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Myocarditis in the Elderly against the Background of Covid-19: Clinical Features and Drug Treatment Tactics

Naimov Dilshod Qayim o'g'li

Bukhara State Medical Institute, Uzbekistan, Bukhara

Summary: Myocarditis associated with novel coronavirus infection (COVID-19) is a difficult diagnosis from all points of view. The clinical manifestations of this pathology may be nonspecific or erased; while it's long-term consequences for the patient are unknown. Diagnostic approaches are complex and practically impossible in covid clinics. Therapy carried out in patients with COVID-19 carries a potential threat to the myocardium.

The aim of this review was to summarize the information available to date on the clinical aspects and medical treatment of inflammatory myocardial injury in COVID-19. More than 300 relevant literature sources have been analyzed, and the most significant information in the light of the problem under discussion is given in the article.

The results of the analysis of the current world literature have shown convincing evidence of the possible development of myocarditis as part of a new coronavirus infection. Histological verification of myocardial damage associated with COVID-19 presents significant difficulties, since end omyocardial biopsy is not always possible in conditions of severe infection. In this regard, the statistics do not reflect complete information on the prevalence of myocarditis associated with COVID-19. Due to insufficient knowledge of the pathogenesis of inflammatory myocardial damage, drug approaches have not been developed and are mainly empirical in nature. Due to the ambiguity of the prognosis of patients with myocarditis associated with COVID-19, further study of the problem is required.

Keywords: COVID-19, SARS-CoV-2, myocarditis, myocardial damage, cardiovascular system, clinical manifestations, treatment, drug effects.

Introduction

In March 2020, the World Health Organization declared a pandemic of the novel coronavirus infection (COVID-19) caused by the SARS-CoV-2 virus. The primary target of the virus was the respiratory system; however, as the number of clinical observations increased, the involvement of the cardiovascular system in the pathological process became obvious.

Myocarditis is an inflammatory heart disease in which viruses are considered the most likely etiological factor [1]. At the same time, the pathogenetic mechanisms of the effect of viruses on the heart are not completely clear. Both the direct damaging effect of viruses on myocardial cells and the immune-mediated one are known [2]. The cardiotropism of SARS-CoV-2 is currently under discussion. The direct damaging effect of SARS-CoV-2 is associated with its penetration into cardiomyocytes through angiotensin-converting enzyme-2 (ACE-2) receptors, which probably leads to the development of myocarditis. The immune-mediated effect can be explained by the formation

of a pathological systemic inflammatory response, also called "cytokine storm", in which there is hyperproduction of cytokines (interleukins (IL) -6, IL-7, IL-22, IL-17, etc.), which leads to damage to myocardial tissue and multiple organ failure [3, 4]. An additional role in myocardial damage can be played by damage to the microvasculature associated with the direct damaging effect of the virus on endothelial cells and the development of endothelial dysfunction, as well as a metabolic imbalance between myocardial oxygen demand and its delivery [5]. The latter violation is due to the development of hypoxemia against the background of damage to the lung tissue and the direct damaging effect of the virus on erythrocytes described by some authors, in which SARS-CoV-2 is able to bind to the beta chain of hydroxyhemoglobin, as a result of which porphyrin dissociates from iron, which leads to hemic hypoxia [6]. A significant role is given to imbalance in the renin-angiotensin-aldosterone system (RAAS), which develops due to a decrease in the expression of ACE-2 receptors with a high viral load of SARS-CoV-2. At the same time, the level of protective angiotensin (AT) decreases against the background of an increase in the amount of AT II, which causes activation of the sympathetic-adrenal system, an increase in blood pressure, an increase in myocardial oxygen demand, vasoconstriction, the development of fibrosis, activation of inflammatory cytokines, and disturbances in the hemostasis system [4, 7]. The described pathogenetic mechanisms can contribute to the development of myocardial damage in the context of COVID-19, as well as lead to the progression of existing cardiovascular diseases in the patient. Cardiotoxicity of drugs used in the treatment of COVID-19 deserves special discussion as an etiological factor in the development of myocardial damage. According to some authors [8, 9],

