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Subacute and chronic post-covid myoendocarditis: clinical presentation, role of coronavirus persistence and autoimmune mechanisms

Aim — To study clinical features of myoendocarditis and its possible mechanisms, including persistence of SARS-Cov-2 in the myocardium, in the long-term period following COVID-19.

Material and methods — This cohort, prospective study included 15 patients aged 47.8±13.4 years (8 men) with post-COVID myocarditis. The COVID-19 diagnosis was confirmed for all patients. Median time to seeking medical care after COVID-19 was 4 [3; 7] months. The diagnosis of myocarditis was confirmed by magnetic resonance imaging (MRI) of the heart (n=10) and by endomyocardial biopsy of the right ventricle (n=6). The virus was detected in the myocardium with PCR; immunohistochemical (IHC) study with antibody to SARS-Cov-2 was performed; anticardiac antibody level was measured; and echocardiography and Holter monitoring were performed. Hemodynamically significant coronary atherosclerosis was excluded for all patients older than 40 years.

Results — All patients showed a clear connection between the emergence or exacerbation of cardiac symptoms and COVID-19. 11 patients did not have any signs of heart disease before COVID-19; 4 patients had previously had moderate arrhythmia or heart failure (HF) without myocarditis. Symptoms of myocarditis emerged at 1–5 months following COVID-19. MRI revealed typical late gadolinium accumulation, signs of hyperemia, and one case of edema. The level of anticardiac antibodies was increased 3–4 times in 73% больных. Two major clinical variants of post-COVID myocarditis were observed. 1. Arrhythmic (n=6), with newly developed extrasystole or atrial fibrillation without systolic dysfunction. 2. Decompensated variant with systolic dysfunction and biventricular HF (n=9). Mean left ventricular ejection fraction was 34.1±7.8%, and left ventricular end-diastolic dimension was 5.8±0.7 cm. In one case, myocarditis was associated with signs of IgG4-negative aortitis. SARS-Cov-2 RNA was found in 5 of 6 biopsy samples of the myocardium. The longest duration of SARS-Cov-2 persistence in the myocardium was 9 months following COVID-19. By using antibody to the Spike antigen and nucleocapsid, SARS-Cov-2 was detected in cardiomyocytes, endothelium, and macrophages. Five patients were diagnosed with lymphocytic myocarditis; one with giant-cell myocarditis; three patients had signs of endocarditis (infectious, lymphocytic with mural thrombosis).

Conclusion — Subacute/chronic post-COVID myocarditis with isolated arrhythmias or systolic dysfunction is characterized by long-term (up to 9 months) persistence of SARS-Cov-2 in the myocardium in combination with a high immune activity. Endocarditis can manifest either as infectious or as nonbacterial thromboendocarditis. A possibility of using corticosteroids and anticoagulants in the treatment of post-COVID myoendocarditis should be studied.

Keywords — Post-COVID myocarditis; post-COVID endocarditis; COVID-19; SARS-Cov-2; endomyocardial biopsy

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Introduction

The ongoing novel coronavirus infection (COVID-19) pandemic, which was officially announced in March 2020, significantly affects the routine clinical practice of doctors of various specialties, including cardiologists. There are number of reasons why analogies made with flu and other viral infections during the first months of the pandemic do not stand up to criticism. We will not discuss the expansion of the COVID-19 pandemic and associated mortality rates since they are self-evident. From a cardiological perspective, an evident negative influence on the course of chronic heart diseases [1] and the ability to induce prolonged myocarditis are the most significant differences between the disease caused by severe acute respiratory syndrome-related coronavirus 2 (SARS-Cov-2) and the other viral diseases. In terms of such consequences, COVID-19 is hardly comparable with any other respiratory infection.

At the time of writing (March 2021), from 50% to 80% of patients in our Cardiology Department had a history of COVID-19 which was associated with worsening of their condition (increased dyspnea, palpitations, blood pressure destabilization, arrhythmias, a significant decrease in exercise tolerance, etc.). The course following acute COVID-19 varies from a few weeks to six months or more. In some patients, a progression of cardiac symptoms led to the study of immunoglobulin G (IgG) levels related to SARS-Cov-2 and retrospective diagnosis of the infection. Patients with previously diagnosed chronic myocarditis receiving immunosuppressive therapy (IST) form a separate category. Although initial observations of such patients show a relatively good course of COVID-19 in chronic myocarditis [2], a special long-term study is required. The same applies to patients with various cardiomyopathies (hypertrophic cardiomyopathy, etc.).

The primary subject of the present study is myocarditis directly induced by SARS-Cov-2. The possibility of the virus causing typical inflammation associated with direct myocardial damage was subject to a certain skepticism on the part of experts in the early months of the pandemic; non-inflammatory mechanisms of cardiac involvement were more often discussed in this connection. Coronavirus-associated myocarditis was eventually verified by a consecutive series of publications of several authors. Here, we should mention the first detection SARS-Cov-2 (electron microscopy) with minimal infiltration in intravital myocardial biopsies of a patient with COVID-19 and cardiogenic shock [3], as well as the identification of the viral RNA in the myocardium of patients with morphological and clinical myocarditis [4, 5]. Our description of pancarditis in the autopsy observations in patients with COVID-19 [6] was among those publications; SARS-Cov-2 RNA was subsequently found in the myocardium of all patients.

However, these and a few subsequent descriptions only covered cases of acute coronavirus-associated myocarditis. The maximum time following acute COVID-19, in which morphological signs of myocarditis were detected in combination with SARS-Cov-2 persistence, was only 4 weeks [7]. Although the term «post-COVID» is not in use with respect to heart diseases, such as myocarditis, the ability of COVID-19 to induce sustained stable symptoms of both a general (fatigue, cognitive decline) and a specific nature is a generally recognized feature, which resulted in the appearance of the term «post-COVID syndrome» [8]. The additionally referred to concept of «long COVID» usually means a sustained inflammatory response in patients with COVID-19 [9]. Thus, myocardial inflammation may be both a component of the syndrome and the cause of sustained systemic inflammation, requiring a special study using intravital morphological diagnosis (myocardial biopsy).

Objective

Study clinical features of myocarditis and its possible mechanisms (including the persistence of SARS-Cov-2 in the myocardium) following acute COVID-19.

Material and methods

A single-center, prospective cohort trial included 15 patients (8 male and 7 female patients, mean age 47.8±13.4, 24–65 years) diagnosed with «post-COVID myocarditis». Examinations and treatment were performed in the Cardiology Department of the V. N. Vinogradov Clinic of Intermediate Level Therapy, Sechenov University.

Inclusion criteria comprised a history of serologically verified COVID-19, the onset or significant progression of symptoms of heart disease [arrhythmias, chronic heart failure (CHF)] following COVID-19, the presence of at least two of the three Lake Louise criteria (LLC) of myocarditis (2018) according to contrast-enhanced cardiac magnetic resonance imaging (MRI) and/or the Dallas morphological criteria of myocarditis according to ESC 2013 [10, 11].

Exclusion criteria were history of myocarditis verified by MRI and/or endomyocardial biopsy (EMB), immunosuppressive therapy (IST), hemodynamically significant (more than 50%) coronary stenosis (in patients older than 40 years), acquired heart valve disease, hypertensive heart (hypertrophy of more than

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14 mm), diffuse connective tissue diseases, systemic vasculitis, sarcoidosis.

Characteristics of acute COVID-19

The diagnosis of COVID-19 was confirmed by positive PCR tests in 40% of cases, followed by the appearance and preservation of IgG to SARS-Cov-2 in all patients. However, PCR tests at admission to the hospital were negative in all patients. The low percentage of positive nasopharyngeal swabs is due to delayed tests or failure to perform the tests (COVID-19 was suspected during fever). The history of COVID-19 was suspected and confirmed retrospectively in every third patient (5 of 15). There were no cases of severe COVID-19.

