DELAYED MANIFESTATION OF POST-COVID MYOCARDITIS

IVA POPOV[1,2], MILA KOVAČEVIĆ[1,2], BRANISLAV CRNOMARKOVIĆ[1,2], MILENKO ČANKOVIĆ[1,2], MILANA JARAKOVIĆ[1,2], STEVAN KEČA[2], SONJA DIMIĆ[2], SRĐAN MALETIN[1,2], MILENA SPIROVSKI[1,3], MAJA STEFANOVIĆ[1,2], MILOVAN PETROVIĆ[1,2], ALEKSANDRA MILOVANČEVA[1,2]

[1]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia; [2] Institute of Cardiovascular Diseases of Vojvodina, Cardiology Clinic, Sremska Kamenica, Serbia; [3] Oncology Institute of Vojvodina, Sremska Kamenica, Serbia

Introduction: Myocardial involvement of coronavirus disease 2019 (COVID-19) varies and is considered to be more serious in patients with severe COVID-19 clinical presentation. Although myocarditis is usually recognized in the setting of acute SARS-CoV-2 infection, delayed manifestations are recognized as well. *Case report.* A 51-year-old male patient was admitted due to the clinical signs of congestive heart failure, two months after moderate clinical expression of COVID-19 pneumonia, treated as an outpatient. Transthoracic echocardiography (TTE) revealed dilated cardiomyopathy with the presence of diffuse left ventricular (LV) hypokinesia, severely reduced ejection fraction (EF 18%) and diastolic dysfunction with increased left atrial filling pressure. Baseline laboratory tests revealed elevated hs-troponin I, NT-proBN. Diagnostic workout excluded coronary artery disease. Cardiac magnetic resonance imaging strongly pointed in the direction of unrecognized post-COVID myocarditis. The patient was treated according to current guidelines for heart failure with reduced EF. Eight months after discharge, the patient had no limitations of physical activity and TTE showed significant improvement in the systolic function of the left ventricle, EF was 47%, with normal LV filling pressure. *Conclusion:* Myocarditis is not an infrequent manifestation of COVID-19 infection, especially in hospitalized patients with severe clinical presentation, and commonly manifests within the first week after initial symptoms. Our case report represents an example that also patients with mild form of COVID-19 treated as outpatients can have delayed onset of heart failure as a consequence of COVID-19-induced myocarditis. Therefore, COVID-19 patients deserve a comprehensive approach with systematic clinical and echocardiographic follow-up in order to establish a timely diagnosis, provide appropriate treatment, and prevent serious complications.

Key words: COVID-19, myocarditis, dilated cardiomyopathy, magnetic resonance imaging

Address for correspondence: Mila Kovačević, MD, PhD
University of Novi Sad, Faculty of Medicine
Institute of Cardiovascular Diseases of Vojvodina
Novi Sad, Serbia
Tel. +381601594444
E-mail: mila.kovacevic@mf.uns.ac.rs

INTRODUCTION

Myocarditis is an inflammation of the myocardium which usually follows a microbial infection, although it can be caused by various pathogens (1). It is a common cause of death in young subjects, as well as a relatively frequent underlying cause of dilated cardiomyopathy (1). It is estimated that around 20% of patients with myocarditis develop chronic dilated cardiomyopathy (2). Myocarditis is most commonly caused by a viral infection and until now, the most frequently detected pathogens are adenoviruses, enteroviruses (coxsackievirus A and B), parvovirus B19, hepatitis C virus, human immunodeficiency virus, human herpesvirus 6, influenza A and B viruses, and lately viruses from Coronaviridae family, particularly severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2 (3-5).

Until now, the COVID-19 pandemic has caused loss of over 5 million lives around the globe (6). The disease might be asymptomatic, but the usual symptoms include fever, cough, nasal congestion, fatigue, and other signs of upper respiratory tract infections (6). The infection can progress to severe disease corresponding to pneumonia in more than 50% of patients (6). De-

spite the fact that respiratory symptoms predominate, COVID-19 infection shows a significant cardiovascular component (6).