The frequency of myocarditis associated with COVID-19 has not been precisely established. Diagnosis of myocarditis presents certain difficulties, especially in the management of patients with COVID-19. Endomyocardial biopsy (EMB) remains the “gold standard” for diagnosis, which is not always possible in patients with COVID-19 [10]. Electrocardiography (ECG) and echocardiography (EchoCG), as well as laboratory methods (troponins, brain natriuretic peptide, C-reactive protein, etc.) remain the most accessible methods of instrumental examination of patients with suspected heart damage in covid clinics [11, 12]. However, the results of these studies do not always directly indicate the inflammatory nature of myocardial damage. In this regard, the term "myocardial injury" is often used in the literature. And not “myocarditis”, implying that this concept hides a fairly large range of pathologies, including inflammatory myocardial damage [3, 4, 9, 13]. Having analyzed the available literature sources containing the results of EMB and autopsies of patients with a new coronavirus infection, R Kawakami et al. [5] concluded that myocarditis associated with COVID-19 is a rather rare clinical manifestation; the incidence of confirmed myocarditis in myocardial tissue samples totaled 4.5%. According to another source [14], about 7% of deaths in patients with COVID-19 are due to myocarditis. Magnetic resonance imaging (MRI) of the heart - an informative non-invasive imaging method for diagnosing myocarditis - unfortunately, is also not publicly available.

Clinical manifestations of myocarditis associated with COVID-19

The clinical manifestations of myocarditis are very diverse due to the difference in forms, the nature of the course of the disease, gender characteristics, and the presence of comorbid conditions in the patient [2, 15, 16]. The spectrum of clinical manifestations can vary from mild symptoms such as chest discomfort; dyspnea and fatigue to more severe symptoms associated with right and left ventricular failure, cardiogenic shock, arrhythmia and sudden cardiac death in fulminant myocarditis [15]. According to a large meta-analysis [17] of 10 studies involving 1995 patients with COVID-19, their common symptoms were fever (88.5%), cough (68.6%), myalgia or fatigue (35.8%), cough with sputum (28.2%) and shortness of breath (21.9%), as well as headache or dizziness (12.1%), diarrhea (4.8%), nausea and vomiting (3.9%). As noted, the actual frequency of myocarditis, associated with COVID-19 has not been established. For a comparative assessment of the clinical manifestations that occur in patients with myocarditis associated with a new coronavirus infection, we present the data of several of the most significant meta-analyses [18–21], which included clinical observations of patients diagnosed with myocarditis (see table).

Таблица. Клинические симптомы у пациентов с миокардитом, ассоциированным с COVID-19, по данным нескольких метаанализов

Table. Clinical presentations COVID-19-associated myocarditis according to several meta-analyses

Источник, дата публикации References	**Количество пациентов (жен./муж.)** Number of patients (Women/men)	**Медиана возраста, лет** Median of age, years	**Коморбидность, %** Comorbidities, %	**Встречаемость клинических проявлений, %** Clinical presentations, occurrence, %
Pirzada A. et al. [18], 2020 г.	2/7	32/61	**Нет информации** No data	**Одышка** / Dyspnea 100/85,7 **Боль в грудной клетке** / Chest pain 50/28,6 **Кашель** / Cough 50/71,4 **Мокрота** / Sputum 50/14,3 **Лихорадка** / Fever 50/28,6 **Диарея** / Diarrhea 50/42,9 **Судороги** / Seizures 50/0 **Утомляемость** / Fatigue 0/42,9 **Рвота** / Vomiting 0/14,3 **Тошнота** / Nausea 0/14,3 **Потеря сознания** / Loss of consciousness 0/14,3
Çınar T. et al. [19], 2020 г.	6/10	45,8/49,6	**Артериальная гипертензия** Hypertension 16,7/40 **Ожирение** / Obesity 33,3/10 **Бронхиальная астма** Asthma 0/10 **Саркоидоз** / Sarcoidosis 0/10 **Эпилепсия** / Epilepsy 0/10 **Беременность у 2 пациенток (сроки: 33 и 39 нед.)** Pregnancy (two women, 33 weeks and 39 weeks)	**Одышка** / Dyspnea 50/80 **Боль в грудной клетке** / Chest pain 33,3/30 **Кашель** / Cough 33,3/20 **Лихорадка** / Fever 16,7/40 **Рвота** / Vomiting 16,7/0 **Диарея** / Diarrhea 16,7/20 **Утомляемость** / Fatigue 16,7/10 **Миалгия** / Myalgia 0/30
Sawalha K. et al. [20], 2021 г.	6/8	48,3/52	**Неишемическая кардиомиопатия (фракция выброса левого желудочка 40%)** Non-ischemic cardiomyopathy (left ventricular ejection fraction 40%) 16,7/0 **Туберкулез лимфоузлов** Lymph node tuberculosis 16,7/0 **Артериальная гипертензия** Hypertension 16,7/37,5 **Мигрень** / Migraine 16,7/0 **Аллергический кашель** Allergic cough 0/12,5 **Курение** / Smoking 0/12,5	**Одышка** / Dyspnea 66,7/75 **Кашель** / Cough 66,7/50 **Лихорадка** / Fever 66,7/62,5 **Боль в грудной клетке** / Chest pain 50/50 **Боль в левом плече** Left shoulder pain 16,7/0 **Утомляемость** / Fatigue 16,7/0 **Диарея** / Diarrhea 0/37,5 **Тошнота** / Nausea 0/25 **Миалгия** / Myalgia 0/12,5

