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Case Report | Internal Medicine

A Case of Long COVID-19 Myocarditis with Asymptomatic Manifestation in a Young Male

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Abstract

Background. Myocarditis is one of the most dangerous complications of both the acute phase of COVID-19 and long COVID-19, with a rather heterogeneous clinical presentation that ranges from asymptomatic to life-threatening. The diverse clinical presentation with a high risk of further complications, on the one hand, and a good prognosis in case of appropriate treatment, on the other hand, demand great attention from doctors.

Case Report. We report a case of a 27-year-old male presented to a cardiologist with complaints of dyspnea, chest pain, palpitation occurred eight months after a mild COVID-19 episode. The diagnostic search commenced with a detailed questioning and physical examination with further laboratory testing and instrumental procedures, including resting electrocardiography, resting two-dimensional speckle-tracking echocardiography, and stress echocardiography. Gadolinium-enhanced cardiac magnetic resonance was the final step in diagnosis establishment. Half-a-year follow-up period of the patient with asymptomatic manifestation of COVID-19 myocarditis demonstrated the normalization of the condition after prescribed pathogenetic treatment.

Conclusions. This case report raises awareness of the need for prolonged follow-up of patients after an episode of COVID-19 and proposes a comprehensive approach to a possible differential diagnostic search for precise diagnosis and treatment in a young male with rationale based on the relevant literature.

Keywords

Case Report; Myocarditis; Long COVID-19; Cardiovascular Magnetic Resonance; Speckle-Tracking Echocardiography; Stress Echocardiography; Combination Therapy

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has provoked an evolving world health crisis with more than 753 million confirmed cases of coronavirus disease (COVID-19) [1]. It is associated with a significant disease severity due to multiple organ involvement [2], causing more than 6.8 million deaths [1].

SARS-CoV-2 affects the respiratory system as well as other structures of the human organism [2], including kidneys [3] and cardiovascular system [4], for instance, myocarditis manifestation [5] leads to systemic immune dysregulation [6] and endothelialitis [7]. The control of the pandemic has been increasing due to transmission reduction strategies, natural immunity, and the global vaccination program [8]. However, long COVID is another growing health concern with a rather heterogeneous clinical presentation [9] and myocarditis as one of the consequences [10].

In a young patient with a long interval between the COVID-19 episode and cardiovascular manifestations, the diagnostic search for the cause of complaints may be challenging and require a thorough examination strategy.

The current clinical report presents a case of myocarditis diagnosed in a young, fully COVID-19 vaccinated male eight months after the COVID-19 episode. The peculiarity of this case is an asymptomatic course of the acute phase of diffuse myocarditis mimicking acute respiratory viral infection of mild severity.

Case Report

Patient Information

A 27-year-old male patient D., an IT specialist, visited the cardiologist with complaints of episodic stabbing pain behind the sternum and in the region of the heart with irra-

diation to the fingers of both hands, which was accompanied by palpitation (according to the patient, his heart rate (HR) was under 130 bpm). The attack was accompanied by a feeling of anxiety and an increase in blood pressure (BP) up to 160/90 mmHg and occurred 10 minutes after physical exertion (workout exercises on the horizontal bar); additionally, he experienced psychoemotional stress before training. The patient visited the cardiologist immediately the next day as he had never had such complaints before.

History of Present Illness

According to the patient's medical history, it was the first episode in his life.

Personal History

No health disorders, traumas, surgeries, allergic reactions, harmful habits as well as taking any medicines were registered. Ten months before the patient was vaccinated with the mRNA COVID-19 vaccine (COMIRNATY®, BioNTech Manufacturing GmbH): two doses at an interval of 21 days. The vaccination was tolerated satisfactorily. Two months after the second dose of the vaccine the patient suffered a mild form of COVID-19, which was clinically manifested as a 3-day subfebrile temperature and general weakness. Since then, no other episodes of health disorders were noticed util the current one.