Various studies that used cardiac magnetic resonance imaging (MRI) have shown variable cardiac involvement among COVID-19 patients (7). Most of them find the prevalence of myocardial injury underestimated. It is, however, considered higher in patients with severe COVID-19 clinical presentation (8). According to a recent meta-analysis of intensive care unit (ICU) hospitalized patients, heart failure as a complication of COVID-19 infection was identified in nearly 50% of patients who died and merely 3% of patients who recovered (9).

We report a case of a previously healthy male patient who presented with dilated cardiomyopathy with heart failure symptoms as a sequel of unrecognized delayed onset of SARS-CoV-2 myocarditis.

CASE REPORT

A 51-year-old, previously healthy male patient was admitted to ICU at the end of January 2021 due to the clinical signs of congestive heart failure. The symptoms began two weeks prior to admission with progressively worsened shortness of breath, fatigue and swelling of lower legs, ankle joints and feet. The patient denied having fever, chest pain or fainting.

In November 2020, he suffered COVID-19 caused pneumonia and he was treated as an outpatient. The patient reported having palpitations and occasional oppressions in the chest area during the acute phase of infection, but those symptoms had gradually declined and finally disappeared. The clinical expression was moderate and he was considered fully recovered.

At admission to ICU, physical examination revealed that the patient was hypertensive (blood pressure 140/100 mm Hg), tachycardic (heart rate 120/min), tachypneic (respiratory rate 30/min), without heart murmurs, but with late inspiratory crackles in the lower third of the chest, and with swollen ankles, New York Heart Association Class III (NYHA III).

Arterial blood gas analysis showed slight hypoxemia with SaO_2 95%, pO_2 68 mm Hg, pCO_2 38 mm Hg, pH 7.48, lactate 1.2 mmol/L, HCO_3^- 28.3 mmol/L, BE 4.6 mmol/L. A 12-lead electrocardiogram (ECG) revealed sinus tachycardia of 130 bpm without ST-segment changes (Figure 1).

Table 1. *Laboratory findings on admission*

Laboratory finding	Result	Reference range
Hemoglobin (g/L)	146	120.0-170.0
Leukocytes (x10^9/L)	7.9	4.0-10.0
Platelets (x10^9/L)	263	150-400
International normalized ratio (INR)	1.23	1.2
Urea (mmol/L)	9	2.5-7.5
Creatinine (μmol/L)	124	50.0-120.0
Uric acid (μmol/L)	538	150.0-420.0
AST (U/L)	96	10.0-37.0
ALT (U/L)	221	10.0-40.0
GGT (U/L)	199	2.0-55.0
Total proteins (g/L)	54	64-83
Albumin (g/L)	30	34-50
CRP (mg/L)	6	0.0-5.0
hsTroponin I (ng/L)	21.4	00-34.2
NT-proBNP (pg/mL)	4831	0.0-125.0
D dimer (ng/mL)	728	0.0-500.0

AST = aspartate aminotransferase; ALT = alanine transaminase; GGT = gamma-glutamyl transferase; CRP = C-reactive protein

Baseline laboratory tests showed elevated high-sensitivity troponin I (hs-troponin I, 21.4 ng/L), NT-proBNP (4831 pg/mL) and D-dimer (728 ng/mL). The real-time polymerase chain reaction (RT-PCR) for SARS-CoV-2 was negative. Baseline laboratory analysis are shown in Table 1.

Two-dimensional transthoracic echocardiography (TTE) revealed dilated left ventricle with end-systolic diameter of 5.3 cm, end-diastolic diameter of 6.0 cm, with the presence of diffuse left ventricular hypokinesia, severely reduced ejection fraction (EF 18%) and diastolic dysfunction with increased left atrial pressure (E/e'=15.3). There was also moderate mitral and tricuspid regurgitation, elevated right ventricular systolic pressure of 56 mm Hg, and dilated inferior vena cava (2.5 cm) without respiratory collapsibility (Figure 2).

The patient was initially treated with intravenous diuretics and nitroglycerin infusion (5 mcg/min), while angiotensin-converting enzyme inhibitor (ACE-I), mineralocorticoid receptor antagonist (MRA) eplerenone and beta blocker were introduced after satisfactory cardiac compensation.

In addition to chest x-ray, diagnostics was supplemented with computed tomography (CT) of the chest, which uncovered discrete scars in the apical part of the right lung, as well as linear atelectasis in S10 on the left (Figure 3).

