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Miocarditis in Patients with COVID-19 Confirmed by Immunohistochemical

Aim	Despite the regular heart damage in patients with coronavirus pneumonia caused by SARS-Cov-2, a possibility of developing lymphocytic myocarditis as a part of COVID-19 remains unsubstantiated. The aim of this study was to demonstrate a possibility of lymphocytic myocarditis and to study its morphological features in patients with the novel coronavirus infection (COVID-19) with a severe course.
Material and methods	Postmortem data were studied for 5 elderly patients (74.8±4.4 years; 3 men and 2 women) with the novel coronavirus infection and bilateral, severe polysegmental pneumonia (stage 3–4 by computed tomography). COVID-19 was diagnosed based on the typical clinical presentation and positive polymerase chain reaction test in nasopharyngeal swabs. All patients were treated in different hospitals repurposed for the treatment of patients with COVID-19. A standard histological study was performed with hematoxylin and eosin, toluidine blue, and van Gieson staining. Serial paraffin slices were studied immunohistochemically with antibodies to CD3, CD68, CD20, perforin, and toll-like receptors (TLR) 4 and 9.
Results	In none of the cases, myocarditis was suspected clinically, added to the diagnosis or indicated as a possible cause of death. IHD and acute myocardial infarction were mentioned as error diagnoses not confirmed by the postmortem examination. The morphological examination of the heart identified signs of lymphocytic myocarditis consistent with Dallas criteria for this diagnosis. Myocardial infiltrate was characterized in detail, and a combined inflammatory damage of endocardium and pericardium was described. The immunohistochemical study with cell infiltrate typing confirmed the presence of CD3-positive T lymphocytes and the increased expression of TLR-4. A picture of coronaritis, including that with microvascular thrombosis, was found in all cases.
Conclusion	A possibility for development of lymphocytic viral myocarditis in COVID-19 was confirmed morphologically and immunohistochemically. Specific features of myocarditis in COVID-19 include the presence of coronaritis and a possible combination of myocarditis with lymphocytic endo- and pericarditis.

Keywords	COVID-19; SARS-CoV-2; coronavirus; myocarditis; endocarditis; CD3 T lymphocytes; perforin; TLR-4, TLR-9
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There is still little information about the nature, much less the morphology, of myocardial damage associated with the new coronavirus infection. Clinical physicians were the first to notice the infrequent yet natural involvement of the heart in a single pathological process in this disease. According to the Wuhan researchers, myocardial damage was diagnosed in 12% of cases (of a total of 41 patients studied) [1]. There was a clear correlation between the severe course (transfer to the intensive care units) and lethal outcomes with cardiac symptoms [2, 3].

Several clinical variants of heart disease were reported:

1) deterioration of the course of chronic cardiovascular diseases (coronary artery disease (CAD), heart failure, arrhythmias) [4];
2) development of acute myocardial infarction (MI) due to thrombosis of both infarcted and intact coronary arteries [5];
3) development of cardiogenic shock, and acute heart failure in patients without a history of cardiac diseases [6];
4) less severe manifestations, such as arrhythmias, changes in the electrocardiogram (ECG), echocardiogram, etc. (not always clinically manifested) [7];

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5) increased levels of blood cardiac biomarkers (troponin, NT-proBNP, etc.) observed in 8% of patients and not always accompanied by clinical deterioration [2].

In this case, such a vague concept as «acute myocardial injury» is most often used to explain the symptoms and laboratory changes. According to the latest European consensus on MI [8], acute myocardial injury can be diagnosed based on increased levels of biomarkers (troponin) with no ischemia. Its morphological evidence is the death of cardiomyocytes. This concept is too abstract. For example, myocardial necrosis in severe (including viral) myocarditis also meets this definition. However, clinical physicians try to avoid the term «myocarditis» when describing patients with the new coronavirus disease.