Таблица (продолжение). Клинические симптомы у пациентов с миокардитом, ассоциированным с COVID-19, по данным нескольких метаанализов

Table (Continued). Clinical presentations COVID-19-associated myocarditis according to several meta-analyses

Источник, дата публикации References	Количество пациентов (жен./муж.) Number of patients (Women/men)	Медиана возраста, лет Median of age, years	Коморбидность, % Comorbidities, %	Встречаемость клинических проявлений, % Clinical presentations, occurrence, %
Castiello T. et al. [21], 2021 г.	9/29	42,6/46,5	**Сахарный диабет 1 типа** / Type 1 diabetes 11,1/0 **Сахарный диабет 2 типа** / Type 2 diabetes 0/10,3 **Бронхиальная астма** / Asthma 11,1/6,9 **Депрессия** / Depression 11,1/0 **Хроническая болезнь почек** Chronic kidney disease 11,1/0 **Ожирение** / Obesity 0/10,3 **Артериальная гипертензия** / Hypertension 0/24,1 **Почечный трансплантат** / Kidney transplant 0/3,4 **Саркоидоз** / Sarcoidosis 0/3,4 **Эпилепсия** / Epilepsy 0/3,4 **Дислипидемия** / Dyslipidemia 0/3,4 **Фибрилляция предсердий** / Atrial fibrillation 0/3,4 **Инсульт** / Stroke 0/3,4 **Ишемическая болезнь сердца** Coronary heart disease 0/3,4 **Курение** / Smoking 0/3,4 **Рак груди** / Breast cancer 11,1/0 **Роды 1 мес. назад** / Delivery 1 month ago 11,1	**Одышка** / Dyspnea 55,6/44,8 **Боль в грудной клетке** Chest pain 44,4/20,7 **Кашель** / Cough 22,2/20,7 **Лихорадка** / Fever 22,2/51,7 **Утомляемость** / Fatigue 22,2/24,1 **Потеря сознания** Loss of consciousness 11,1/13,8 **Сердцебиение** / Palpitation 11,1/6,9 **Рвота** / Vomiting 11,1/0 **Диарея** / Diarrhea 11,1/0 **Летаргическое состояние** Lethargy 11,1/0 **Желудочно-кишечное расстройство** Gastrointestinal distress 0/24,1 **Головная боль** / Headache 0/6,9 **Миалгия** / Myalgia 0/6,9 **Головокружение** / Dizziness 0/3,4 **Одинофагия** / Odynophagia 0/3,4 **Бессимптомно** / Asymptomatic 0/3,4

