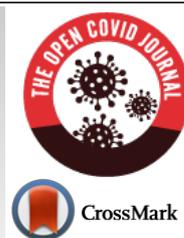




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REVIEW ARTICLE

COVID-19 Cardiac Complication- Myocarditis

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Abstract:

Based on the clinical experience, it has been observed that when it comes to the impact of SARS-CoV-2 virus on the cardiovascular system, it is significant. In patients with COVID-19 infection, the development of myocarditis occurs a few days after the onset of fever. The mechanism of myocardial injury alone, as well as most pathologies caused by the SARS-CoV-2 virus, is the subject of research by many experts, but two basic ways can certainly be assumed: a direct toxic effect of SARS-CoV-2 on myocardial cells and another possible way of myocardial injury is to activate the innate immune response by releasing proinflammatory cytokines, as well as to activate the adaptive mechanisms of the autoimmune type by molecular mimicry. The approach to treatment is the same as for other viral myocarditis; it is non-specific, applied supportive treatment, such as anti-inflammatory drugs, low-dose corticosteroid therapy, and immunoglobulins. The aim of this review is to present the previous experiences of physicians around the world on the clinical presentation of myocarditis caused by COVID-19 infection, diagnostic and therapeutic approach in a specific situation of high-risk infection.

Keywords: Myocarditis, COVID-19, Cardiovascular disease, Angiotensin-converting enzyme-2, Acute cardiac injury, Case study.

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1. INTRODUCTION

In December 2019, when the first cases of pneumonia of an unknown case appeared in China, Hubei Province, in Wuhan City, nobody could even imagine what consequences this pneumonia would have on the infected individual, and especially on the whole world, given its rapid spread potential. Now, when there are 38 million patients globally and with the experiences of doctors around the world during the past months, we can write about the current knowledge in the approach to diagnosis and treatment of cardiovascular consequences. Acute respiratory disease COVID-19 (according to the coronavirus disease) is caused by a new coronavirus, which, according to the international taxonomy, is called SARS-CoV-2 virus. At the beginning of the pandemic, the SARS-CoV-2 virus was known to primarily cause a respiratory infection, whose disturbances span a wide range: from asymptomatic infection through acute respiratory infection to severe pneumonia with multiorgan failure.

Based on the clinical experience, it was realized that when it comes to the impact of SARS-CoV-2 virus on the cardiovascular system, it is significant. People with known

cardiovascular comorbidity are known to be at an increased risk of developing COVID-19 infection, and those with the disease are at an increased risk of death. As expected, the risk of complications increases with the age of the patients. It has been found that a direct myocardial injury as a part of COVID-19 infection occurred, with possible consequential development of arrhythmias. The involvement of the cardiovascular system is associated with an unfavorable outcome. According to the latest data, cardiovascular involvement is present in 59% of patients who died [1]. Cardiac manifestations of COVID-19 infection can be identified with those caused by MERS infection (Middle Eastern Respiratory Syndrome), such as acute heart failure, myocarditis, arrhythmias and sudden cardiac death. The development of myocarditis as a part of SARS CoV-2 virus infection is one of the unfavorable prognostic indicators of outcome. It is difficult to talk about the prevalence of myocarditis in patients, given that new data arrives every day, compared to the current 7-17% [2]. Given the existence of a number of unknowns and that they are simultaneously the subject of many studies, from the mechanism of occurrence, through the spectrum of the clinical picture, to the approach to treatment, the aim of this paper is to present the current knowledge.

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2. COVID-19 AND MYOCARDITIS – THE MECHANISM OF OCCURRENCE

Myocarditis is an inflammatory disease of the heart muscle, most often of viral etiology and the most important cause of dilated cardiomyopathy [3]. In about 20% of cases, the disease turns into a chronic form, which results in the development of dilated cardiomyopathy. Myocarditis presents itself in asymptomatic forms, which is the most common case, to fulminant ones, with the development of acute heart failure, malignant arrhythmias, and sudden cardiac death. In patients with COVID-19 infection, the development of myocarditis occurs a few days after the onset of fever. [2] This indicates myocardial damage caused by a viral infection.