Clinical Findings

Objectively: the patient's general condition was satisfactory. He was asthenic, with body mass index of 23.9 kg/m^2. The skin and visible mucous membranes were clean. The borders of the heart were slightly shifted to the left and were along the left midclavicular line. On auscultation, heart sounds were muffled, regular; no murmur was present. The pulse rate - 78 bpm, rhythmic, with satisfactory properties; BP - 130/80 mmHg. Physical examination of the lungs and abdominal cavity revealed no pathological changes, no peripheral edema.

Diagnostic Assessment

On the electrocardiogram (ECG) (Fig. 1), normal sinus rhythm was registered, with the HR of 96 bpm; there were no other pathological findings.

According to the results of 5-day Holter monitoring, the mean HR was 63 bpm, the minimal heart rate (HR min) was 37 bpm (at night 02:44:08), the maximum heart rate (HR max) was 141 bpm (at 08:46:22). Thirty-one hours fifty-four minutes of sinus bradycardia, predominantly at night, and three hours forty-four minutes of sinus tachycardia, predominantly at daytime, were registered; no pauses. There were 347 supraventricular premature complexes (< 0.1% out of total), particularly 65 single atrial premature complexes, 5 episodes of paired supraventricular extrasystoles, 4 triplets, 30 episodes of ectopic supraventricular rhythm (at night). Ventricular ectopic activity included 6 single complexes. Heart conduction disorders included 210 complexes (predominantly at daytime). An episode of second-degree sinoatrial block (SA block) type 1 was registered. Intraventricular conduction

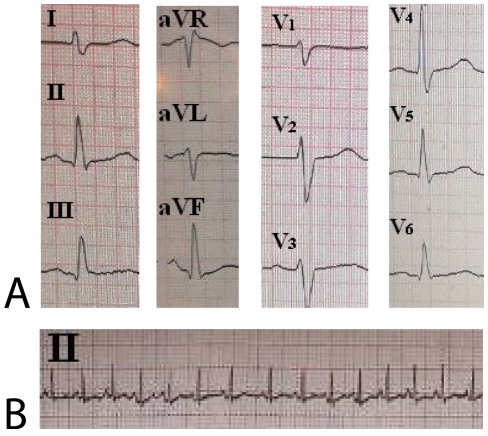

Figure 1. Resting ECG of the patient: A – 12 leads, B – rhythmogram (10 mm/mV, 50 mm/s).

disorders comprised 22, 229 complexes (5.18% out of total complexes). The mean PQ-interval was 145 ms (the maximum PQ interval (PQ max) at HR max was 123 ms, the minimal PQ interval (PQ min) at HR min was 171 ms). The mean QTc interval was 419 ms (the minimal QTc interval (QTc min) at HR min was 394 ms). No changes in ST-segment and T-wave were registered.

The patient underwent resting echocardiography (EchoCG) (Table 1), which revealed a slight dilatation of the left ventricle (LV) and a zone of pronounced hypoki-

Table 1. Resting echocardiography of the patient.

Parameter	Result	Ref. Range
Aortic diameter, mm	31	20-37
Aortic valve opening, mm	22	17-25
Left atrial diameter, mm	37.1	20-40
Interventricular septum thickness at end-diastole, mm	8.6	6-11
Left ventricular posterior wall thickness at end-diastole, mm	8.3	6-11
Anterior wall of the right ventricle, mm	3.4	<5
Right ventricular dimension at end-diastole, mm	28.7	9-30
Right atrial diameter, mm	35.8	20-40
Ejection fraction, %	67	>55
End-diastolic volume, mL	164.9*	51-160
End-systolic volume, mL	67.5	14-70
Stroke volume, mL	100.4*	30-100
E/A	1.4*	1.5-1.6
Deceleration time of early diastolic transmitral flow, ms	150*	160-220
Isovolumic relaxation time, ms	96	60-100
Peak diastolic velocity, cm/s	64.1	62-80
Pulmonary artery systolic pressure	21.5	<30
Inferior vena cava, mm	17.8	
Mitral valve	Regurgitation 0/+	
Aortic valve	Normal	
Tricuspid valve	Regurgitation 0/+	
Pulmonary valve	Regurgitation +	

Notes: * - out of reference ranges, E – peak velocity of early diastolic transmitral flow (m/s), A – peak velocity of late transmitral flow (m/s).