This is mainly due to the strict commitment of European experts on myocardial diseases to the mandatory morphological and immunohistochemical verification of myocarditis [9]. When this article was being prepared, there may have been only two alleged verified cases of myocarditis in COVID-19 [10, 11]. At the same time, the clinical data (both individual cases and series of observations) indicate a high rate of «acute myocardial injury». Thrombosis, including of large coronary arteries, is one of the critical mechanisms of such damage.

The following mechanisms of heart damage in COVID-19 are also listed: binding of the virus by the angiotensin-converting enzyme 2 abundant in the myocardium (as in the lungs) as a functional receptor followed by dysregulation of the renin-angiotensin system; hypoxemia-induced oxidative stress with the development of intracellular acidosis and mitochondrial dysfunction; involvement of the microcirculatory bed (increased permeability, angiospasm, microthrombosis with the formation of perfusion defects); systemic inflammatory response syndrome (cytokine storm, uncontrolled inflammation) [4]. Severe respiratory infection is thought to lead independently to increased troponin levels. Moreover, some drugs used in COVID-19 are potentially cardiotoxic.

The morphological manifestations of myocardial damage specific to the new coronavirus disease remain insufficiently studied in the situation concerned. The possibility of developing true lymphocytic viral myocarditis in COVID-19 is still not proven, thus making this study highly relevant.

Objective: to prove the possibility of developing lymphocytic myocarditis and study its morphological features in patients with severe new coronavirus disease (COVID-19).

Material and methods

Autopsy findings of 5 elderly patients (mean age 74.8±4.4 years old, 3 male and 2 female) with the new coronavirus disease and severe bilateral polysegmental pneumonia (stage 3–4 according to the computed tomography (CT)) were studied.

The diagnosis of COVID-19 was established based on typical clinical manifestations and virus-positive nasopharyngeal swabs using the polymerase chain reaction (PCR). All patients were treated in a number of hospitals converted to COVID-19 treatment centers. Autopsy studies were performed in the pathology department of the Central Tuberculosis Research Institute.

All patients underwent a standard clinical in-life examination, the results of which will be presented below. Detailed analysis of the clinical manifestation was not a part of the objective of this study (due to the post-mortem nature).

A conventional morphological study was performed consisting of: an autopsy with macroscopic observation; and a histological examination of heart using hematoxylin and eosin, toluidine blue, and Van Gieson's staining. Immunohistochemical examination of serial paraffin sections was performed using standard methods. An expanded panel of antibodies was used: anti-CD3, anti-CD68 (CellMarque, rabbit monoclonal antibodies, dilution titer 1:1000), anti-CD20 (CellMarque, rabbit monoclonal antibodies, dilution titer 1:500), anti-perforin (CellMarque, mouse monoclonal antibodies, dilution titer 1:50), anti-TLR4 (toll-like receptors, TLR4; GeneTex, rabbit polyclonal antibodies, dilution titer 1:200), TLR9 (GeneTex, rabbit polyclonal antibodies, dilution 1:50) antibodies.

The findings from the myocardial examination were estimated on the basis of the Dallas criteria [9].

Results

Clinical characteristics of patients

Four patients were obese, and all patients had hypertensive heart disease. The clinical diagnosis of CAD was not sufficiently grounded. The final diagnosis of a 79-year-old patient was acute MI, which was not confirmed by macro- and microscopic examination.

Two patients had ST-elevation in ECG, one patient (see below) had negative labile T waves. There were no reliable clinical signs of sepsis. Artificial respiration was used in all cases. Cardiopulmonary insufficiency deterioration was the reason for lethal outcomes on days 10–14 of the disease.

A 75-year-old male patient was treated at Sechenov University from 8 to 22 April 2020. His medical history included moderate arterial hypertension (high blood pressure (BP) up to 160 and 70 mm Hg). He was admitted to the Sechenov University Clinic on day 6 after the onset of fever up to 39.0 °C, dry cough, pain in the left chest. There were no signs of respiratory or heart failure. SaO_2 98%, heart rate (HR) 86 bpm, regular rhythm, BP 110 and 80 mm Hg. Multispiral computed tomography (MSCT) of the chest revealed the signs of aortic and coronary calcifications, bilateral polysegmental pneumonia; ground-glass opacities in all parts of the lungs with a lesion area of 50–75% and

consolidations. The diagnosis of COVID-19 was confirmed by PCR testing of a nasopharyngeal swab. Therapy, including hydroxychloroquine, ceftriaxone, and enoxaparin 40 mg/day, was administered.