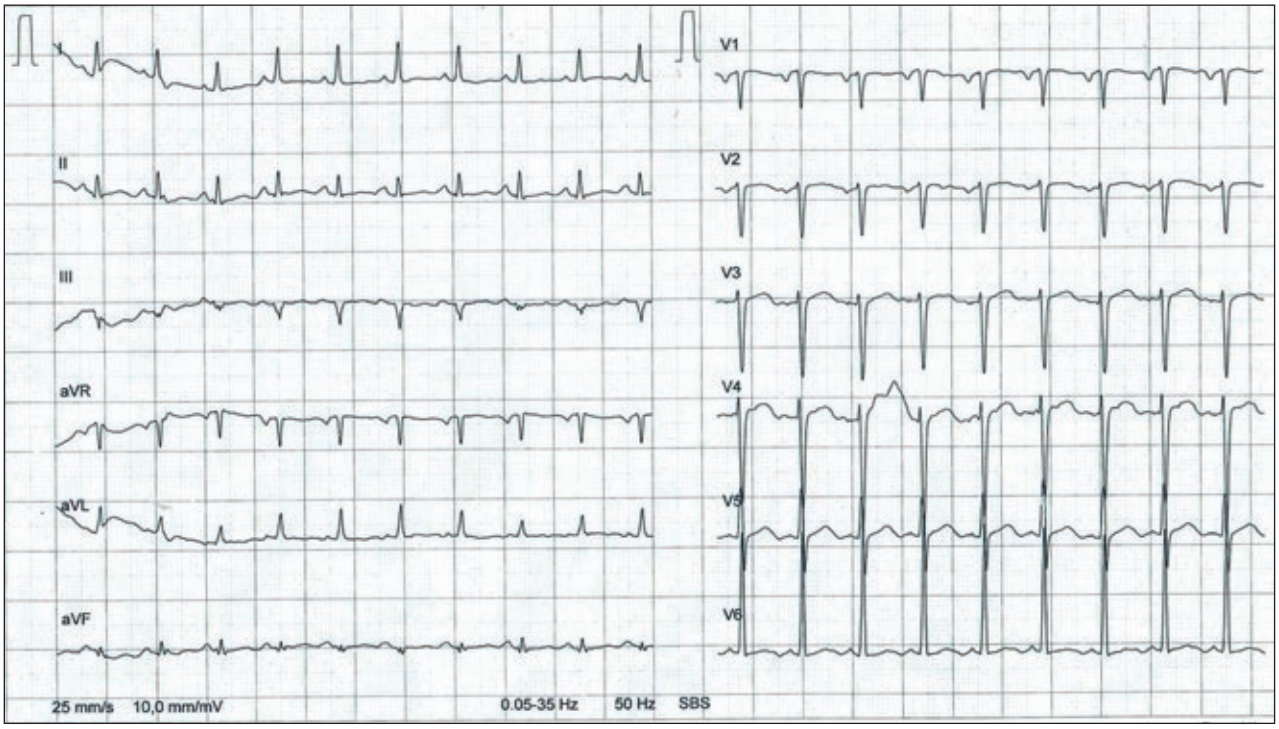

Figure 1. *Electrocardiogram: sinus tachycardia without ST-T changes.*

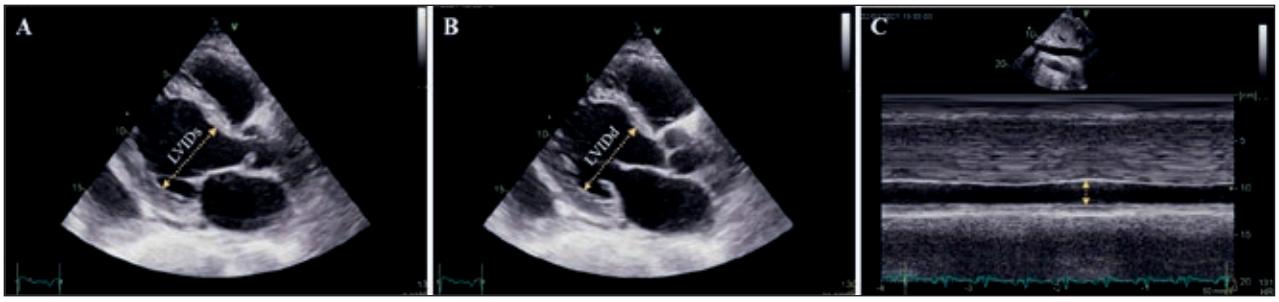

Figure 2. *Transthoracic echocardiography: (A) parasternal long axis-systole: LVIDs (left ventricular internal diameter end-systole) 5.3 cm (yellow dotted line); (B) parasternal long axis-diastole: LVIDd (left ventricular internal diameter end-diastole) 6.0 cm (yellow dotted line); (C) inferior vena cava without respiratory collapsibility (yellow line).*