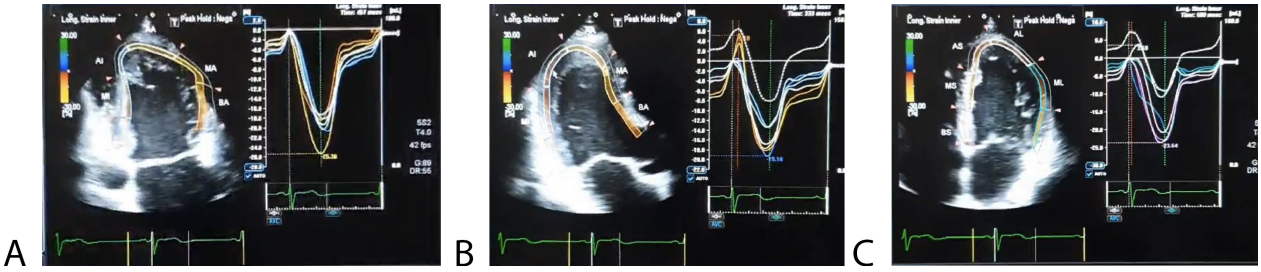

Figure 2. 2D speckle-tracking EchoCG: A – 2-chamber view: B – 3-chamber view; C – 4-chamber view.

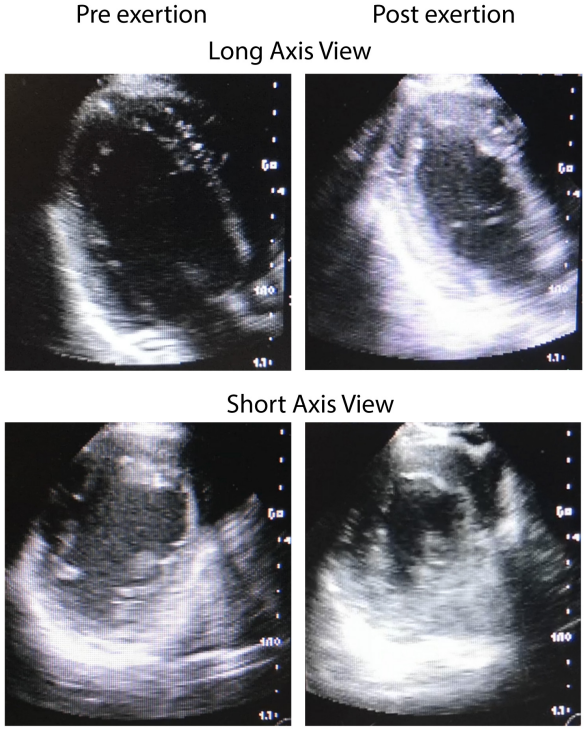

Figure 3. Stress EchoCG of the patient.

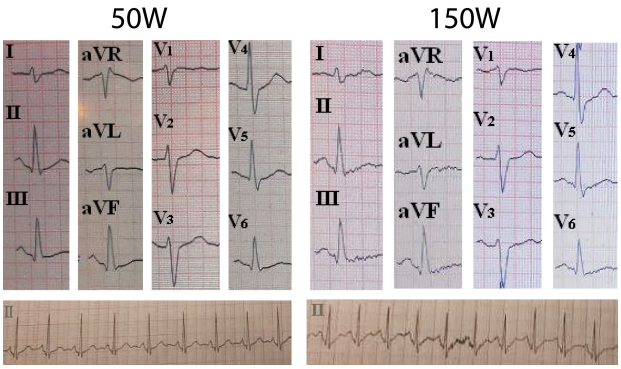

Figure 4. Stress ECG of the patient: upper – 12 leads, lower – rhythmogram (10 mm/mV, 50 mm/s).

nesis in the apical-anterior and apical-lateral segments of the LV with normal ejection fraction (EF) (67%), spontaneous echo contrast in the LV apex.

