohort of people hospitalized with COVID-19 in 2020, for example, developed in more than 8% of cases. The SARS-CoV-2 S-protein can directly bind to human ACE2 to enter cells. SARS-CoV-2 has a polybasic insertion (PRRAR) at the S1/S2 cleavage site that can be cleaved by furin. This new cleavage site, absent in SARS-CoV-1 or other coronaviruses, appears to facilitate processing of the S protein at the S1/S2 boundary which is required for SARS-CoV-2 entry into cells. Similar cleavage sites have been described for highly pathogenic avian influenza and Newcastle disease viruses. There is a hypothesis that this remarkable feature plays a significant role in the multicellular tropism of SARS-CoV-2, contributing to the multiorgan effects of COVID-19. In vitro infection of

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cardiomyocytes with the S1 subunits of the SARS-CoV-2 spike protein can alter their transcriptome, induce fragmentation of myofibrils and destruction of nuclei. Thus, the S1 protein itself is dangerous for cardiac cells, and SARS-CoV-2 is characterized by the ability to cause hypertrophic myocardial remodeling, cardiac dysfunction and myocarditis [4]. In coronavirus myocarditis (as in myocarditis caused by enteroviruses and herpes group viruses), both lymphocytic infiltration of the myocardium and autoantibodies against cardiac antigens are detected [6]. This testifies in favor of the autoimmune component of delayed myocardial damage in COVID-19, probably with the contribution of the molecular mimicry phenomenon and an immunostimulatory adjuvant like effect of hypercytokinemia [2]. The pathogenesis of myocarditis in COVID-19 seems to include not only immune-mediated inflammatory cytotoxicity, but also dysfunction of receptors and ion channels caused by autoantibodies. A number of functional blocking and/or stimulating autoantibodies to various proteins, including those expressed in the heart, have been identified in patients with severe COVID-19. Autoimmune phenomena in COVID-19, including those related to the cardiovascular system, can be facilitated by a shift in the differentiation of T-helpers towards Th1 cells, which occurs against the background of hypercytokinemia (see below). It should be also noted that myocarditis cases after receiving mRNA-based COVID-19 vaccines (with largely favorable outcomes) have been reported worldwide, especially in adolescents and young adults. Potential mechanisms of myocarditis in this case include the activation of pro-inflammatory cascades in the heart by viral mRNA, molecular mimicry between the spike protein of SARS-CoV-2 and cardiac self-antigens and sex hormone related factors. Finally, the death of cardiomyocytes can be caused by excessive exposure to certain cytokines, both coming from inflammatory cells that have infiltrated the heart and those circulating in the blood at extremely high concentrations under cytokine storm conditions. A multiple increase in serum levels of IL-2, IL-6, IL-10, GCSF, IFNγ, MCP-1, MIP-1-α and TNF-α seems to contribute to myocardial injury in progressive hemodynamic shock of any etiology, for example, in chimeric antigen receptor (CAR) T cell therapy-induced cytokine release syndrome. Severe COVID-19 is often associated with acute circulatory failure with blood flow centralization. However, in terms of critical care medicine and general pathology, this is nothing more than a special case of hemodynamic shock. Pro-inflammatory mediators, in relation to COVID-19, are referred to as a “cytokine storm” [1]. Moreover, in shock associated with polytrauma, infectious-septic or immunopathological factors, excessive systemic action of pro-inflammatory mediators is a very early link of the pathogenesis . Similar processes also occur in shock-like states (in particular, those associated with hyperstimulation of immune-inflammatory mechanisms—hemophagocytic syndrome, hyperferritinemic syndrome and side effects of immunotherapy for oncological diseases, for example, chimeric antigen receptor of T-cells) [2]. At the same time, some studies of atherogenesis reported transformation of regulatory T-lymphocytes of the arterial wall from the initial protective phenotype (FoxP3+), which restrains autoimmune inflammatory processes, into the pathogenic one (RORyt, T-bet, Bcl-6), which contributes to the progression of the atherosclerotic plaque formation [7]. Such transformation is facilitated by high concentrations of pro-inflammatory autacoids, and COVID-19, obviously, can contribute to this process. Elevated serum levels of the C5a serine protease, which is important for the complement-mediated pro-inflammatory response, is a potential biomarker of disease severity in patients with COVID-19. The deposition of the terminal complement complex C5b-9 on endothelial cells promotes the release of thrombotic factors, triggering the production of pro-inflammatory cytokines [5]. Thrombus formation with recruitment and activation of neutrophils serves as a source of neutrophil extracellular traps (NETs). Like the serum level of circulating components of the complement system, serum levels of NETs positively correlate with the severity of both COVID-19 and atherosclerosis due to their cytotoxic effect on endothelial cells. Some practically significant aspects of the interaction between COVID-19 and the clinical manifestations of atherosclerosis in

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healthcare are not biological but are social in nature. Thus, a meta-analysis of 27 international studies showed that against the backdrop of a pandemic, there was a 40–50% decrease in the number of hospitalizations for acute coronary syndrome and an increase in the time "from door to device" for cardiac patients. The observed increase in pre-hospital mortality and out-of-hospital cardiac arrests indicates the negative impact of the pandemic on overall mortality rates from acute myocardial infarction, associated with a decrease in the availability of qualified inpatient cardiac care for somatic patients in the COVID-19 pandemic. In other words, one disease interfered with the control of another not only at the pathophysiological level but also at the medical and social levels.

This review aims to generalize the pathophysiology of COVID-19, an unexplored field that we have encountered recently, to the circulatory system. Based on this, it can be said that understanding the role of the components of cytokine status and assessing their impact in this context allows us to form a set of criteria for choosing drugs (antiatherogenic, anti-inflammatory and immunomodulatory effects) in the treatment process of atherosclerosis-associated diseases in COVID-19 in hepatocompromised individuals diseases correlate with death. Therefore, the study of the characteristics of the degree of liver damage in COVID-19 in patients with atherosclerosis-associated cardiovascular diseases requires a detailed assessment of clinical data, which can play an important role in the development of future therapeutic strategies.

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