To exclude coronary artery disease, CT coronarography was done and revealed nonsignificant stenosis of coronary arteries. A 24-hour Holter monitoring discovered two episodes of non-sustained ventricular tachycardia (both of 4 beats), thus the beta blocker was increased to a maximally tolerated dose.

In order to get to the underlying cause of heart failure, we performed serological tests that would detect potential cardiotropic viral infection. The patient tested negative for adenovirus, coxsackie virus, Epstein-Barr virus, cytomegalovirus, hepatitis B, human immunodeficiency virus (both IgG and IgM antibodies), influenza virus type A, influenza virus type B, and parainfluenza virus. Considering the x-ray result, we decided to exclude a possible atypical pneumonia causing microorganism. The patient's results were negative for *Coxiella burnetii, Chlamydia psittaci* and *Mycoplasma pneumoniae* infection.

Although the clinical presentation did not point in the direction of immune disease, we performed an essay in order to exclude the most common immune cause of heart failure (Table 2).

Cardiac magnetic resonance imaging (MRI) was done in order to establish if there were any signs of potential, previously unrecognized post-COVID myocarditis. Cardiac MRI revealed dilated left ventricle with moderately thickened myocardium, and globally and severely impaired kinetics. T2-weighted cardiovascular MRI showed increased intensity of the myocardi-

Table 2. *Immune assay results*

C3	C4	ANA	ASA	ASTO	Latex RF	CiC
Negative	Negative	Negative	Negative	Negative	Negative	Negative

C3 = complement component 3; C4 = complement component 4; ANA = antinuclear antibodies; ASA = anti-streptavidin antibodies; ASTO = antistreptolysin O test; RF = rheumatoid factor; CIC = Certification in Infection Control

um in comparison to the bone tissue. Myocardial late gadolinium enhancement (LGE) imaging highlighted the area with pathological coloring in the septal part of the mesocardium (mesocardial enhancement) (Figure 4), suggesting myocarditis as a possible cause of dilated cardiomyopathy.

The patient gradually recovered and after twelve days of hospital treatment, he was discharged with the following therapy: acetylsalicylic acid, beta-blocker, sacubitril/valsartan, furosemide and eplerenone. Laboratory tests on the day of discharge showed reference values (Table 3).

On the three-month follow-up, the patient had no limitations on ordinary physical activity although sustained effort was followed by discomfort, TTE showed increased EF to 30%, and 24-hour ECG demonstrated isolated ventricular ectopic beats without other heart rhythm abnormalities. The therapy continued without any significant changes, apart from the addition of dapagliflozin. We discussed the implantable cardioverter-defibrillator (ICD) placement but decided to temporarily give it up due to the EF increase.

On the second follow-up, eight months after discharge, the patient had no complaints or limitations of physical activity and TTE showed significant improvement in systolic function of the left ventricle, EF was 47%, with normal left atrial pressure (E/e' 7.0) and mild mitral and tricuspid insufficiency. Left ventricular global longitudinal strain showed slightly reduced values (peak global longitudinal strain was -15), mainly based on decreased values of regional strain for basal segments of anterior, anteroseptal and inferoseptal walls, and slightly decreased values for mid anterior, anteroseptal and inferoseptal segments (Figure 5). The medicamentous treatment was continued without changes.