Fever (up to 39.6 °C) was registered every day. Dyspnea and desaturation worsened (up to 70%). He was transferred to the intensive care unit due to the insufficient effect of oxygen therapy through nasal cannulas (SaO_2 87%). At admission, crackles were heard in the lower parts of both lungs, HR 114 bpm, BP 90/50 mm Hg. ECG showed sinus rhythm, no signs of myocardial hypertrophy, and pathologic Q waves, but there were negative T waves in all thoracic leads, which disappeared later (Figure 1, A – C).

Single echocardiography revealed no local contractility abnormalities. Left ventricular ejection fraction was 58%, and pulmonary artery systolic pressure 42 mm Hg. Blood tests showed an increase in white blood cell counts from 4.4 to a maximum of 31.9×10^9/L, a decrease in lymphocyte counts from 1.3 to 0.5×10^9/L, an increase in ESR from 32 to 62 mm/h, levels of C-reactive protein from 75 to 254 mg/L, and D-dimer from 1.14 to 30.63 mg/L. The troponin level was 100 ng/mL (on day 8 after the deterioration and the appearance of negative T waves in ECG). Invasive mechanical ventilation, meropenem, vancomycin, lopinavir-ritonavir, tocilizumab, intravenous prednisone 60 mg/day, and furosemide up to 100 mg had no significant effect. The patient died on day 14 of hospitalization of asystole and ventricular fibrillation with multiple-organ system failure. In an autopsy examination, stenosis of the coronary arteries did not exceed 25%, and there was no data confirming MI. The results of the microscopic examination of the myocardium (Figure 1, D-G) will be described below.

Macroscopic examination of the hearts of all 5 patients showed dilatation of the heart chambers, parietal blood clots mainly in the right atrium and ventricle, left ventricular hypertrophy (heart weight ranged from 300 to 430 g, left ventricular wall thickness 1.4–1.9 cm, right ventricular wall thickness 0.3–0.5 cm). The myocardium was flabby with small yellowish-reddish foci in the section.

Microscopic examination (Figure 2) of the myocardiums of 5 patients showed that the interstitium was unevenly expanded and swollen and contained lymphomacrophagal infiltrates (more than 14 lymphocytes in 10 fields of view, Figure 2, A) and lipomatosis foci (Figure 2, E). Single mast cells with signs of degranulation were detected in the toluidine blue stained infiltrate. In one case, there were significant lymphohistiocytic infiltrates containing single white blood cells. Destructively productive vasculitis (coronariitis) of small coronary arteries with fresh blood clots found in the lumen (Figure 2, B). Endothelial cells of large and small vessels, microvessels were swollen and proliferating (severe endothelitis).

Cardiomyocytes were unevenly hypertrophied with signs of overconversion, dystrophic changes, no transverse striation in individual fibers, as well as deposits of lipofuscin granules. Cardiomyocyte nuclei were preserved, and hyperchromic (nuclear lysis was observed in some cardiomyocytes). There was one case of severe cardiomyocyte dystrophy with karyopycnosis, lysis, and fragmentation of the cytoplasm and nuclei. Hemorrhages were observed in all cases. There were small foci of myocardial calcification in one case.

One patient had myocarditis combined with lymphocytic endocarditis, and two patients had myocarditis combined with lymphocytic pericarditis (Figure 1, F; Figure 2, C) in one patient. The walls of small coronary arteries had signs of endotheliitis (metachromasia indicating dystrophic processes in the vascular connective tissue).