The mechanism of myocardial injury alone, as well as most pathologies caused by the SARS-CoV-2 virus, is the subject of research by many experts, but two basic ways can certainly be assumed. The mechanisms of myocardial injury may be due to the direct toxic effect of SARS-CoV-2 on myocardial cells. Another possible way of myocardial injury is to activate the innate immune response by releasing proinflammatory cytokines, as well as to activate the adaptive mechanisms of the autoimmune type by molecular mimicry. A key role in the direct toxic effect of SARS-CoV-2 virus on myocardial cells is their binding to the ACE2 receptor (angiotensin-converting enzyme 2), which is found in lung, heart and blood vessel cells and plays an important role in neurohumoral regulation of the cardiovascular system, both in healthy individuals and with various pathological conditions. ACE2 is a key member of the renin-angiotensin system, a multifunctional protein, and is primarily responsible for the conversion of angiotensin II to angiotensin I [4 - 6]. Binding of SARS-CoV-2 to the ACE2 receptor facilitates the virus entry into cells. After entering the host cells within the cytoplasm, the genetic material of the virus (RNA of the viral genome) is released, and it replicates, leading to the formation of a new virus particle that is stored in vesicles that fuse with the cell membrane, allowing the further release of the virus. The analysis of the scRNA-seq from the human heart showed that more than 7.5% of myocardial cells have a positive ACE2 expression, suggesting that the heart may be at high risk of 2019-nCoV infection, especially in the presence of the virus in the blood or viremia [2, 7]. Another receptor through which the SARS-CoV-2 virus can enter cells is CD209, which is expressed at macrophages that promote virus invasion into immune cells in cardiovascular tissue [8]. A more important mechanism for the development of myocarditis, especially in severe cases of COVID-19 infection, is immune-related myocardial damage mediated by the systemic release of numerous cytokines, interleukin-6 (IL-6), interleukin-2 (IL-2), interleukin-7 (IL-7), granulocyte colony-stimulating factor (G-CSF), chemokine CXCL10, ligand 2 chemokine (CCL2), and tumor necrosis factor- α , which corresponds to the characteristics of the phenomenon of the so-called “cytokine storm”. Consequently, generalized endothelial dysfunction, that is, an increase in vascular permeability, occurs and results in the development of multiorgan failure [9]. High serum IL-6 levels are a common feature of the “cytokine storm”. It is IL-6 that appears to play a key role in the development of the cytokine storm leading to the proinfla-

mmatory response, resulting in T lymphocyte activation, further cytokine release or positive feedback, immune activation, and myocardial damage. T-lymphocyte cardiotropism is thought to result from the interaction between cardiac produced hepatocyte growth factor (HGF) and c-Met, the HGF receptor on naive T-lymphocytes. Cytokines exert their harmful effects by direct and indirect action on myocardial cells [8]. Studies have shown that IL-6 is a clinical predictor of mortality from COVID-19 infection. Therefore, targeted determination of IL-6 levels in patients is considered justified to control the so-called “cytokine storm”, and the further therapeutic approach in COVID-19 infection [10]. A special entity is the development of Takotsubo cardiomyopathy in patients with COVID-19 infection proposed to be the result of a combination of the effect of cytokine storm, intense inflammatory response and psychophysical stress. Consequently, we have elevated levels of cortisol and catecholamines, which leads to microvascular dysfunction, coronary artery spasm and consequent contractility disorder [11].

3. COVID-19 AND MYOCARDITIS - CLINICAL PRESENTATION AND DIAGNOSIS

The first study to describe “myocardial injury” caused by the SARS CoV-2 virus was that of Wuhan, which described that 5 of the first 41 patients with confirmed COVID-19 infection had significantly elevated levels of a highly sensitive troponin I (hs-cTnI) > 28 pg/ml. Four of the 5 patients were later treated for the severity of their condition in the Intensive Care Unit. One study found that 7% of deaths in patients with COVID-19 infection were associated with the development of myocarditis [12]. The autopsy results in some of the deceased confirmed the presence of myocarditis based on the pathohistological findings of infiltration of myocardial cells by the virus itself and mononuclear cells. In patients with COVID-19 infection, myocarditis showed itself in the clinical presentation through the presence of chest pain, dyspnea, cardiac arrhythmias and clinical signs of acute heart failure.