Only four patients required hospitalization for acute COVID-19. Bilateral viral pneumonia was diagnosed in 7 of 10 patients who underwent chest computed tomography (CT): pulmonary involvement was ≤25% (CT-1) in 5 cases and 25–50% (CT-2) in 2 patients [12]. Three patients developed respiratory failure grade 1; non-invasive or invasive ventilation was not required in any case. Troponin levels were not evaluated. While the treatment varied, only one patient received steroid therapy (intramuscular dexamethasone). Systolic dysfunction was detected in this patient during hospitalization [reduced left ventricular ejection fraction (LVEF)]; other patients had no cardiac symptoms.

Concomitant diseases

The mean body mass index was 26.0±4.6 kg/m 2; obesity grade 1 was identified in 3 patients. One patient had type 2 diabetes mellitus and a history of acute lymphocytic leukemia in childhood, 6 patients had hyperlipidemia, while a further 6 patients had (a history of) arterial hypertension grade 2–3, which was well managed and did not cause significant left ventricular (LV) hypertrophy.

The majority of patients (11 of 15) had no cardiac symptoms prior to the onset of COVID-19. One of the asymptomatic patients during COVID-19 had a bicuspid aortic valve without significant valvular dysfunction diagnosed as a teenager. Four patients had symptoms of suspected heart disease of an unclear nature prior to the onset of COVID-19. One case involved multifocal arrhythmias [ventricular premature beats (VPB, atrial fibrillation (AF)] without significant systolic dysfunction, while another three cases had LV dysfunction (moderately reduced LVEF of 45–50%), which could be assessed retrospectively as a debut of myocarditis. However, the diagnosis was not delivered; in any case, no IST was performed.

All patients had severe cardiac symptoms and a significant deterioration in their condition following COVID-19. Myocarditis was not diagnosed or suspected during COVID-19 in any case. The median time to seeking medical care following COVID-19 was 4 months [3; 7] (from 2 to 9 months), while the time after the onset of symptoms ranged from 3 weeks to 5 months after COVID-19.

Methods of examination

The diagnosis of myocarditis was confirmed in 10 patients by cardiac MRI and in 6 patients by EMB of the right ventricle (RV). The myocardial biopsies were studied at the A.I. Strukov Department of Pathology, Sechenov University. The study included hematoxylin-eosin staining and Van Gieson's staining, immunohistochemical (IHC) staining with anti-CD3, anti-CD20, anti-CD45, anti-CD68, anti-Tull-like receptors 4 and 9 antibodies, as well as anti-SARS-Cov-2 antigen (nucleocapsid and Spike antigens) antibodies. The most recent study was carried out under grant No. 2031590021/20 of the Russian Fund of Fundamental Investigations (RFFI).

The myocardial biopsies were also studied by PCR for DNA of parvovirus B19, herpes viruses 1, 2, 6, 8, herpes zoster, Epstein-Barr virus, cytomegalovirus, adenovirus (OOO «DNK-Tekhnologia») and SARS-Cov-2 RNA (the biopsies were sent to the Central Research Institute for Tuberculosis). The total RNA extract was isolated from these heart tissue fragments using a RNeasy Mini Kit (Qiagen, Germany). SARS-CoV-2 was identified using a QuantiTect kit (Qiagen) for real-time one-step PCR. Primers were selected based on the materials of the DNA and mRNA sequences available in the NCBI database using the Primer-BLAST application.

Blood levels of anticardiac antibodies (ACAs) were determined by indirect immunofluorescence; echocardiography and Holter electrocardiogram (ECG) were performed in all patients. Hemodynamically significant coronary atherosclerosis was excluded in all patients older than 40 years (in 7 patients using coronary angiography and 4 patients using multislice cardiac CT).

Statistical analysis was performed using IBM SPSS Statistics v.22. The sampled data are represented as the absolute and percentage, while continuous data are expressed as the mean±standard deviation in case of normal distribution (tested by the Kolmogorov-Smirnov method) or as quartiles (50 [25; 75]) in case of non-normal distribution.

Ethics committee

All patients signed an informed consent document for clinical examinations (including myocardial biopsy)

Table 1. Clinical characteristics of patients with post-COVID myocarditis

Parameter	Arrhythmic form	Decompensated form	All patients
#	6	9	15
Male/female	2/4	6/3	8/7
Mean age, years	34 [27; 57]	55 [45; 60]	47.8±13.4
No symptoms before COVID-19	6 (100%)	5 (55.6%)	11 (73.4%)
Time to seeking medical care after COVID-19, months	3 [2; 4.75]	6 [4; 7]	4 [3; 7]
Duration of symptoms, months	2 [2; 3]	6 [3.5; 18]	3 [2; 10]
CHF FC (NYHA)	0	3 [3; 3.5]	3 [0; 3]
White blood cells, 10^9/L	5.4 [4.42; 6.65]	6.6 [5.2; 11.15]	6.37 [4.7; 7.49]
Neutrophils, 10^9/L	2.7 [2.2; 3.6]	3.2 [2.65; 8.7]	2.89 [2.46; 4.33]
Lymphocytes, 10^9/L	2.0 [1.3; 2.9]	1.7 [1.35; 2.5]	1.81 [1.38; 2.9]
Hemoglobin, g/L	146.5±18.2	136.8±25.0	140.7±22.4
CRP, mg/L	1 [0.75; 1.25]	5 [2; 30]	2 [1; 13]
Specific ANAs, n	3 (50%)	5 (55.6%)	8 (44.4%)
≥3-fold increase of ACAs, n	6 (100%)	8 (88.9%)	14 (93.3%)
LVEDD, cm	4.7±0.4	5.8±0.7	5.3±0.8
LVEDV, mL	82.3±18.3	153.8±46.2	125.2±51.5
LVESV, mL	33.2±8.2	104.8±37.6	60 [37; 128]
LVEF, %	59.2±5.3	34.1±7.8	44.1±14.4
Left atrium, cm	3.4±0.6	4.5±1.0	4.1±1.0
Left atrial volume, mL	43.8±17.5	66 [52; 99]	58 [38; 78]
Right atrial volume, mL	37.5±13.7	52 [37.5; 73.5]	43 [33; 65]
Right atrium, cm	2.1±0.4	3.5±0.4	2.9±0.8
PASP, mm Hg	24.2±4.3	40.7±11.2	34.1±12.2
Mitral regurgitation, grade	0.25 [0; 1.125]	1 [1; 1.75]	1 [0.5; 1.5]
Tricuspid regurgitation, grade	0.5 [0; 1]	1 [1; 1.75]	1 [0.5; 1]
Methylprednisolone, n	3 (50%)	8 (88.9%)	11 (73.3%)
Methylprednisolone dose, mg/day	16 [16; 16]	28 [12; 32]	16 [16; 32]
Hydroxychloroquine 200 mg, n	6 (100%)	–	6 (40%)

CHF – chronic heart failure; CRP – C-reactive protein; ANAs – antinuclear antibodies; ACAs – anticardiac antibodies; LVEDD – left ventricular end-diastolic dimension; LVEDV – left ventricular end-diastolic volume; LVESV – left ventricular end-systolic volume; LVEF – ejection fraction; PASP – pulmonary artery systolic pressure

approved by the Ethics Committee of the Sechenov University.

Results

The general clinical characteristics of patients are provided in Table 1. The analysis of the clinical patterns of the disease allowed two main forms of post-COVID myocarditis to be identified (which was combined with endocarditis in some patients): arrhythmic and decompensated.