The diagnosis of lymphocytic myocarditis is valid if there are at least 7 CD3+ lymphocytes per 1 mm^2 in the myocardium according to the international Dallas criteria and the guidelines of the European Society of Cardiology and the European Society of Pathologists [9].

In order to confirm the diagnosis, an immunohistochemical study was performed with an expanded panel of antibodies (anti-CD3, anti-CD20, anti-perforin, anti-TLR4, anti-TLR-9 antibodies). The expression of CD3 is a diagnostic marker of T-lymphocytes. CD20 allows the detection of B-lymphocytes. Perforins are a family of cytotoxic granule proteins found in NK cells. Toll-like receptors are a family of protein receptors located on the surface of immunocompetent cells (macrophages, lymphocytes) and activated by infectious agents.

According to an immunohistochemical study, there was a significant expression of CD3+ lymphocytes in the interstitial tissue (more than 7 cells per 1 mm^2) and thrombotic masses (Figure 1, G; Figure 2, D). CD20+ B-lymphocytes were absent in all cases. NK cells make up about 25% of all infiltrate cells. There was a clear expression of TLR4 in the cytoplasm of all cardiomyocytes, lymphomacrophagal, and leukocyte elements of the infiltrate, vascular endothelial cells, pericytes, and vascular smooth muscle cells (Figure 2, E). A dim reaction of the cytoplasm of cardiomyocytes and individual leukocytes was observed on TLR-9 (Figure 2, F).

Thus, all patients included in the study were diagnosed with highly active and severe lymphocytic myocarditis (more than 7 CD3+ T-lymphocytes per 1 mm^2).

Discussion

The study demonstrated (for the first time in a series of cases) morphologically and immunohistochemically verified cases of acute lymphocytic myoendocarditis in the new coronavirus disease (COVID-19).

Some authors estimate the rate of clinically diagnosed myocarditis at 4.8% [12]. A group of physicians from