Примечание. *Через / указаны показатели для женщин и мужчин.*

Note. *Women/men.*

Summarizing the data of the presented meta-analyses [18–21], it can be concluded that patients with COVID-19-associated myocarditis mostly have non-specific complaints: shortness of breath, fever, cough. These clinical manifestations are also expected in patients without cardiac involvement. Pain in the chest, "interruptions" in the work of the heart was not the leading symptoms. In their review, K. Sawalha et al. [20] also noted that among patients with myocarditis associated with COVID-19, hemodynamic disturbances in the form of shocks were often recorded (64%), of which 71% were cardiogenic, 29% were mixed (cardiogenic and septic shock). Virtually all meta-analyses show a male predominance among patients with myocarditis associated with novel coronavirus infection. The age of the patients in the samples was different, but the majority were over 50 years old. There, where it was possible to establish the comorbidity of patients with COVID-19, arterial hypertension, diabetes mellitus, and obesity prevailed in men. Among women of childbearing age, several patients developed myocardial damage in late pregnancy and in the postpartum period, perhaps these periods can be dangerous in terms of the development of inflammatory myocardial damage [22]. According to most researchers [20, 23], mortality in patients with comorbidities was higher than in patients without concomitant diseases. these periods can be dangerous in terms of the development of inflammatory myocardial damage [22]. According to most researchers [20, 23], mortality in patients with comorbidities was higher than in patients without concomitant diseases. these periods can be

dangerous in terms of the development of inflammatory myocardial damage [22]. According to most researchers [20, 23], mortality in patients with comorbidities was higher than in patients without concomitant diseases.

The recently published results of the CORONA Germany prospective epidemiological cohort study [24] demonstrated an almost five-fold increase in the risk of death in hospitalized patients with COVID-19 with clinical manifestations of acute cardiovascular events. However, it should not be forgotten that there is a category of patients in whom there are no symptoms from the cardiovascular system, while there is laboratory confirmation of myocardial damage in the form of an increase in the level of cardiac troponins. Some authors [25, 26] associate cases of sudden cardiac death in patients with mild COVID-19 who are at home on outpatient treatment or quarantine with the likely development of ventricular tachycardia and acute myocarditis. The researchers emphasize the need for MRI of the heart in patients with a new coronavirus infection, even after a course of treatment and hospitalization, due to the fact that structural changes such as atrial and ventricular fibrosis can become a substrate for life-threatening cardiac arrhythmias. There are publications [18, 26, 27], according to which myocarditis can be an accidental finding at autopsy in patients with a new coronavirus infection who did not have clinical manifestations of the pathology of the cardiovascular system.

Medical approaches to the treatment of myocarditis associated with COVID-19 infection

It is known that the penetration of SARS-CoV-2 into the patient's body occurs indirectly through ACE-2 receptors [4, 7, 28]. More and more publications [28, 29] confirm the presence of the intracellular location of the virus and the possibility of its direct damaging effect on myocardial cells. At the same time, there is no understanding of the role and mechanisms of influence of drugs that block the RAAS. Currently, if a patient received drugs of this group before contracting a new coronavirus infection, then it is recommended to continue taking them [28]. It is likely that in patients with myocarditis associated with COVID-19, as well as with myocarditis of a different etiology, drugs of this group can play a positive role in preventing the development or progression of symptoms of circulatory failure, but should they be prescribed to patients with COVID-19 who have not received before that, it is not yet clear [30].

Considering the “cytokine storm” as a predictor of the severe course of COVID-19, practitioners prescribe various forms of glucocorticosteroids (GCS) to a significant number of patients [18–20]. According to Russian and European recommendations for the diagnosis and treatment of myocarditis [2, 15], the appointment of GCS requires a reasonable and balanced approach: exclusion of the acute period of the infectious process, the absence of a positive effect from ongoing therapy with first-line drugs (RAAS blockers, β-blockers, diuretics, antiarrhythmic drugs etc.). The highest efficiency of corticosteroids is described in patients with myocarditis on the background of rheumatic diseases [4]. Data on the effect of corticosteroids on the outcomes of patients with a new coronavirus infection are contradictory. A meta-analysis conducted by Chinese scientists [31] of 15 studies involving 5270 patients showed that corticosteroids are most often prescribed for severe SARS-CoV-2 infection. Prescribing drugs of this group worsens survival, increases the duration of hospitalization, the addition of bacterial co-infection and hypokalemia in patients with pneumonia. At the same time, according to the large clinical trial RECOVERY (Randomized Evaluation of COVid-19 thERapY) [32], dexamethasone showed its advantage in reducing mortality in patients on mechanical ventilation (ALV) and oxygen therapy, and is currently included in guidelines for the management of patients with severe COVID-19. Some authors [33] cite their own positive clinical experience with the use of corticosteroids in the observation of fulminant forms of myocarditis associated with a new coronavirus infection. Other researchers [34] describe observations with a favorable outcome of the acute course of myocarditis without the appointment of GCS. Thus, the ultimate role of these drugs in treating myocardial inflammation in COVID-19 remains unclear.