Two-dimensional (2D) speckle-tracking EchoCG (Toshiba Artida) showed a significantly reduced global longitudinal strain (GLS) and local deformation of the myocardium in the apical-lateral and medial-lateral segments from the 4-chamber view, and in the apical-lateral and medial-posterior segments from the 3-chamber view (Fig. 2).

Myocardial cardiosclerosis was established as a preliminary diagnosis. Depending on the etiology, such diagnoses as anterior descending artery myocardial bridging, stunned myocardium or acute myocarditis were in question.

The results of laboratory assessments are aggregated in Table 2.

Complete blood count revealed erythrocytosis with low RDW but normal hemoglobin level, relative lymphocytosis, neutropenia, and monocytosis. Dyslipidemia (increased levels of serum total cholesterol, low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C) and decreased serum levels of high-density lipoprotein cholesterol (HDL-C), normal thyroid gland function, 25-hydroxy vitamin D insufficiency (25-OH D) were noticed. The glomerular filtration rate was 81/min/1.73 m^2 (estimated by the 2021 CKD-EPI equation). In addition, the quantity of receptor-binding domain of S1 S-protein SARS-CoV-2 and SARS-CoV-2 IgG increased significantly.

Renal ultrasound, adrenal gland ultrasound, and abdominal duplex ultrasound (abdominal aorta, renal arteries) (Vinno G86) registered no pathological changes.

To make a differential diagnosis between myocardial bridge, atherosclerotic plaque, and cardiosclerosis after myocarditis, a stress EchoCG was performed (Schiller 500 recumbent bicycle ergometer). The protocol of stress EchoCG is presented in Table 3 (target workload - 196 W, target HR - 183 bpm). Echocardiogram was recorded after each stage. The test was stopped due to shortness of breath and general weakness.

Hypokinesis in the apical-anterior and apical-lateral segments of the LV from the 3-chamber, 4-chamber, and 2-chamber views at the initial stage changed to normokinesis during low-level physical activity that remained even at high-grade workload (Fig. 3, Table 3).

No ischemic exercise-induced changes were registered on the ECG (Fig. 4) and EchoCG (Fig. 3).

The results of stress EchoCG were more likely to indicate a diagnosis of cardiosclerosis after myocarditis. Consequently, gadolinium-enhanced cardiovascular magnetic resonance (CMR) unlike cardiac computed tomography was the preferable method of choice to confirm the cause of myocardial cardiosclerosis.

CMR revealed LV expansion (LV end-diastolic size=62

Table 2. Laboratory findings of the patient.