The diagnostic procedure itself posed one of the challenges due to the high contagiousness of the virus itself, which can be seen from the cases shown. According to the guidelines of the American Heart Association (AHA) and the European Society of Cardiology (ESC), the diagnostic procedure includes non-invasive cardiac treatment, and the key diagnostic procedure is an endomyocardial biopsy (EMB) [13, 14]. EMB, in addition, serves as an opportunity to make an accurate diagnosis and ensures the possibility of the development of specific biomarkers, further pathohistological analysis, which could be useful for the development of a diagnostic test for SARS-CoV-2 myocarditis. In the case of a patient's death, an autopsy is also suggested, which will allow the observation of macroscopic and microscopic pathology of the heart [2]. Different degrees of abnormalities can be found in the electrocardiogram; they are mostly nonspecific or may correspond to those in acute coronary syndrome; changes are presented as ST elevation/depression, the inversion of T waves. Echocardiographically, a global or regional contractility disorder can be identified, with globally preserved or reduced left ventricular myocardial contractility.

Acute myocardial injury in laboratory findings was accompanied by elevated troponin levels. New evidence shows that elevated troponin levels after day 4 of hospitalization are associated with an increased risk of a lethal outcome, and the development of cardiogenic shock results in a lethal outcome in 33% of cases. Chen *et al.* also presented work showing myocardial involvement as a part of COVID-19 infection in 27.5% of cases [4]. Elevated levels of troponin, as well as NT pro BNP (brain natriuretic peptide), are not only a biomarker of myocardial involvement as part of SARS-CoV-2 virus infection but also an indicator of a severe course of the disease and an extremely poor outcome [4]. Particularly in vulnerable COVID-19 patients with pre-existent endothelial dysfunction, due to old age, male gender, smoking, diabetes, obesity, and established cardiovascular disease in addition to myocarditis, it can be COVID-19 endothelialitis, which is presented as MINOCA (myocardial infarction with non-obstructive coronary arteries) [9]. It can be concluded that for patients with COVID-19 infection and myocardial injury, the same concept applies to other patients. This concept is based on periodic monitoring of troponin values to distinguish whether it is an acute or chronic myocardial injury [15].

4. CASE STUDY

The first case of the development of myocarditis as a part of COVID-19 infection was described by Zeng *et al.* It concerned a 63-year-old man, a smoker, with no known cardiovascular comorbidity. The patient presented himself with a high fever and chest pain with shortness of breath. In the laboratory findings, he had elevated levels of troponin I (11.37 g / L), NT pro BNP (22600 pg / ml), the electrocardiogram described sinus tachycardia without ST-segment changes, and echocardiographically, a globally reduced left ventricular contractility LVEF 32% was determined. Following the administration of mechanical ventilation, antiviral (lopinavir / ritonavir) and antibiotic (piperacillin-tazobactam) therapy, interferon, methylprednisone, immunoglobulins, and continuous renal replacement therapy (CRRT), followed by extracorporeal membranous ECO recovery of LV, the systolic function was monitored [16]. Another case of fulminate myocarditis was described in a 47-year-old female who presented herself with a clinical picture of shortness of breath, chest pain, dry cough, hypotension, tachycardia. Serum troponin I levels were elevated, but the echocardiogram showed normal left ventricular function with pericardial effusion [4]. The next case of myocarditis presented by Inciardi *et al.* described a 53-year-old patient who was confirmed to be infected with the SARS-CoV-2 virus and who presented himself with hypotension upon admission, without the presence of fever (according to anamnestic data, she was previously febrile and had a dry cough for a week) [2]. Diffuse ST elevation was present on the electrocardiogram, with elevated values of troponin T and NT pro BNP, with slightly elevated CRP values. After admission, an urgent coronary angiography was performed, and obstructive coronary disease was ruled out, followed by the magnetic resonance imaging (MR) of the heart, which revealed diffuse biventricular hypokinesia, with interstitial edema in the T2 sequence with extensive postcontrast imbibition. The treatment was supportive,

including inotropic support in addition to the previously described antiviral and corticosteroid therapy and hydroxychloroquine [2]. Kim *et al.* described a case of a 21-year-old boy with myocarditis confirmed by cardiac MR, with bilateral interstitial pneumonia [12].