Arrhythmic form of post-COVID myocarditis (6 patients)

The main manifestation of this form comprises the development of cardiac arrhythmias, which were subjectively poorly tolerated and never felt/recorded before. Acute COVID-19 was mild in all patients: minimal pneumonia (CT-1) was revealed only in two cases; in one case, there were no CT changes, while the remainder of the patients did not undergo examination. No patient was hospitalized for COVID-19; in two patients, it was diagnosed retrospectively. No patient had arrhythmia in the acute phase, which appeared 1 to 3 months later and led to them seeking medical care after 3 months on average. In one patient, the onset of arrhythmia coincided with the second wave of fever (in 3–4 weeks from the onset of the disease); the rest of the patients developed isolated cardiac symptoms later.

Arrhythmias included continuous recurrent AF (2 male patients), isolated rates of supraventricular (4–15 ths./day) or ventricular (22–36 ths./day) premature beats in female patients Figure 1 A-D. There were no other changes in ECG. Echocardiography revealed no hypertrophy, dilation of the heart chambers, decreased wall motion, or pericardial effusion. Myocarditis was confirmed by MRI: diffuse or focal subepicardial/intramyocardial delayed accumulation of gadolinium in the ventricles and atria, signs of hyperemia,

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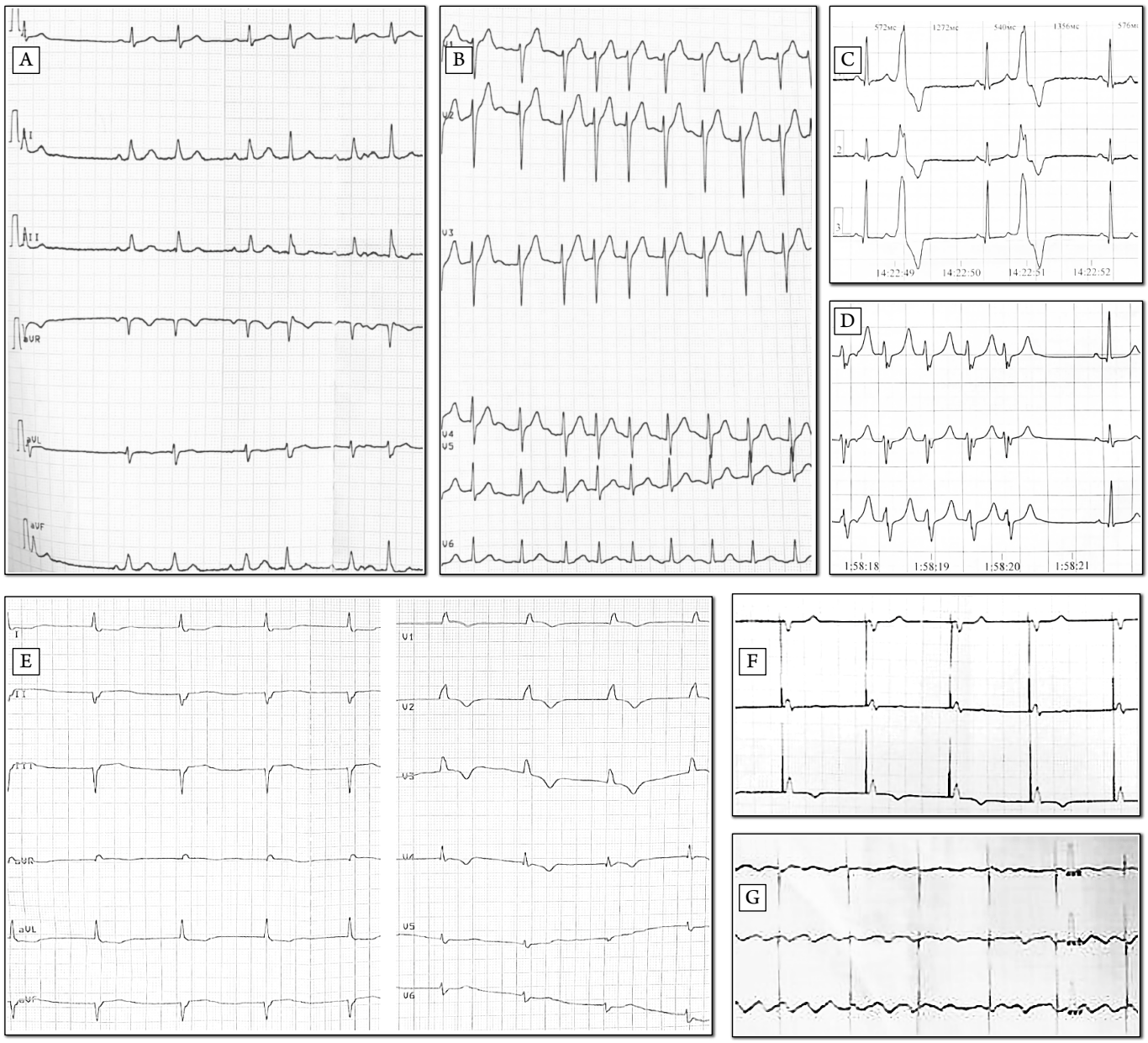
increased myocardial relaxation time in T2 and native myocardium in T1 – in rare cases, edema (Figure 2 H, I). No data confirming other arrhythmogenic diseases (right ventricular cardiomyopathy, noncompact myocardium) were received for this form of myocarditis.

Moreover, all patients showed a 3–4-fold increase in the levels of antibodies to various cardiac antigens (mainly conduction fiber antigens). Antibodies to the cardiomyocyte nuclei [specific antinuclear antibody (ANA)] from 1:40 to 1:160 were detected in three patients (normally absent). General inflammatory changes in the blood, including increased creatine phosphokinase levels were not detected in any case.

Approaches to the treatment of arrhythmic post-COVID myocarditis

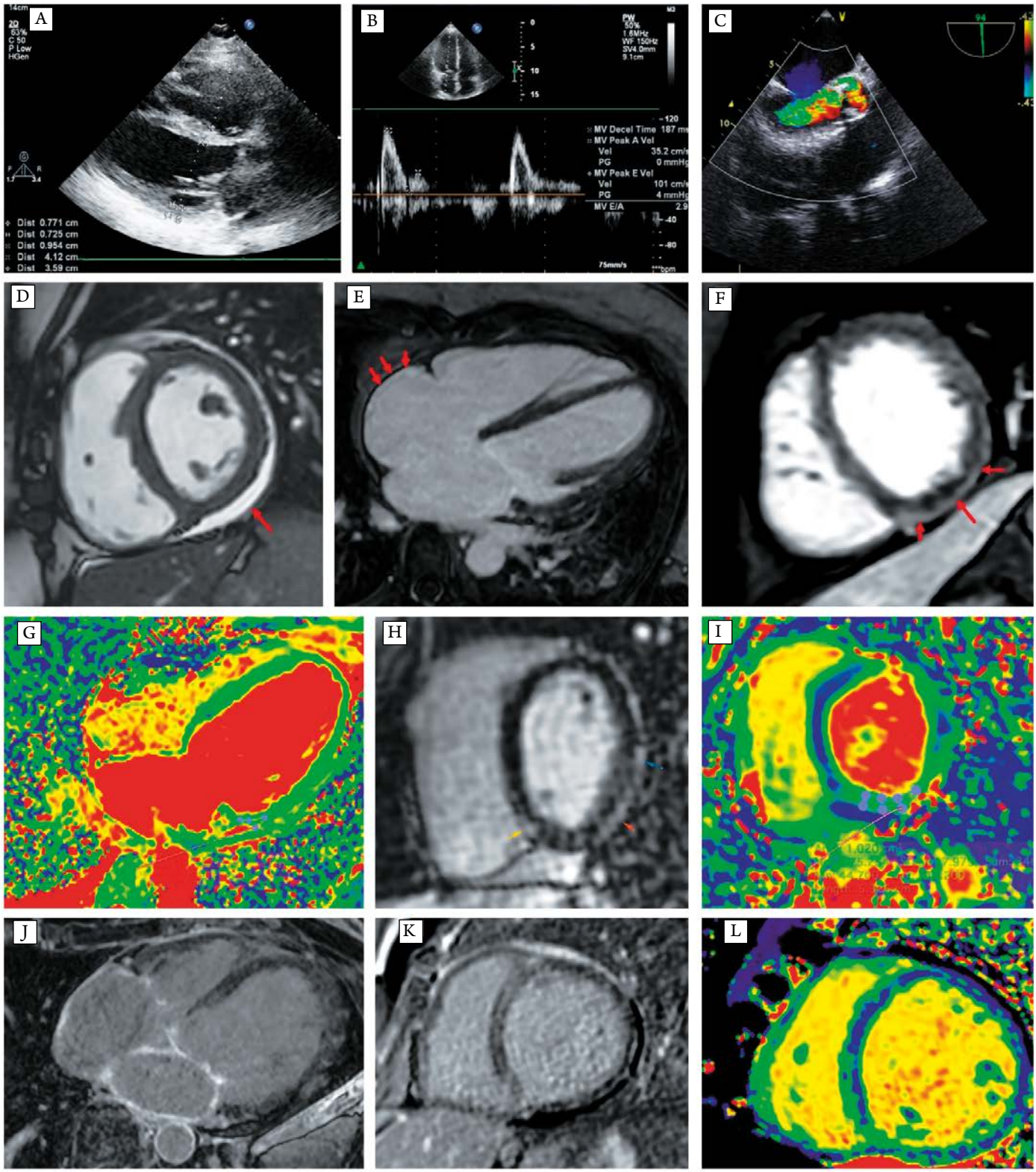
Patients with AF were administered amiodarone, while the remainder of the patients achieved the full antiarrhythmic effect using lappaconitine hydrobromide – in one case, in combination with sotalol. The background therapy of myocarditis included methylprednisolone 16 mg/day in combination with