Table 3. *Laboratory test results on the day of discharge*

Laboratory findings	Result	Reference range
Hemoglobin (g/L)	140	120.0-170.0
Leukocytes (x10^9/L)	7.4	4.0-10.0
Platelets (x10^9/L)	270	150-400
International normalized ratio (INR)	1	1.2
Urea (mmol/L)	6	2.5-7.5
Creatinine (μmol/L)	109	50.0-120.0
Uric acid (μmol/L)	379	150.0-420.0
AST (U/L)	20	10.0-37.0
ALT (U/L)	27	10.0-40.0
GGT (U/L)	40	2.0-55.0
Total proteins (g/L)	65	64-83
Albumin (g/L)	37	34-50
CRP (mg/L)	6	0.0-5.0
hsTroponin I (ng/L)	21.4	00-34.2
NT-proBNP (pg/mL)	300	0.0-125.0
D dimer (ng/mL)	<500	0.0-500.0

AST = aspartate aminotransferase; ALT = alanine transaminase; GGT = gamma-glutamyl transferase; CRP = C-reactive protein

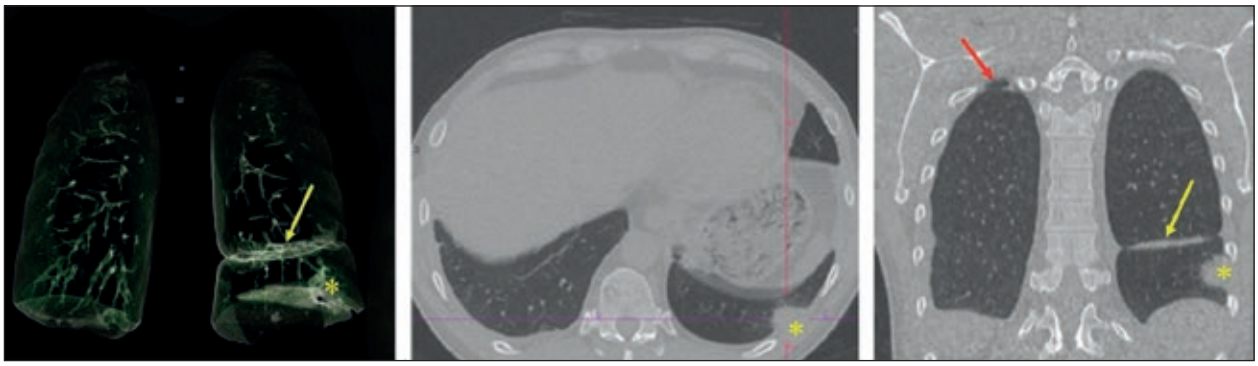

Figure 3. *Computed tomography of the chest: discrete scars in the apical part of the right lung (red arrow), subpleural nodule (asterisk), and linear atelectasis in S10 on the left (yellow arrow).*

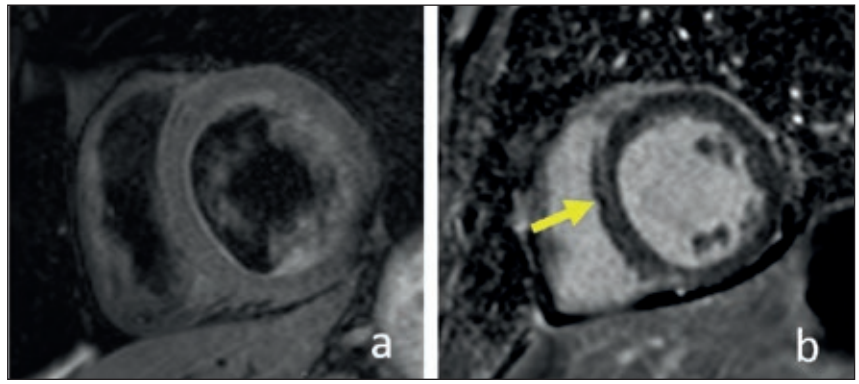

Figure 4. *Cardiac magnetic resonance imaging: short axis T2-weighted (A) and late gadolinium enhancement (B) images show areas of septal late gadolinium enhancement (mesocardial enhancement – yellow arrow), without visible edema.*