Parameter	Result	Ref. Range	Parameter	Result	Ref. Range
Complete blood count			**Biochemistry**		
White blood cells, $x10^9$/l	4.79	4.0-9.0	γ-glutamiltranspeptidase, U/l	13	8.0-61.0
Red blood cells, $x10^{12}$/l	5.06*	4.0-5.0	Alkaline phosphatase, U/l	80	40.0-129.0
Hemoglobin, g/l	152	130.0-160.0	Total bilirubin, mcmol/l	17.1	<21.0
Hematocrit, %	44.2	35.0-54.0	Direct bilirubin, mcmol/l	4.8	<5.0
Mean corpuscular volume, fl	87.5	76.0-96.0	Indirect bilirubin, mcmol/l	12.3	75% of TBil
Mean corpuscular hemoglobin, pg	30.1	28.0-32.0	Creatinine, mcmol/l	111*	62.0-106.0
Mean corpuscular hemoglobin concentration, g/dl	34.4	32.0-36.0	Urea, mcmol/l	5.5	2.76-8.07
Platelets, $x10^9$/l	186	180.0-360.0	Uric acid, mcmol/l	426	202.3-416.5
Red cell distribution width (RDW-SD)	37.9	35.0-46.0	Total protein, g/l	77.5	66.0-87.0
Red cell distribution width (RDW-CV)	11.6*	12.0-15.0	Albumin, %	66.19	53.0-63.0
Platelet distribution width, fl	17.9	10.0-18.0	Globulin, %	33.81	37.0-47.0
Mean platelet volume, fl	12.6	6.0-13.0	Albumin/globulin ratio	1.96	1.0-2.0
Plateletcrit, %	0.23	0.1-0.5	C-reactive protein, mg/l	<0.6	<5.0
Erythrocyte sedimentation rate, mm/h	2	<15	**Lipid profile**		
Blood differential test			Cholesterol, mmol/l	5.51*	<5.2
Neutrophils, $x10^9$/l	1.87	1.78-5.38	Triglycerides, mmol/l	0.91	<2.26
Neutrophils, %	39.1*	47.0-72.0	High-density lipoproteins, mmol/l	1.16*	>1.45[#]
Lymphocytes, $x10^9$/l	2.08	1.32-3.57	Low-density lipoproteins, mmol/l	4.04*	<2.59[##]
Lymphocytes, %	43.4*	19.0-37.0	Very low-density lipoproteins, mmol/l	0.31*	0.26-1.00
Monocytes, $x10^9$/l	0.74	0.30-0.82	Troponin I, ng/ml	<0.01	<0.16
Monocytes, %	15.4*	3.0-10.0	NT-proBNP, pg/ml	10.55	<90.8
Eosinophils, $x10^9$/l	0.06	0.04-0.54	D-dimer, mcg	<0.15	<0.5
Eosinophils, %	1.3	0.5-5.0	Serum glucose, mmol/l	5.2	4.11-5.89
Basophils, $x10^9$/l	0.02	0-0.02	Glycosylated hemoglobin, %	5.45	4.8-5.9
Basophils, %	0.6	0.0-1.0	25-hydroxyvitamin D (25-OH D), ng/ml	25	>30(normal)
Immature granulocytes, $x10^9$/l	0.01	<0.06	Thyrotropic hormone	2.56	0.27-4.2
Immature granulocytes, %	0.2	<0.09	Thyroxine	1.23	0.93-1.7
Biochemistry			SARS-CoV-2 IgG, BAU/mL	1059.6*	>7.1[###]
Alanine aminotransferase, U/l	14	<41.0	Receptor-binding domain of S1 S-protein SARS-CoV-2, AU/mL	7461.9*	>50.0[###]
Aspartate aminotransferase, U/l	15	<40.0			

Notes: * – out of reference ranges; [#] – no risk for males; [##] – optimal level; [###] – positive.

Table 3. Protocol of stress echocardiography of the patient.

Stage	Workload, W	Time, min:s	HR, bpm	BP, mm Hg	ECG	EchoCG	Complaints
Initial (0)	0	3:00	81	120/70	N	Hypokinesis of the left ventricular apical-anterior and apical-lateral segments	None
1	50	3:00	87	130/70	N	Normokinesis	None
2	100	3:00	130	130/80	N	Normokinesis	None
3	150	2:47	145	180/95	N	Normokinesis	Dyspnea, weakness
Restitution	0	3:00	105	125/75	N	Normokinesis	None
Rest	0	5:00	67	120/70	N	Hypokinesis as initially	None

mm, EDI=55.7 ml/m^2) with normal EF=73%, no edema, necrosis, normal resting myocardial perfusion (Fig. 5). No early accumulation of the contrast was noted; however, a diffuse delay in contrast washout was recorded in the subepicardial/submesocardial sections of the LV with involvement of the interventricular septum. At the same time, no subendocardial changes were detected. No thrombi and changes in the pericardium were registered. The detected changes in the myocardium might be due to diffuse myocardial fibrosis of non-ischemic genesis, most likely the result of previous myocarditis (Lake Louise criterion 1). MR signs of the active inflammatory process were not detected.