Figure 1. Arrhythmias and conduction disturbances in patients with arrhythmic (A-D) and decompensated (E-G) forms of post-COVID myocarditis



A, B – ECG paper speed – 25 mm/s; frequent supraventricular premature beats and atrial fibrillation in a 33-year-old patient;
C, D – fragments of Holter ECG; ventricular bigeminal rhythm, unsustained ventricular tachycardia in a 28-year-old patient;
E–G – ECG paper speed – 25 mm/s: replacing AV junctional rhythm (E) and paced ventricular rhythm (F);
46-year-old female patient with giant cell myocarditis and atrial standstill;
ventricular fibrillation-flutter with ineffective pacing and complete electromechanical dissociation (G).

Figure 2. Echocardiography (A–C) and MRI manifestations (E–L)
of post-COVID myoendocarditis in patients with arrhythmic form (H, I) and decompensated form (A–G, K–L)



46-year-old female patient with giant cell myocarditis and atrial standstill:
A – RV dilation with normal LV; B – restrictive diastolic dysfunction (E/A 2.9); D – pericardial effusion (arrow); E – delayed accumulation foci in the RA myocardium (arrow); F – delayed accumulation foci in the LV posterior wall and posterior septal segment (arrows).
A 39-year-old patient with a combination of infective endocarditis and lymphocytic myocarditis:
C – vegetation on the bicuspid aortic valve (arrow) and grade II regurgitation;
G – T2 map, swelling edema of the lateral basal third. A 28-year-old female patient with arrhythmic myocarditis:
H – delayed LV opacification; I – T2 map, swelling of the posterior LV wall. 44-year-old patient with a combination of arrhythmogenic cardiomyopathy and myocarditis: delayed opacification in the atrial (J) and ventricular (K) myocardium;
L – T1 map – diffuse changes of the posterior septal segment.

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hydroxychloroquine 200 mg daily in half the cases; the remainder of the patients received hydroxychloroquine monotherapy. No adverse reactions were reported during the hospital stay.

Decompensated form of post-COVID myocarditis (9 patients)

All patients with this form were admitted with congestive CHF FC III–IV, which was biventricular (peripheral edema, hepatomegaly, effusion) in 7 of 9 patients. There were no cases of severe acute COVID-19: two patients found out retrospectively that they had COVID-19, while the remainder of the patients underwent lung CT, which demonstrated the absence of pneumonia in two patients and the presence of bilateral viral pneumonia in the others (three and two patients had CT-1 and CT-2, respectively). Four patients were hospitalized for this reason; however, heart failure was not an indication for hospitalization in any case.

In this subgroup, four patients had experienced symptoms of heart disease prior to contacting COVID-19, but myocarditis had not been diagnosed in any of them and IST had not been performed. For example, a 44-year-old patient with the longest history of heart disease (Table 2 and Figures 2 K-M, 3 D) had experienced arrhythmias (frequent VPBs, paroxysmal AF) for many years and undergone effective radiofrequency pulmonary vein isolation in 2019; however, the origin of arrhythmia was not established and he had no severe left ventricular dysfunction.

Another three patients had signs of left ventricular dysfunction (moderate reduction of LVEF to 45–50%, retrospectively suspected debut of myocarditis); yet it was infection by SARS-Cov-2 that had led to a pronounced worsening of symptoms and, above all, the progression of CHF. Myocarditis was confirmed morphologically in all four patients with a prior history; moreover, its direct relation with COVID-19 was proven (SARS-Cov-2 RNA was identified in the myocardium, see below), which allowed them to be included in the trial. The remaining five patients had absolutely no cardiac symptoms or echocardiographic abnormalities before COVID-19.

The onset and/or progression of congestive CHF was observed in the period from 2 to 5 months following COVID-19 infection; patients sought medical care within six months on average (Table 1). According to echocardiographic findings, most patients had dilatation of all (including right) heart chambers with reduced LVEF 20–30%, but LV dilatation was moderate, which confirmed that the process was recent (Figures 2 A, B). There were no cases of high pulmonary hypertension or symptoms of pulmonary embolism, i.e., the myocardial dysfunction was not of a secondary nature. Only two patients had persistent AF, which contributed to the worsening of CHF but was not decisive. Two out of three patients had VPBs and nonsustained ventricular tachycardia (VT). One patient had a first-detected left bundle branch block and atrioventricular block with pauses up to 5 seconds during AF – an implantable cardioverter-defibrillator (ICD) had been implanted.

The most malignant arrhythmias and conduction disorders combined with atrial standstill were experienced by a 46-year-old female patient; these symptoms had developed within a few months, with substituting junctional rhythm, alternating left and right bundle branch blocks emerging only at the end of VPB and sustained VT, which led to her sudden death and unsuccessful resuscitation with complete electromechanical dissociation. She had no solid indication for ICD implantation (EF was 37%), pacemaker implantation was technically challenging, and pacemaking was only implemented through the ventricular electrode (Figures 1 E-G). MRI (Figures 2 D-F) detected a portion of delayed intramyocardial opacification in the interventricular septum, but only EMB and autopsy revealed the severity of myocarditis (Table 2).

Four of the nine patients with decompensated myocarditis still had elevated C-reactive protein (CRP) levels at the time of the trial, while three of them had moderate leukocytosis. The ACA titers were 3–4-fold in all patients but one; specific antinuclear antibodies (ANAs) were detected in more than half of patients. The most severe general inflammatory changes were observed in patients with asymptomatic aortitis shown by CT (without criteria for Takayasu arteritis, anti-neutrophil cytoplasmic antibodies, and IgG4) and a 39-year-old patient with concomitant infective endocarditis (IE) (Table 2).

Cardiac MRI detected signs of myocardial edema only in a patient with IE; the remainder of the patients had 1–2 criteria of myocarditis (delayed subepicardial and intramyocardial accumulation of gadolinium mainly in LV, increased relaxation time of the native myocardium in T1, increased extracellular volume (ECV), extracellular volume fraction, perfusion disorders, and pericardial effusion. MRI findings in a 44-year-old patient with a history of arrhythmia and clinically suspected hemochromatosis with cardiac involvement were of particular interest. MRI showed a combination of local iron overload (heterozygous HFE mutation), possible signs of arrhythmogenic cardiomyopathy and myocarditis. In this situation, only

EMB could give a precise explanation of severe post-COVID-19 LV dysfunction (Table 2).