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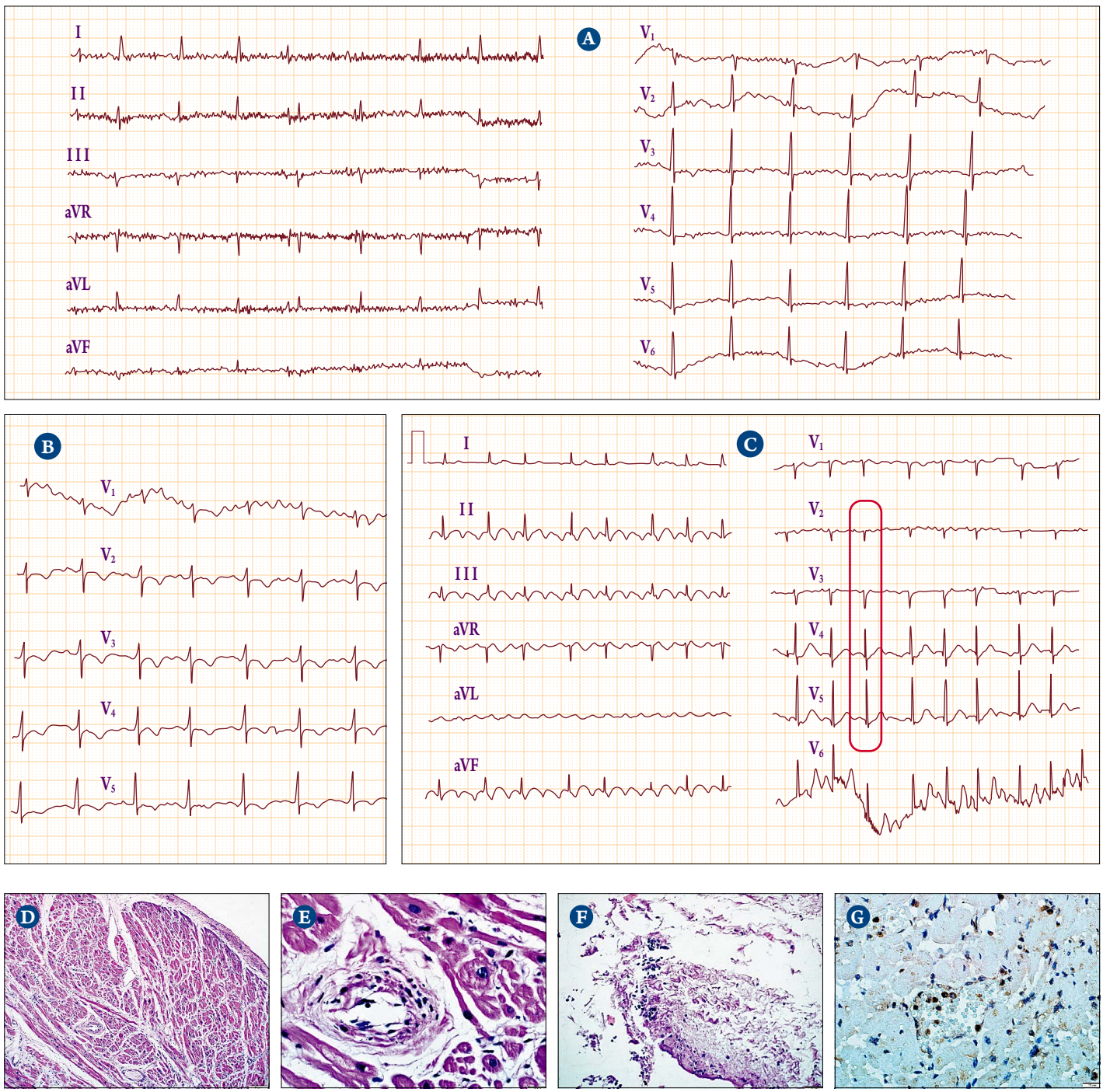
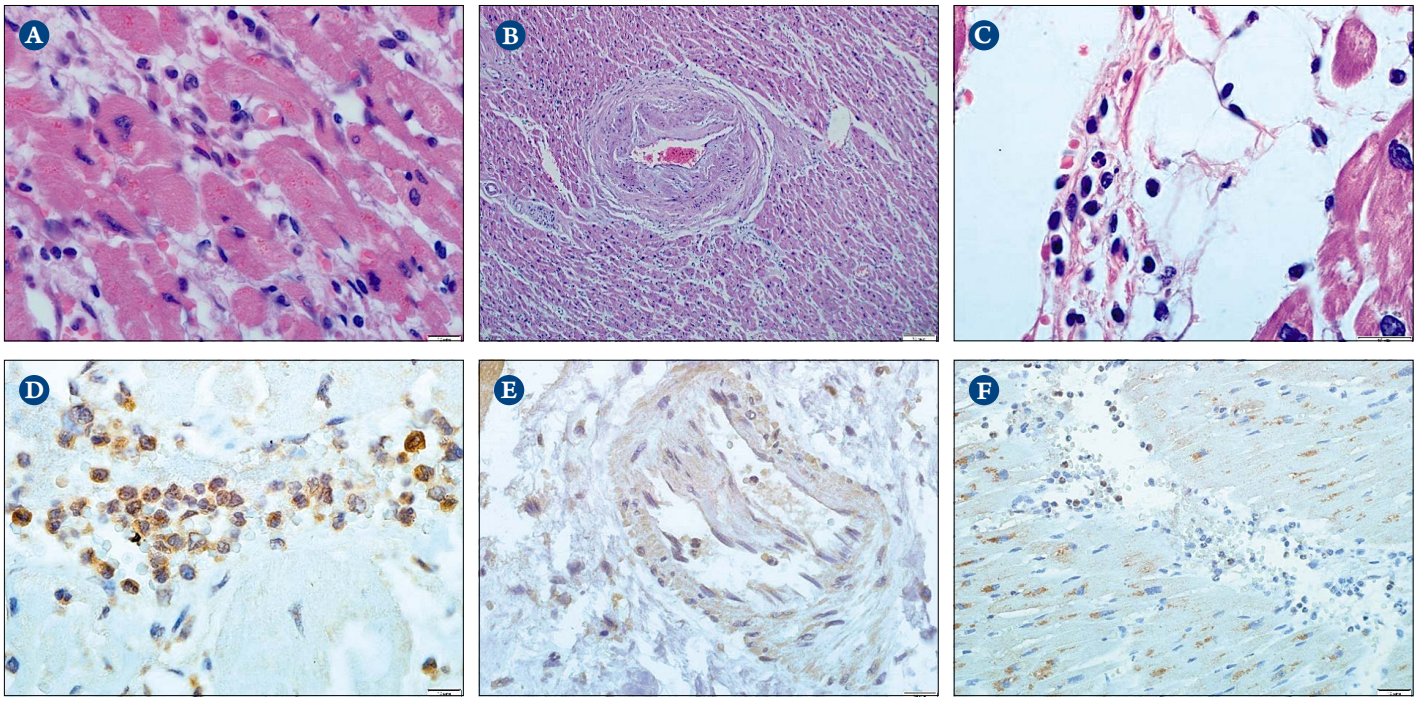
Lombardy (Italy) presented one of the first convincing clinical descriptions of severe heart disease regarded as myopericarditis. A 53-year-old woman with no pre-existing heart disease developed severe systolic dysfunction (reduced ejection fraction to 35%) one week after the onset of AVRI symptoms. Magnetic resonance imaging (MRI) signs of diffuse myocardial edema and pericardial effusion as well as increased blood levels of highly sensitive troponin (0.59 ng/mL) and NT-proBNP (8,465 pg/mL) were also found [6]. The diagnosis of COVID-19 was confirmed serologically despite the absence of pneumonia. A myocardial biopsy was not performed. Treatment with cardiotropic, antiviral drugs, steroids, and hydroxychloroquine had a distinct positive