Therapeutic Intervention

The patient was prescribed rosuvastatin 10 mg per day, dipyridamole 25 mg 3 times a day for a month, oral suspension of L-arginine hydrochloride 6 g three times daily

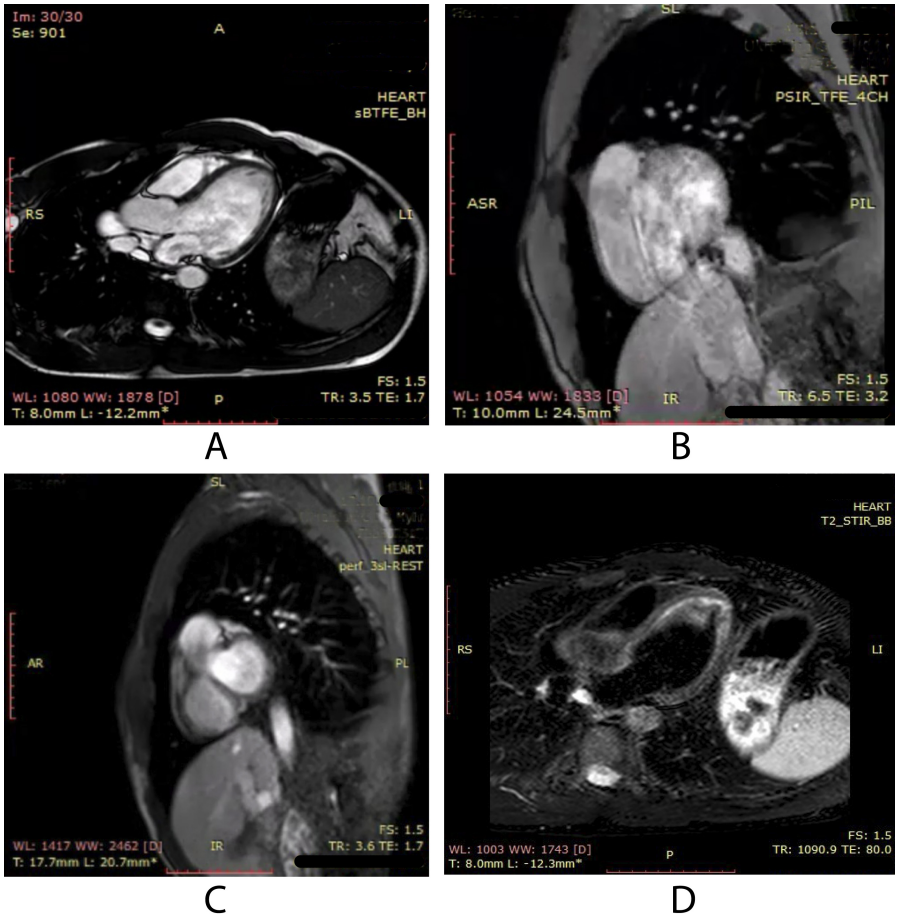

Figure 5. A – sBTFE_BH sequence, long axis; B – PSIR sequence; C – perfusion; D – T_2 STIR sequence; PSIR – phase-sensitive inversion recovery, STIR – short tau inversion recovery.

for 3 weeks, vitamin D3 4000 IU once daily, trimetazidine hydrochloride MR 35 mg twice a day for 2 months.

Follow-up and Outcomes

No complaints, including pain or any discomfort in the region of the heart, palpitation, dyspnea at rest or dyspnea on exertion, have been concerned the patient for 6 months after prescribed treatment.

Discussion

The presented clinical episode demonstrates the possibility of the differential diagnostic search for precise diagnosis in a young male with a primarily asymptomatic course of myocarditis, but cardiovascular manifestation 8 months after a mild COVID-19 episode.