Results of morphological and IHC examinations of the myocardium

RV endomyocardial biopsy was performed in patients with more severe and treatment-resistant CHF, including with prior cardiac history, when verifying the diagnosis became particularly challenging. Clinical and morphological characteristics of patients who underwent EMB are presented in Table 2 and Figure 3.

The diagnosis of active myocarditis was confirmed in all cases. The activity was evidenced by the signs of cardiomyocyte death (necrosis, lysis) and severe degeneration, as well as the presence of interstitial edema in all patients (Figures 3 A-E). Cellular infiltrates were presented by lymphohistiocytes; multinucleated giant cells were also detected in one case (Figure 3 B), which allowed myocarditis in a 46-year-old female patient with atrial standstill to be classified as giant cell myocarditis (GCM). Myocarditis was characterized by coronaritis (endotheliitis), which was detected in 83% of cases. Microvessel ehrombosis was found in 2 of 6 patients (Figure 3 D).

Patients with GCM had the most severe fibrosis. The other cases of perimuscular and perivascular fibrosis were moderate (Figure 3 F), which corresponded to recent myocarditis, including in patients with a prior cardiac history. Intramyocardial lipomatosis (up to 20% of a biopsy area, Figure 3 D) was detected in a patient with suspected arrhythmogenic cardiomyopathy by clinical and MRI signs, combined with initial

Table 2. Patients with morphologically verified post-COVID myocarditis (decompensated form)

Parameters/patients	1	2	3	4	5	6
Sex	M	F	M	F	M	M
Age, years	56	46	64	45	44	39
CHF functional class	III	III–IV	III	III–IV	III–IV	IV
Time after the onset of COVID-19 symptoms, months	6	5	4	2	9	7
Duration of cardiologic history, months	6	10	180	16	230	3
Results of EMB	LM	GCM	LM	LM	LM	LM
Endocarditis shown by EMB	–	+	+	–	–	–
Thrombosis shown by EMB	endocardium	endocardium. vessels	endocardium	vessels	–	–
SARS-Cov-2 RNA in the myocardium	–	+	+	+	+	+
Other viruses in the myocardium	–	Parvovirus B19	–	Parvovirus B19	–	–
CD3 lymphocytes per 1 mm2	15	40	15	10	12	40
CD45 lymphocytes per 1 mm2	20	60	20	15	35	60
Necrosis/cytolysis	+	++	+	+	+	++
Endotheliitis	++	+	-	++	+	+
Fibrosis	+	+++	+	+	+	–
Lipomatosis	–	++	–	–	+++	–
ACA level	+	+++	+++	+++	++	+++
Specific ANA	–	–	–	–	1:80	1:160
Reduced QRS voltage	+	+	+	++	+	–
MRI (Lake Louise criteria)	–	+ (2)	+ (1)	–	+ (2)	+ (2)
LVEDD, cm	5.5	4.1	6.4	6.4	5.6	6.4
LVEDV, mL	158	63	177	167	163	193
PASP, mm Hg	37	50	57	29	40	50
Initial LVEF, %	43	37	27	21	20	25
Methylprednisolone, mg/day	24	500 i/v 32	32	32	32	–
Changes in LVEF*, %	46	–	48	47	41	39
Implanted devices	–	Pacemaker	ICD	–	–	–
Sudden cardiac death	–	+	–	–	–	–

CHF – chronic heart failure; EMB – endomyocardial biopsy; LM – lymphocytic myocarditis; GCM – giant cell myocarditis; RNA – ribonucleic acid; ACA – anticardiac antibody; ANA – antinuclear antibody; MRI – magnetic resonance imaging; LVEDD – left ventricular end-diastolic dimension; LVEDV – left ventricular end-diastolic volume; LVESV – left ventricular end-systolic volume; PASP – pulmonary artery systolic pressure; LVEF – left ventricular ejection fraction; ICD – implantable cardioverter-defibrillator; * 1–2 months after the beginning of the background t herapy; the severity of morphological symptoms was assessed qualitatively from the minimum (+) to the maximum (+++).

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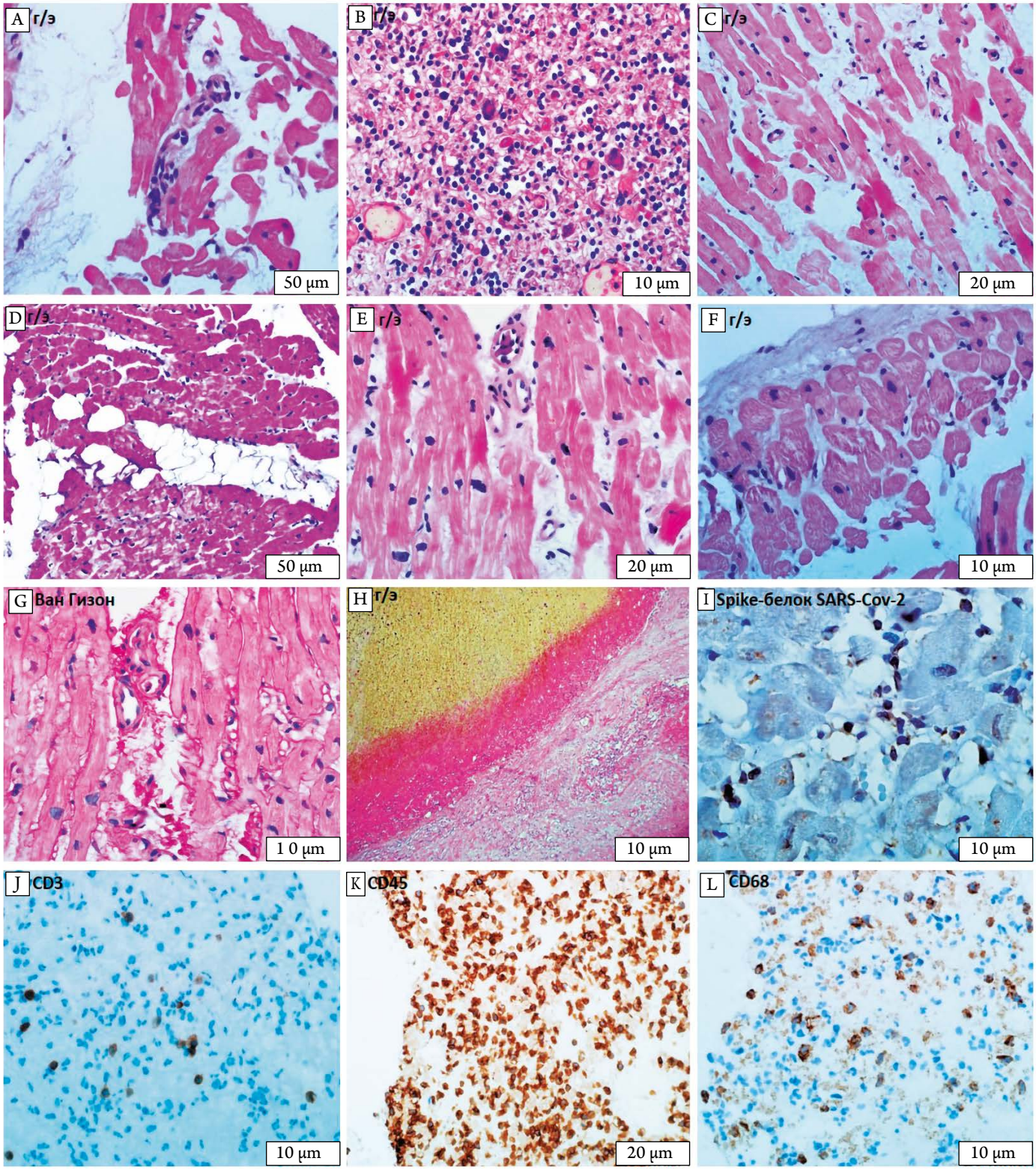
Figure 3. Morphological (A-H) and immunohistochemical (I-L) study of the myocardium in patients with decompensated post-COVID myoendocarditis