As a promising alternative treatment for patients with severe COVID-19 and the clinical picture of a "cytokine storm", doctors of some clinics [8, 9, and 35] practice prescribing tocilizumab, a recombinant humanized monoclonal antibody against IL-6. This drug is expected to improve outcomes in patients with severe infection and reduce the risk of invasive mechanical ventilation in

patients with pneumonia associated with COVID-19, but the number of observations is small [35]. There are also no data on the effect of the drug on the course of myocarditis associated with COVID-19.

In the literature [36, 37], there is still evidence of the use of cardiotoxic drugs with weak immunomodulatory properties, such as hydroxychloroquine, colchicine, as well as antibiotics (azithromycin, fluoroquinolones), in a new coronavirus infection. It is known that their use both alone and as part of combinations contributes to an increase in the duration of the QT interval, as a result of which polymorphic ventricular tachycardia and ventricular fibrillation may develop [8, 9]. A similar side effect was observed with the antiviral drug lopinavir (ritonavir) [8]. Drug interactions of favipiravir with anticoagulants, statins, antiarrhythmic drugs are also undesirable [8, 9]. A direct cardiotoxic effect of interferons α and β has been described [9]. Obviously, that the appointment of these drugs in the conditions of a presumptive or established diagnosis of myocarditis is undesirable. Some authors [9] emphasize that the use of these drugs in itself can contribute to the development of myocardial damage and worsen the patient's prognosis.

Taking into account the development of endothelial dysfunction and hypercoagulability in conditions of systemic inflammation in patients with COVID-19, in addition to drugs blocking the RAAS, statins, anticoagulants, antiplatelet agents are used in clinical practice [37, 38].

Non-steroidal anti-inflammatory drugs (NSAIDs) are not indicated for inflammatory myocardial injury, their use is possible in the presence of concomitant pericarditis [15]. There is evidence that they are able to increase the expression of ACE-2 receptors on cell membranes, which theoretically can increase the penetrating ability of SARS-CoV-2 into cells [39]. In contrast, there is a publication [40] on a decrease in the synthesis of SARS-CoV-1 RNA in vitro, regardless of the activity of cyclooxygenase while taking indomethacin. Given the conflicting data on the use of NSAIDs, studies of the efficacy and safety of these drugs in the new coronavirus infection should be continued.

Conclusion

Currently, information is being accumulated on extrapulmonary multi-organ manifestations of a new coronavirus infection. Obviously, patients with initially combined pathology are at risk for a favorable prognosis of the course of the disease [42-44]. Myocardial damage that develops against the background of COVID-19 is in the area of special attention of researchers, as it causes an increase in mortality [45]. Several pathogenetic mechanisms are thought to be responsible for the development of myocarditis associated with COVID-19. The most likely is an immune-mediated mechanism resulting from a "cytokine storm". However, the direct cytopathic effect of the virus on cardiomyocytes continues to be discussed. Also, endothelial dysfunction, disruption of the RAAS,

Establishing the diagnosis of "myocarditis", taking into account the peculiarities of the clinical picture and the non-specificity of symptoms, presents significant difficulties. The term “myocardial injury”, which is based, according to the literature, on the definition of an increase in the level of cardiac troponin, is, in fact, a more capacious concept than “myocarditis”, since it can also include conditions caused by myocardial ischemia and Takotsubo cardiomyopathy [46] . To confirm the diagnosis of myocarditis, additional diagnostic manipulations are required: ECG, echocardiography, MRI, and ultimately endomyocardial biopsy, which is not always possible in a covid hospital [47].

Drug therapy for patients with inflammatory myocardial damage associated with a new coronavirus infection has not been developed. Several meta-analyses have reported that patients are being treated according to protocols for managing COVID-19, and the effect of most drugs on the course of myocarditis is unknown. Many drugs used to treat patients with novel coronavirus infection have potentially negative effects on the myocardium and may themselves provoke myocardial damage. Many questions can be answered by conducting an epidemiological study of patients with myocarditis associated with novel coronavirus infection.

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