The current report corresponds to the data of meta-regression analysis conducted by Voleti *et al.*, according to which men and younger populations are at higher risk of myocarditis after COVID-19 infection [11]. SARS-CoV-2 virus increases the risk of myocarditis from a baseline of 9 cases per 100,000 population to 150 cases per 100,000 population [12]. Scientific publications elucidate mostly acute myocarditis [4, 13], while data regarding long COVID-19 myocarditis cases are quite limited in the literature [14].

Establishing the diagnosis of COVID-19 myocarditis remains rather challenging due to nonspecific symptoms, lack of specific blood biomarkers [15], and high importance of cardiac imaging [16].

On the one hand, in the particular clinical case under discussion, the differential diagnosis was performed by laboratory analysis in the absence of inflammatory changes in blood tests, namely the normal level of C-reactive protein, erythrocyte sedimentation rate as well as troponin I, and D-dimer but the increased level of receptor-binding domain of S1 S-protein SARS-CoV-2 and SARS-CoV-2 IgG [17, 18]. On the other hand, a number of instrumental methods were aimed at establishing the diagnosis.

Thus, during the exercise test, the trend of converting hypokinesis toward normokinesis may be noticed both in patients with myocardial bridge and those with atherosclerotic plaque or cardiosclerosis after myocarditis. With a greater workload in myocardial bridge [19] or atherosclerotic plaque, it is projected to register further progression toward hypokinesis, unlike persistent normokinesis in cardiosclerosis after myocarditis. Another important diagnostic sign of atherosclerotic plaque or myocardial bridge is the absence of systolic thickening of the myocardium in the blood supply zone of the affected coronary artery [20], which was not registered in the current patient's test.

Gadolinium-enhanced CMR was the final step in the diagnostic search as it emerged to be the first-line diagnostic tool (ESC class 1, level C recommendation) [18], and myo-

cardial biopsy is not mandatory if its results would influence neither treatment nor prognosis of the patient [18, 21]. The absence of edema and hyperemia of the myocardium confirmed the absence of acute myocarditis, while the accumulation of the contrast in the subepicardial and intramural layers of the myocardium during the late gadolinium phase was the evidence of diffuse myocarditis episode leading to cardiosclerosis. In addition to this, dilation of the LV and signs of intramural fibrosis proved this. These findings correspond with CMR peculiarities in patients after COVID-19 myocarditis [22]. Moreover, both EchoCG and CMR draw attention to normal EF [23].

In addition, the value of speckle-tracking EchoCG should be highlighted, namely the determination of the longitudinal deformation of the myocardium [24]. Comparing regional longitudinal strain obtained with the help of EchoCG and CMR data showed an almost complete coincidence of segments with transmural fibrosis of the apical-lateral segment and partial coincidence with transmural fibrosis of the medial-lateral segment. Furthermore, speckle-tracking EchoCG showed a significant decrease in GLS in the 4-chamber and 3-chamber views, which is an early unfavorable sign of heart failure development [25]. However, pro-brain natriuretic peptide (pro-BNP) level and EF [23] were still normal.

We aimed to highlight the nonspecific clinical picture of myocarditis. For instance, dyspnea was reported by 25% (95% CI=20%-30%) of patients 6-9 months after a COVID-19 episode [26]; more specific cardiovascular symptoms such as chest pain (53%) and palpitation (68%) were reported by reconvalescents 7 months after a COVID-19 episode [10]. Moreover, clinical manifestations can be asymptomatic [22]. Francone *et al.* recognized three clinical patterns of myocarditis: infarct-like, cardiomyopathic, and arrhythmic [27]. Thus, stabbing pain behind the sternum and in the region of the heart, similar to angina attacks, is one of the signs of long COVID-19 myocarditis as well as arrhythmia [14]. As no signs of coronary artery stenosis were registered, the author team hypothesized that pain was associated with microcirculatory disorders after COVID-19 microvasculitis [28], which could manifest as endothelial dysfunction of arterioles and their spasm as well as a decrease in the number of functioning capillaries per unit area of the myocardium [29].