Hematoxylin-eosin staining, Van Gieson's staining, IHC study with anti-CD3, anti-CD45 lymphocytes, anti-CD68 (macrophages) and anti-SARS-Cov-2 Spike-protein antibodies. Interstitial lymphohistiocytic myocardial infiltration (A–F), endotheliitis (A, E), microvessel thrombosis (E), giant multinucleated cells in the infiltration (B), necrosis and severe degeneration of cardiomyocytes with loss of cross-striped striation (C, E) interstitial edema (C), perivascular and perimuscular cardiosclerosis (G) and lipomatosis (D), sclerosis and endocardial thickening with lymphoid infiltrates and mural thrombus (E), slight thickening of the RV endothelium without infiltrations against effective antimicrobial therapy of infective endocarditis (F), mural thrombus (H). Expression of the SARS-Cov-2 Spike-protein in vascular endothelium and infiltration cells (I). Myocardial infiltration with macrophages (M) and T-lymphocytes – more than 7 CD3-positive cells (J) and more than 14 CD45-positive cells (K).

fibrosis and active myocarditis; DNA diagnostics had to be performed to verify primary cardiomyopathy. Subendocardial lipomatosis was also detected in a patient with GCM and severe arrhythmias.

The comparison of the morphological and clinical data revealed a very strong positive correlation between CRP and the numbers of CD3 positive ($r=0.926$, $p<0.01$) and CD45 positive cells ($r=0.883$, $p<0.05$) in the biopsy sample, as well as with the number of CD68 positive cells (macrophages) and erythrocyte sedimentation rate (ESR) ($r=0.883$, $p<0.05$).

Results of virological examination of the myocardium (PCR and IHC)

The real-time PCR test of the myocardium detected no adenovirus or herpes genomes. Parvovirus B19 DNA was identified in two patients, including the one with GCM (Table 2). Myocarditis was not characterized by any morphological features in these cases.

SARS-Cov-2 RNA was detected in 5 of 6 patients. The minimal amounts of tested material can explain the absence of the virus in the remaining patient. Since this patient had less severe myocarditis than virus-positive patients, no significant increase in ACA titer was detected and time to biopsy after acute COVID-19 was average (6 months), this could not alone explain the negative result. The maximum time after COVID-19 to detecting the virus in the myocardium of patients with active myocarditis was 9 months (a 44-year-old patient, Table 2).

An IHC test with antibodies to the anti-nucleocapsid antibodies and SARS-CoV-2 Spike protein was performed. Strong positive expression of virus nucleocapsid was detected in cardiomyocytes and infiltrate cells (mainly macrophages). The reaction to the Spike-protein was positive in the vascular endothelium6 infiltrate cells, including in endocardial and pericardial infiltrate (Figure 3 I).

Endocarditis in patients with post-COVID myocarditis

A small pericardial effusion (with less than 1 cm separation of layers) was observed in three patients with post-COVID myocarditis; this was regarded as concomitant pericarditis in a patient with arrhythmic myocarditis; in two patients with decompensated myocarditis, the effusion could be a manifestation of congestive CHF. Following diuretic therapy, the effusions regressed.

Endocarditis concomitant with post-COVID myocarditis can be discussed more specifically. Despite the small number of cases, it is necessary to distinguish between two clinical forms.

IE meeting the 2015 criteria of the disease was diagnosed in a 39-year-old patient with severe myocarditis (Table 2) and a bicuspid aortic valve. Manifestations of IE included prolonged pyretic fever (with chills and sweats), which resumed in about a month after acute COVID-19 and was recorded irregularly over 5 months (regular use of nonsteroidal anti-inflammatory drugs smoothed the picture); weight loss of more than 20 kg; the progression of echocardiographic signs of aortic stenosis (aortic valve area was 0.9–1.1 cm^2; maximum gradient ≤50 mm Hg, aortic velocity ≤4.4 m/s) and aortic regurgitation up to grade 2; movable (≤5 mm) and fixed echo-positive masses on the valve leaflets (Figure 2 C); moderate splenomegaly; anemia up to 84 g/L with increased ferritin levels (1,832 mg/L) and moderate splenomegaly; general inflammatory changes in the blood (CRP 177 mg/L, ESR 25 mm/hour, leukocytes up to 21×109/L with left deviation); increased procalcitonin up to 1.94 ng/mL (normal ≤0.07 ng/mL), immunologic phenomena (rheumatoid factor ≤41 IU/mL). Repeated blood culture showed no growth.

Simultaneously, progressive dyspnoea and sustained reduction in LVEF to 25%; peripheral edema, bilateral pleural and pericardial effusion; increased ACA titer (including specific ANA titer 1:160); myocardial edema according to MRI (Figure 2 G). Severe systolic dysfunction was preserved three weeks after the initiation of antibiotic therapy with ceftriaxone 2 g/day, vancomycin 2 g/day and immunoglobulin A 50 g i/v. Administration of adequate cardiotropic treatment was not possible due to severe hypotension (80/60 mm Hg.) and ischemic hepatitis. EMB detected the picture of active lymphocytic myocarditis with interstitial edema, but there were no signs of RV endocarditis (both bacterial and lymphocytic); only endocardial thickening was observed (Figure 3 F). Biopsy culture showed no growth; PCR detected SARS-Cov-2 RNA.

Nonbacterial thrombotic endocarditis (NBTE) in 46-year-old and 64-year-old patients with decompensated post-COVID myocarditis, including GCM (Table 2). There were no clinical suspicions for IE and mural thrombosis (neither MRI signs); one patient received anticoagulant therapy to treat AF. EMB detected signs of lymphocytic endocarditis with endocardial thickening and sclerosis; individual biopsies were represented completely by thrombotic masses composed of fibrin and erythrocytes and permeated with neutrophils (Figure 3 H). There was

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also one case (a 56-year-old patient, Table 2) of mural thrombosis detected by biopsy without endocarditis.

SARS-Cov-2 RNA in the myocardium and very low blood titer of anti-endothelium antigen antibodies were a common feature of patients with a combination of myocarditis and endocarditis (both IE and NBTE), which can be treated as a result of a release of these antibodies in the endothelium within immune complexes. Titers of other ACAs were increased significantly.

Approaches to the treatment of decompensated post-COVID myocarditis

The majority (7 of 9) of patients received corticosteroid therapy in combination with cytostatics (mycophenolate mofetil 2 g/day or azathioprine 150 mg/day) if SARS-Cov-2 was not detected in the myocardium. Methylprednisolone pulse therapy (500 mg) was ordered for the patient with GCM. IST was not administered to one patient who refused to undergo EMB, including in view of his poor compliance. All patients undergoing IST (except for the patient with GCM) achieved a good direct response to the treatment in 1–6 months, such as the reduction of the severity of CHF, general inflammatory changes in the blood, and the increase in LVEF (Table 2). This also applies to the patient with pre-treated IE, who only started steroid therapy.

At the time of writing, all patients (except for diseased) were followed up for at least 1–2 months from the beginning of the background treatment of myocarditis: significant clinical improvements increased LVEF were observed (Table 2). However, the evaluation of long-term results of the treatment requires a longer follow-up period.

Discussion

This study presents for the first time a series of 15 cases of post-COVID myocarditis, which manifested clinically following acute COVID-19 and was diagnosed 2–9 months later, including by myocardial biopsy.