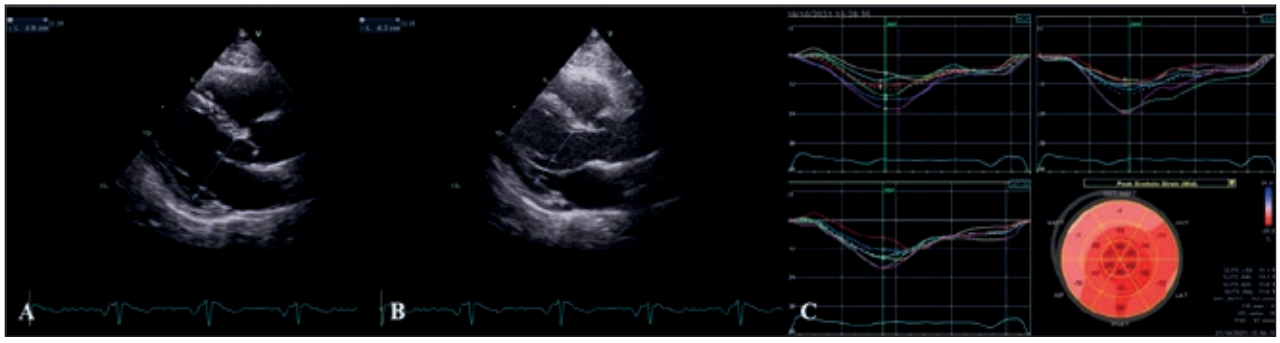

Figure 5. *Transthoracic echocardiography at eight-month follow-up: (A) parasternal long axis-diastole; (B) parasternal long axis-systole; (C) left ventricle global longitudinal strain.*

DISCUSSION

Myocarditis is a challenging diagnosis not only due to the heterogeneity of clinical presentations, but also because the endomyocardial biopsy as the diagnostic gold standard is not widely used (10). Myocarditis symptoms vary from mild chest pain and palpitations to cardiogenic shock and ventricular arrhythmia (10). Typically, myocarditis has a viral prodrome including fever, myalgias, and respiratory/gastrointestinal symptoms, but this can be exceedingly variable (11). It happens often, similar to the case we have chosen to describe, that the acute myocarditis symptoms remain unrecognized, and the patient first presents with the new onset of heart failure with corresponding symptoms (10).

Whenever myocarditis is suspected, it is required to exclude coronary artery disease and other cardiovascular or extra-cardiac non-inflammatory diseases that could explain clinical presentation (10). We did the same in our case, the patient was fully noninvasively examined and the coronary artery disease was excluded.

According to the current knowledge (8-10), endomyocardial biopsy (EMB) is the gold standard and should be done in order to set a definitive diagnosis. Being quite an invasive and highly specific method, it is not available in a vast number of centers (11). In circumstances where EMB cannot be obtained, cardiac MRI is described as a reasonable alternative (11-13). Furthermore, EMB is shown to be prone to a sampling error that can lead to false-negative results (14) and is not a routine clinical practice in our institution. We performed cardiac MRI in our patient. Cardiac MRI using Lake Louise criteria (that target three aspects of myocardial inflammation, i.e., edema, hyperemia, and necrosis and/or fibrosis) is shown to be highly specific and rather sensitive when it comes to diagnosing of myocarditis (11-13). Image interpretation relies upon analysis of signal intensities on T2-weighted, early gadolinium enhancement and late gadolinium enhancement (LGE) images (14). In our case, the T2 weighted sequence did show increased signal intensity of myocardium in comparison to the bone tissue, although not to the extent to diagnose myocardial edema (15). Myocardial LGE imaging did show changes in the septal part of the mesocardium that pointed strongly in the direction of possible myocarditis diagnosis (11,14,15). especially when combined with history data. We believe that the viral prodrome, constellation of symptoms, history of SARS-CoV-2 infection two months prior to admission, in relationship with MRI finding and myocardial recovery in the follow-up

period strongly support the diagnosis of delayed manifestation of post-COVID-19 myocarditis as the cause of heart failure in our patient.

The pathophysiology of COVID-19 caused myocardial injury is still elusive. It is thought to be a combination of direct viral injury and damage through the host's immune response (16). The presence of so-called cytokine storm with observed elevation of inflammatory cytokines (interleukin (IL)-2R, IL-6, IL-10, and tumor necrosis factor α) is so far considered to be crucial (11,16). Another theory implies that the virus uses the angiotensin-converting enzyme 2 *via* its S-spike to bind to the receptors, which becomes the entry point to the cell, cardiomyocytes as well (11). COVID-19 is recognized as a systemic vasculitis that affects not only the lung but all organs, such as the myocardium, which could be another possible mechanism of cardiac injury (17).