Unlike previous cases, in which myocarditis developed as a part of systemic inflammation and there was evidence of involvement of the lungs, in France, a case of isolated myocarditis, without the involvement of the respiratory system, had been described. It was a 35-year-old man without fever and respiratory symptoms; the MRI of the heart confirmed signs of myocarditis; the PCR test confirmed SARS-CoV-2 virus infection [17]. A similar case concerning a 2-year-old child was described in Turkey, but in this case, it was fulminate myocarditis, with bilateral pneumonia, where the confirmation that it was myocarditis caused by SARS-CoV-2 occurred after endomyocardial biopsy [18]. As there were no signs of systemic inflammatory response in the patient, the above example describes a case of a direct toxic effect of the virus on the myocardium. Given the high contagiousness of the virus in the case of COVID -19 infection, the diagnosis was made on the basis of non-invasive methods, although, so far, according to available data, a case from Italy had been described when a 43-year-old patient with myocarditis was diagnosed with SARS-CoV -2 virus. During the diagnostic processing, an endomyocardial biopsy was performed, and lymphocytic inflammatory infiltration with significant interstitial edema was demonstrated; the molecular analysis did not confirm the SARS-CoV-2 virus genome in myocardial tissue. This finding confirms the secondary involvement of the myocardium as a part of the systemic inflammatory response of the organism to COVID-19 infection [19].

5. COVID-19 AND MYOCARDITIS- APPROACH TO TREATMENT

Based on currently available data, it can be concluded that myocardial involvement as a part of SARS-CoV-2 virus infection is significant. Myocarditis, as an inflammatory disease of the heart muscle, is only one of the consequent entities. So far, in most cases, no evidence of the presence of the virus in myocardial tissue cells has been found (endomyocardial biopsy was not performed in most cases), but it is assumed that it is acute lymphocytic myocarditis, and the diagnosis is made using non-invasive diagnostic methods (echocardiography and cardiac MR). The approach to treatment is the same as for other viral myocarditis; it is non-specific. Supportive treatment measures are applied, such as anti-inflammatory drugs, low-dose corticosteroid therapy, and immunoglobulins, to try to act on the course of the disease. [20] There has been no clear evidence of the effectiveness of corticosteroid therapy in the treatment of COVID -19 infection yet, therefore, it is necessary to indeed conduct structured research. Systemic studies to date have shown that there is no significant difference in mortality in patients with viral myocarditis treated with corticosteroid therapy compared to those not treated. The intravenous use of immunoglobulins (IVIG) has been shown to be successful in the treatment of fulminant myocarditis, reducing the inflammatory response and the production of proinflammatory cytokines [21]. The role of

IVIG is not to target the virus but to help reduce the hyperactive immune response while reducing the effect of multiple cytokines pathways. According to available data, the key to anti-immunomodulatory treatment is an early intervention that starts in the acceleration phase, which is usually associated with lymphopenia and elevated inflammatory markers [22]. Despite the proven elevated level of TNF (Tumor necrosis factor) in the peripheral blood of patients, and that inhibitors are readily available and tested, previous reports have not shown significant results. Clinical trials on the effect of recombinant IL-1 antagonist (interleukin 1) in patients with COVID-19 infection are also ongoing. The effect of Janus kinase (JAK) inhibitors, which have the attractive goal of abolishing multiple cytokine pathway signaling, is also being investigated [22]. However, it should be emphasized that their use is associated with an associated risk of thromboembolic incidents and reactivation of Herpes zoster infection. In the treatment of cytokine storm, multicenter studies have been initiated on the use of tocilizumab, a monoclonal anti-IL-6 antibody. Coyle *et al.* presented a case of successful treatment of myocarditis and ARDS in patients with COVID 19 infection with methylprednisone and anti-IL-6 (tocilizumab) [23]. In the most severe cases involving combined respiratory and circulatory instability, the use of advanced treatment methods such as ECMO is indicated [18]. In addition, multiple therapies are currently being evaluated in randomized control trials to conclusively determine efficacy, with >300 registered trials ongoing related to COVID-19 [24, 25]. Antiviral therapies may have a role in the treatment of SARS CoV-2. The use of lopinavir/ritonavir for severe COVID-19 was tested prospectively in 199 patients but, unfortunately, did not lead to a significant reduction in viral load or symptomatic improvement. Remdesivir has also been proposed as an antiviral therapy after originally being developed for Ebola and the Marburg virus [26, 27].

CONCLUSION

The resulting pandemic drew attention to the possibility of developing the inflammatory myocardial disease with severe consequences. This indicates that there is a need for further research and improvement of immunomodulatory therapy that would act on immune mechanisms, which play a key role in the development of this disease and also in the prevention of the development of chronic consequences, such as dilated cardiomyopathy.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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