Microrheological disorders are worth mentioning as well. Decreased RDW with erythrocytosis can cause increased blood aggregability due to changes in the electrical potential of erythrocytes [30]. A phenomenon of local hemorheological changes or spontaneous echo contrast, which can be an indirect sign of increased blood aggregability [31], was registered in the LV apex in the 3-chamber view on the EchoCG.

Considering the above-discussed processes, the patient was prescribed pathogenetic therapy aimed at improving endothelial function and rheological properties of the blood as well as slowing down the sclerosing process.

We expected prescribing statins to affect multiple pathogenetic links. Dyslipidemia itself enhances endothelial dysfunction, systemic low-grade inflammation [32], prothrombotic phenotype [33], vascular stiffness [34], cellular senescence [35], and myocardial remodeling [36]. It should be noted that COVID-19 is associated with derangements of lipid profile [37]. The mechanisms of action of statins are associated with hypolipidemic as well as multiple pleiotropic effects [38]. Laffin *et al.* demonstrated the effectiveness of low-dose rosuvastatin in adults with no history of atherosclerotic cardiovascular disease in impacting lipid and inflammatory biomarkers [39]. The decision to prescribe statins in young adults should be well-balanced and patient-centered, with shared decision-making [40].

Dipyridamole, that acts as a statin synergist, was chosen as the main agent for normalizing hemorheological properties. Notably, it works as antianginal medicine, especially for the treatment of microvascular angina [41]

L-arginine hydrochloride improves endothelial dysfunction and eliminates pro-antioxidant imbalance [42], reduces platelet aggregation and normalizes fibrinogen levels, maintains the histological architecture of the myocardium [43] and positively influences LDL and total cholesterol levels [44].

The relationship between the level of vitamin D and post-COVID-19 symptoms has not revealed clearly yet [45]. Nevertheless, its deficiency may aggravate the course of conditions that manifest both during and after a COVID-19 episode [46]. Multiple effects of vitamin D supplementation in long COVID-19 that may be beneficial in the current clinical case have been revealed, namely normalization of neutrophil count and generally blood, increase in exercise tolerance, diminished fatigue, and immune normalization [47].

Last but not least, we added trimetazidine hydrochloride, an inhibitor of free fatty acid oxidation that shifts cardiac and muscle metabolism to glucose utilization, to the treatment of this patient. It may improve the condition of a patient with long COVID-19 myocarditis via enhancement of glucose oxidation by cardiomyocytes and prevention of intracellular reduction in adenosine triphosphate. Trimetazidine modulates cardiac fibroblast activity (antifibrotic effect) and Akt/caspase-3 signaling pathway, consequently leading to a reduction in ischemic-reperfusion injury [48].

Conclusions

Patients who were previously infected with COVID-19, regardless of the clinical course severity, vaccination history, or patient's age, need further follow-up. Physicians should be aware of such COVID-19 consequences as myocarditis. Even after the asymptomatic clinical presentation, it may manifest itself with symptoms affecting the quality of life, with the risk of further impairment of the patient's condition, particularly due to the risk of heart failure progression, and microvascular or hemorheological disorders. However, after a precise diagnostic process and thoughtful management of long COVID-19 myocarditis, a positive prognosis with a high recovery rate is observed.

Ethical Statement & Informed Consent

The research was conducted according to the WMA Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects". The patient gave written consent to participate in the current observation after the explanation of the purpose and allowed to publish the results of the latter with depersonalized data.

Acknowledgements

The authors are thankful to the patient for permission to share this case with world scientific society.

Data Availability

The data of this clinical episode, including de-identified data such as photos of analysis, electrocardiograms at rest and physical exertion, and videos of stress echocardiography, are available from the corresponding author upon reasonable request. Cardiovascular magnetic resonance data cannot be provided due to identification concerns.

Conflict of Interest

The authors declare that no conflicts exist.

Financial Disclosure

The authors declared no financial support.

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