When it comes to treatment, patients with suspected COVID-19 myocarditis should be treated according to current guideline recommendations for heart failure and/or arrhythmia (11), the same as we did in our patient's case. Supportive care is also important. Some authors find that the routine use of immunosuppressive strategies did not show advantage when it comes to the course of COVID-19 myocarditis, although it may be helpful when it comes to treatment of COVID-19 pneumonia (11,16). Antiviral therapy has been used especially at the very beginning of the pandemic, but it did not show any benefit in mortality compared with placebo (11).

The high prevalence of post COVID-19 complications requires systematic clinical and echocardiographic follow-up of patients who developed COVID-19. Since we are dealing with a new clinical entity, there is still a lot of research to be done considering COVID-19 itself, as well as how it affects various organ systems, cardiovascular system included. By comprehensive approach, we aim to establish timely diagnosis, provide appropriate treatment, and prevent serious complications.

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SAŽETAK

ODGOĐENA MANIFESTACIJA MIOKARDITISA NAKON COVID-A

I. POPOV[1,2], M. KOVAČEVIĆ[1,2], B. CRNOMARKOVIĆ[1,2], M. ČANKOVIĆ[1,2], M. JARAKOVIĆ[1,2], S. KEČA[2], S. DIMIĆ[2], S. MALETIN[1,2], M. SPIROVSKI[1,3], M. STEFANOVIĆ[1,2], M. PETROVIĆ[1,2], A. MILOVANČEV[1,2]

[1]Sveučilište u Novom Sadu, Medicinski fakultet, Novi Sad, Srbija; [2]Institut za kardiovaskularne bolesti Vojvodine, Klinika za kardiologiju, Sremska Kamenica, Srbija; [3]Institut za onkologiju Vojvodine, Sremska Kamenica, Srbija

Uvod: Zahvaćenost miokarda koronavirusnom bolešću 2019 (COVID-19) varira i smatra se ozbiljnijom u bolesnika s teškom kliničkom slikom COVID-19. Iako se miokarditis obično prepoznaje u okruženju akutne infekcije SARS-CoV-2, prepoznaju se i odgođene manifestacije. ***Prikaz slučaja:*** Bolesnik u dobi od 51 godine primljen je zbog kliničkih znakova kongestivnog zatajenja srca dva mjeseca nakon umjerene kliničke manifestacije pneumonije COVID-19, liječen ambulantno. Transtorakalna ehokardiografija (TTE) otkrila je dilatiranu kardiomiopatiju s prisutnošću difuzne hipokinezije lijevog ventrikla (LV), ozbiljno smanjenu ejekcijsku frakciju (18%) i dijastoličku disfunkciju s povećanim osjećajem tlaka u lijevom atriju. Osnovni laboratorijski testovi otkrili su povišen hs-troponin I, NT-proBN. Dijagnostička vježba isključila je koronarnu bolest. Magnetska rezonancija srca snažno je pokazala u smjeru neprepoznatog miokarditisa nakon COVID-a. Bolesnik je liječen prema važećim smjernicama za zatajenje srca sa smanjenom ejekcijskom frakcijom. Osam mjeseci nakon otpusta bolesnik nije imao ograničenja tjelesne aktivnosti, a TTE je pokazao značajno poboljšanje sistoličke funkcije lijeve klijetke, ejekcijska frakcija je iznosila 47%, uz normalan tlak punjenja LV. ***Zaključak.*** Miokarditis nije rijetka manifestacija infekcije COVID-19, osobito u hospitaliziranih pacijenata s teškom kliničkom slikom, i obično se manifestira unutar prvog tjedna nakon početnih simptoma. Naš prikaz bolesnika je primjer da i pacijenti s blagim oblikom COVID-19 koji se liječe ambulantno mogu imati odgođeni početak zatajenja srca kao posljedicu miokarditisa izazvanog COVID-19. Stoga bolesnici s COVID-19 zaslužuju cjelovit pristup uz sustavno kliničko i ehokardiografsko praćenje kako bi se pravodobno postavila dijagnoza, omogućilo odgovarajuće liječenje i spriječile ozbiljne komplikacije.

Ključne riječi: COVID-19, miokarditis, dilatacijska kardiomiopatija, magnetska rezonancija