So far, only acute COVID-associated myocarditis confirmed by EMB in individual cases has been described in the literature (a recent survey revealed only nine such cases, mostly without virological tests [13]). Further development of the process in patients with myocarditis during COVID-19 is not described in the literature or was followed up for a very short time. Any form of viral myocarditis is known to resolve with clinical recovery, death, or chronicity. The first two outcomes have been described so far for CODIV-associated myocarditis. Cases of acute infarction-like myocarditis [14] and myocarditis masked by Takotsubo syndrome [15] are examples of clinical improvement with heart failure regression. The fatalities were SARS-Cov-2 positive eosinophilic myocarditis (a young patient without pneumonia [16]), lymphocytic myocarditis (patients with severe pneumonia [6]), isolated myocarditis positive for SARS-Cov-2 nucleocapsid antigen in the myocardium [17]. While morphologists from Padua (Italy) have revealed lymphocytic myocarditis in 14% of fatal cases of COVID-19 (3 of 21), they did not test virus RNA [18].

The chronicity of COVID-19 in general and with myocarditis in particular is one of the most intriguing and vital issues in terms of long-term prognosis. In vitro experiments have demonstrated that SARS-Cov-2 can directly infect cardiomyocytes and activate innate antiviral immunity [19]. This is confirmed by our data on increased expression of Tull-like receptors 4 and 9 in patients with acute myocarditis [6]. Several trials showed that SARS-Cov-2 could persist in macrophages for a long time [20]; however, the timing and the possibility of its elimination from the body remains unknown. Analogies with the infections with herpes viruses, hepatitis viruses (RNA-containing HCV) persisting in the body for life, supporting the production of both antiviral antibodies and autoantibodies, and causing clinically significant visceral lesions under favorable conditions, may be justified. A comparison can be made with the infection with HIV, which has genome fragments common with SARS-CoV-2 leading to immunosuppression.

There is almost no data on the long-term persistence of the virus in the myocardium or long post-COVID myocarditis. A group of authors of the Charite Hospital describes a case of a 59-year-old patient with symptoms of CHF, in whom EMB showed signs of inflammation within 4 weeks following the onset of pulmonary symptoms and identified SARS-CoV-2 genome [7]. There was no cardiomyocyte necrosis, which did not allow the myocarditis to be regarded as active. Three weeks later, repeat EMB showed a reduction of inflammatory infiltration and elimination of the viral genome (against a clear clinical improvement). COVID-associated myocarditis was described in a patient with severe respiratory symptoms of COVID-19, which had regressed by the end of the second month of the disease.

Another publication presents a case of virus-negative lymphocytic myocarditis, which was diagnosed by EMB a month after the onset of COVID-19 and regressed quickly [21]. We are not aware of later SARS-Cov-2 positive myocarditis. A series of MRI performed within 71 days on average after the confirmation of COVID-19 was published, but revealed changes were

not directly compared with the clinic picture; the diagnosis of myocarditis was confirmed by EMB only in three patients with the most pronounced changes in MRI [22]. Clinical features of this form of myocarditis (remoteness, viral genome?) are also unknown.

We have obtained the first data showing subacute and chronic post-COVID myocarditis. As with other forms of post-virus myocarditis, its main criteria are in clear relationship between the development of pronounced progression of cardiac symptoms with a history of COVID-19, their onset after a certain latency period after fever, and respiratory manifestations of the disease (from 3–4 weeks to 2–4 months). However, there is no clear correlation with the severity of COVID-19 (mainly mild pneumonia, stage CT-1, in our trial) and the possible development of the signs of heart disease during the second wave of fever (autoimmune phase of the disease?), persistent elevation of general inflammatory markers (leukocytes, ESR, CRP, fibrinogen), various immune parameters in the blood (rheumatoid factor, ANA, etc.) in patients with severe myocarditis, a pronounced increase in blood titers of ACA (including specific ANA), MRI findings typical of myocarditis (relatively rare edema), or symptom persistence for several months.

We identified two main clinical forms of post-COVID myocarditis: arrhythmic myocarditis and decompensated myocarditis. We did not observe the transformation of one form into another in the examined patients, suggesting the stability of myocarditis manifestations in each case. Due to its lesser severity, arrhythmic myocarditis was verified only by MRI; thus, we cannot talk about the rate of virus persistence in the myocardium and morphological forms of myocarditis. As in our previous trials, it can be assumed that it is a high incidence of viral persistence in conjunction with keratinocyte death that determines a more severe course of the disease [23]. There were no differences in terms of myocarditis manifestations or ACA levels, but higher levels of CRP were associated with a more severe course of the disease.

The high incidence of lesions in the early stages of the disease is a peculiar clinical feature of decompensated post-COVID myocarditis. Specifically, biventricular CHF was diagnosed in 7 of 9 patients. No conclusive data for chronic or acute pulmonary embolism were obtained in either case, but a single autopsy study detected clots in small branches of the pulmonary artery. Despite a moderate degree of pulmonary hypertension, we cannot exclude a similar mechanism of RV overload and other patients as a consequence of a hypercoagulable within COVID-19 and as a result of embolism of the right heart. It can also be assumed that the degree of damage of different parts of the myocardium is determined by the uneven distribution of receptors to angiotensin-converting enzyme 2, which acts as an intermediary for the penetration of the virus into a cardiomyocyte [19]. The analysis of the three autopsy cases of acute COVID-associated myocarditis revealed RV lesions in all patients; this was severe in one of them [18]. Physicians report preferential RV dilation in severe acute myocarditis in the absence of pulmonary hypertension [24].

Another feature of severe post-COVID myocarditis is the absence of severe LV dilatation (in our study, every third patient did not have it) combined with a pronounced violation of systolic and diastolic functions, including the restrictive type. This may be due to the rapid onset of myocarditis and severe interstitial edema (detected in 100% of biopsies). The essential mechanism of myocardial damage is ischemia due to microvessel thrombosis detected in every third case (according to other sources, up to 80% [25]). The clinical picture also includes various arrhythmias and conduction disorders (including a very uncommon syndrome of atrial standstill in a patient with GCM, atrioventricular block). No particular MRI pattern has been identified so far, but it can be expected with more observations.

The four cases of severe post-COVID myocarditis diagnosed in patients with a cardiac history should also be mentioned. One patient had primary cardiomyopathy verified as likely to be arrhythmogenic RV cardiomyopathy combined with heterozygous hemochromatosis (and local involvement of the heart). In this case, there was no reason to suspect myocarditis prior to COVID-19. Although patients had early symptoms of myocarditis before COVID-19, the diagnosis was not delivered in a timely manner and IST was not performed; rather it was coronavirus disease that led to severe decompensation and justified EMB, which confirmed myocarditis and the persistence of SARS-Cov-2. Thus, it is shown that SARS-Cov-2 can infect previously damaged myocardium and contribute to the progression of prior myocarditis. These cases were particularly clinically severe (arrhythmias and CHF).

SARS-CoV-2 RNA was detected in the myocardium in 5 of 6 patients with decompensated myocarditis who underwent EMB. The longest period after acute COVID-19 was 9 months, during which all signs of myocarditis were activity retained and response to standard cardiotropic therapy was poor. IHC using anti-nucleocapsid antigen antibodies and anti-Spike antigen antibodies showed their presence in the endothelium and cardiomyocytes and macrophages. These data

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БЕРЛИН-ХЕМИ
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indicate that long-term persistence of the coronavirus in the myocardium (directly in cardiomyocytes) is one of the major mechanisms that maintain active myocarditis with the development of necrosis, edema, and clinical decompensation. Recent publications on the use of IHC confirmed the possibility of direct damage of cardiomyocytes [17, 26].