Figure 1. Electrocardiographic (ECG) changes (A–C) and myocardial morphology (D-F) in a 75-year-old patient



A–C – ECG at the rate of 25 mm/s (April 8, 13 and 21): negative T-waves in all chest leads (B) with subsequent disappearance (C); development of a paroxysm of typical atrial flutter, no ischemic ST depression at HR of 138 bpm (C); D–G – left ventricular specimen, hematoxylin and eosin staining (D – lymphocytic myocarditis, thrombovasculitis, ×600; E – necrotizing coronaritis, ×400; F – lymphocytic pericarditis, ×200; G – anti-CD3 antibody immunohistochemical assay, more than 7 CD3+ T-lymphocytes per mm² in the myocardium, ×400).

Figure 2. Histological and immunohistochemical pattern of myocarditis in COVID-19



A – lymphohysteocytic infiltration in the myocardial stroma; B – small vessel coronaritis; C – lymphocytic pericarditis; D – CD3 lymphocytes in the myocardial stroma; E – TLR4 in the inflammatory infiltrate cells, fibroblasts, vessel endothelium, and cardiomyocytes; F – weak TLR9 expression in the stromal cells. Hematoxylin and eosin staining – A, B, C; immunoperoxidase reaction with DAB1 – D, E, F. Zoom in: A, C, D, E – ×600; B, F – ×200.

effect. Other cases of myocarditis diagnosed by MRI were also described, including those in young patients without pneumonia [13, 14], which may indicate a special tropicity of this virus to the myocardium and requires studying the specific mechanisms of its damage.

Several clinical cases were described as fulminant myocarditis. For example, authors from Wuhan (China) used national criteria for diagnosing myocarditis, which does not require morphological verification [15]. The patient died within 1 month when a secondary infection developed despite massive therapy including antiviral drugs, prednisone, immunoglobulin, and restoration of myocardial contractility. Unfortunately, autopsy results have not been reported. In another case (from Spain), a 59-year-old woman with SARS-CoV-2 positive test result with a history of hypertension and tuberculous lymphadenitis (without pneumonia) developed signs of acute heart failure with preserved myocardial contractility. However, she needed extracorporeal membrane oxygenation (ECMO), and myocarditis was diagnosed clinically (ST elevation in ECG, increased troponin levels, myocardial edema, pericardial effusion). No biopsy was performed [16].