However, the fact that full-scale SARS-Cov-2 was not detected among all patients with CHF indicates the possibility of virus-negative post-COVID myocarditis and other mechanisms for its development and persistence. These primarily consist in the production of ACAs, which were found during acute COVID-19 in 73.5% of patients hospitalized with coronavirus-related pneumonia. While ACA levels correlated with the signs of heart disease (AF, pericardial effusion), patients without pronounced cardiac symptoms also had an increase in ACA titers, which could lead to later development of myocarditis [27]. At the same time, ACA levels correlated with the total immune-mediated inflammatory activity of the disease, pneumonia severity, and prognosis: an autoimmune reaction to cardiac antigens was consistent with a generalized autoimmune (cytokine) storm. Several cases of the induction of systemic autoimmune diseases after COVID-19 [28] have been described; we also observed a case of aortitis (high ANA levels) among our patients with post-COVID myocarditis, which requires continuing fol low up.

The high ACA titers detected in 93.3% of patients in this study should be simultaneously considered as a basic pathogenetic mechanism and clinical markers of post-COVID myocarditis irrespective of its severity. A strong correlation established between the number of CD3-positive and CD45-positive lymphocytes in myocardial biopsies and CRP levels (between macrophages and ESR), which reflects the relationship of severe post-COVID myocarditis with the degree of systemic inflammation, should also be considered when making a diagnosis. Thus, the clinical and morphological data allow virus-positive and virus-negative forms of post-COVID myocarditis to be identified with autoimmune mechanisms having an essential role in maintaining inflammation in both these forms. The same obviously applies to the cases of post-COVID endocarditis.

Individual cases of endocarditis, which developed during or after COVID-19, are described in the literature. For example, a young patient with a bicuspid aortic valve developed symptoms of IE of the aortic valve against coronavirus-related pneumonia, combined with the ECG signs of ischemia and atrioventricular block; however, unlike our patient, he did not have reduced LVEF and EMB was not carried out [29]. Another case concerns IE of prosthetic mitral valve [30] and aortic valve [31] developed in acute COVID-19. The growth of Staphylococcus aureus in blood culture was observed in both cases. The predisposing IE mechanisms comprise the ability of SARS-Cov-2 to induce functional depletion of CD4 and CD8 T-lymphocytes [31] and activate procoagulant cascade [32].

In general, no increase in IE rates have yet been reported during the COVID-19 pandemic [33]. However, IE diagnosis is delayed in this setting because of the need to differentiate it from COVID-19 and the corresponding difficulties of hospitalization [34]. It is even more difficult to verify NBTE in COVID-19. In fact, this is only possible with EMB and autopsy: such cases have been described.

For example, EMB did not reveal active myocarditis but showed neutrophil infiltration in the endocardium in a patient with suspected myocarditis (increased levels of troponin, ST-segment depression) [35]. In our opinion, despite the absence of vegetations on the valves, dysfunction, or negative blood cultures, it is still impossible to rule out a bacterial origin of endocarditis. A case of mitral valve IE with embolism in the brain is equally ambiguous [34]. A case of postmortem diagnosis marantic (nonbacterial) endocarditis against COVID-19 has been described [36].

We observed two cases of thrombotic endocarditis, whose nonbacterial nature was verified only by the lymphocytic composition of infiltrates in the myocardium. In both cases, the diagnosis of endocarditis was delivered using EMB and combined with severe SARS-Cov-2 positive myocarditis, which suggests a direct role of the virus in the induction of endocarditis. Its characteristic feature was the formation of RV mural thrombi, which had not been detected clinically; here, tricuspid insufficiency was relative, since there were no apparent signs of valve damage. We believe that such thrombotic endocarditis is specific to SARS-Cov-2 infection and may predispose to IE. However, it is not yet clear whether it can develop independently of myocarditis.

Finally, the patient presenting with a combination of IE of the bicuspid aortic valve and severe SARS-CoV-2 positive lymphocytic myocarditis is of key interest. This combination, which has not been previously described, is directly related to the pathogenesis of COVID-19 and presents the greatests challenges in terms of diagnosis and treatment. Given the negative cultures (including myocardial biopsies) and the absence of signs of endocarditis at EMB, we

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cannot completely exclude the possibility that the valve lesion has a viral cause, although splenomegaly and a sharp increase in the level of procalcitonin in conjunction with the effect of antibiotics argue for IE. Although it is well known that the «classic» form of IE can be associated with myocarditis (both immune-mediated and bacterial), severe myocarditis with a sharp drop in LVEF is rare in practice. There are only few descriptions of such cases [37]. Here, corticosteroids should be avoided and other approaches used in their stead (plasmapheresis, intravenous immunoglobulin) [38]. However, steroids have been successfully administered in combination with antibiotics in patients with IE against coronavirus-associated pneumonia [30].

Corticosteroids (short courses of dexamethasone, hydrocortisone, methylprednisolone in moderate doses) comprise the only group of drugs with a proven positive influence on prognosis (significant reduction in mortality) in patients with severe coronavirus-associated pneumonia [39, 40].

Although their efficacy has not been evaluated in patients with myocarditis or even endocarditis, they have been successfully used in combination therapy [41]. Therefore, the case of successful administration of IST (steroids and cytostatic) for two months in the patient with retrospectively diagnosed COVID-19 is of the most significant interest; initially, the myocardium was not tested for SARS-Cov-2 in February 2020 and the myocarditis was regarded as virus-negative [42]. Detection of RNA in the biopsies was the reason for the urgent cancellation of IST, which can hardly be justified: it is no less reasonable to discuss the feasibility of using anticoagulants in patients with myocarditis, myocardial microvascular thrombosis, and even thrombotic endocarditis.

Thus, it can be stated that the COVID-19 pandemic has created a new reality on top of the understudied area of inflammatory diseases of the myocardium. The present study shows that this applies not only, and not primarily, to chronic myocarditis, but also to chronic myocarditis, which is considered as dilated cardiomyopathy (DCM) in most cases in everyday clinical practice. We have already emphasized more than once that this is a syndromic, umbrella diagnosis: typically only EMB allows the true nature of the disease to be recognized.

The structure of patients with DCM syndrome will undoubtedly change from 2020 onwards to include a significant pool of patients with chronic post-COVID myocarditis, including virus-positive myocarditis. In the first publications on this issue, SARS-Cov-2 positive myocarditis was detected in 5 of 104 patients with DCM [4]. However, the true incidence and approaches to the treatment of such myocarditis are yet to be determined.

Conclusions

1. Infection with SARS-Cov-2 leads to the development of acute and sub-acute / chronic myocarditis, whose clinical manifestations develop from 1 to 4–6 months following acute COVID-19. Post-COVID myocarditis manifests in two main clinical forms – isolated arrhythmic myocarditis and decompensated myocarditis (systolic dysfunction with or without chamber dilation).
2. The main mechanisms post-COVID myocarditis are prolonged persistence of SARS-Cov-2 in the myocardium (cardiac myocytes, endothelium, macrophages) in some patients (83.3% in this study, the maximum time to identify SARS-Cov-2 after COVID-19 is 9 months) combined with high immune activity (high titers of anticardiac antibodies in 93.3% of patients).
3. The features of post-COVID myocarditis include natural RV (preferably the biventricular nature of heart failure), the possibility of severe systolic and diastolic LV dysfunction without its dilation, persistent elevation of acute phase indicators and immune-mediated inflammatory markers in some patients, as well as high-frequency coronaritis with ischemia and combinations with pericarditis and endocarditis. SARS-Cov-2 attaches to prior myocardial diseases (both of a genetic and inflammatory nature) and substantially aggravate their course.
4. Any unclear myocardial dysfunction requires a serological diagnosis of the novel coronavirus disease in the pandemic setting.
5. Infection with SARS-Cov-2 can induce chronic nonbacterial lymphocytic thrombotic endocarditis and infective endocarditis (the latter can develop against the former). The persistence of the virus in the myocardium and autoimmune mechanisms play a significant role in both cases; the combination with lymphocytic myocarditis is typical.
6. The use of corticosteroids and anticoagulants should be considered for treating post-COVID myoendocarditis.

No conflict of interest is reported.

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