The results of the morphological examination of the myocardium in patients with clinical suspicion of myocarditis are undoubtedly of the greatest interest. In a recently described case, a 17-year-old patient died of cardiac arrest, preceded by weakness, headache, nausea, and vomiting over a period of just two days. The nasopharyngeal swab was COVID-19-positive. No blood tests were performed, and no signs of lung inflammation were detected during the autopsy. However, eosinophilic myocarditis was diagnosed [10]. There was no eosinophilia in bone marrow, no signs of vasculitis, fibrinoid necrosis, thrombosis, granulomas, or significant fibrosis. This dramatic case is extremely unusual (given the age of the patient, rapid development of symptoms, absence of pneumonia, and eosinophilic nature of myocarditis) and may be indicative of a special predisposition to such a severe virtually allergic reaction of the myocardium. The role of the virus as a trigger of myocarditis, in this case, is unclear.

Another brief description presents a patient with a clinical picture of Takotsubo syndrome. More than 7 CD3 positive lymphocytes were detected in the in-life myocardial biopsies (myocarditis criterion). The virus itself was not detected in the myocardium making the detected changes taking into account a rather dim infiltration and not altogether typical clinical picture of myocarditis subject to opinion [11]. In the latest editorial commentary on 11 described cases of myocarditis, German experts have identified at least 6 variants (mechanisms) of myocardial-like symptoms in COVID-19, including myocardial dysfunction

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due to cytokines and antibodies in the absence of the virus itself [17]. It is such a cytokine storm that can be discussed as the cause of Takotsubo syndrome development.

Finally, the results of a thorough in-life morphological and virological study of the myocardium in a 69-year-old COVID-19-positive patient need to be mentioned. It was conducted by a group of leading experts from Lombardy using a myocardial biopsy [18]. The typical clinical picture of severe myocarditis was combined with pneumonia. There were no changes in the coronary arteries, and a myocardial biopsy was performed in the ECMO setting. The biopsies revealed only mild interstitial and endocardial inflammation, CD68 positive macrophages with damaged membranes and vacuoles in the cytoplasm. The ultrastructural examination found viral particles with the coronavirus morphology in the altered macrophages, but not in myocytes and endothelium. Focal lysis of myofibrils was observed in cardiomyocytes, no necrosis, and minimal perivascular fibrosis. The patient died. No autopsy data has been provided.

This description does not meet the generally accepted criteria for myocarditis but reveals other possible mechanisms of cytopathic action of the virus in the heart. The authors discuss the possibility of alveolar macrophage migration to other tissues and organs. However, the cases of actual isolated myocardial damage mentioned earlier do not make this assumption the most likely.

No other studies with in-life detection of coronavirus in the myocardium (including more traditional PCR methods) have been published. Only in an oral presentation during a webinar which took place on 5 June 2020, H-P Schultheiss from Berlin presented an article describing 5 cases of myocarditis and inflammatory cardiomyopathy with the SARS-CoV-2 genome identified in the myocardium. However, the possibility of the long-term persistence of the virus or, on the contrary, its trigger role with subsequent rapid elimination is of undoubted interest for further research. There is evidence only of a high viral load in the myocardium of patients who died of various thromboses [19].

One of the key mechanisms of myocardial damage in COVID-19 is thought to be thrombosis of both large and small coronary vessels. Such non-inflammatory changes in the myocardium as mild lymphocytic infiltration [20], infiltration with a small number of monocytes and CD34-positive cells, and interstitial fibrosis (which is regarded as a sign of chronic myocardial damage) [21] were also observed.

However, the changes described in our cases were beyond those presented and fully corresponded to the morphological and immunohistochemical criteria of true acute lymphocytic myocarditis.

No conflict of interest is reported.

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