Journal of Cardiology Cases xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology Cases

journal homepage: www.elsevier.com/locate/jccase

Case Report

Impaired myocardial perfusion and myocardial inflammation of acute myopericarditis associated with COVID-19

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ARTICLE INFO

Article history:
Received 29 March 2024
Received in revised form 3 July 2024
Accepted 19 September 2024
Available online xxxx

Keywords:
Inflammation
Microcirculation
Magnetic resonance imaging
Positron emission tomography
Pathology
Coronavirus disease 2019

ABSTRACT

Myocarditis and pericarditis, or myopericarditis, is a rare, albeit life-threatening, cardiac complication of coronavirus disease 2019 (COVID-19). Although most patients recover from myocardial inflammation within weeks of the acute infection, there are concerns about acute and long-term myocardial injury. Coronary microvascular dysfunction and myocardial inflammation in the affected myocardium might be key factors in developing acute COVID-19-associated myopericarditis. In this case report, we describe a 38-year-old woman diagnosed with acute COVID-19-associated myopericarditis who was treated successfully. This case highlights the remarkable recovery in coronary microcirculation and myocardial inflammation assessed using multi-imaging modalities from the acute phase to 3-month follow-up using histopathological assessments.

Learning objective: Acute myopericarditis is one of the serious cardiac complications associated with severe acute respiratory syndrome coronavirus 2 infection, although an accurate diagnosis might be challenging. We emphasize a novel combination of magnetic resonance imaging and positron emission tomography focusing on serial changes in coronary microcirculation and myocardial inflammation from acute to recovery phases. Our findings may elucidate the pathophysiology of this entity at the micro and macro levels.

Introduction

A causal relationship among myocardial inflammation, infection of vascular endothelial cells, and coronary microvascular dysfunction (CMD) has been recently investigated in patients with acute myocarditis associated with coronavirus disease 2019 (COVID-19) [1–3]. Myocardial inflammation induced by a viral infection is associated with increased endothelial expression of the human leucocyte antigen system and adhesion molecules and correlates with systemic endothelial dysfunction [1]. In addition, CMD is commonly seen in patients with COVID-19 and is linked with the severity of the infection, suggesting that CMD may play a significant role in developing a severe form of myocardial injury [4]. CMD might explain persistent exertional dyspnea in patients post-COVID-19 due to a significant reduction in myocardial perfusion reserve [5]. However, there are no clear data on serial changes in myocardial inflammation and perfusion from the acute to recovery phases in patients with COVID-19-associated myocarditis.

Case report

A 38-year-old woman presented with worsening chest pain and a dry cough for 3 days, which was preceded for 7 days by high-grade fever. She had not been vaccinated against COVID-19 and had no remarkable medical history. At admission, her blood pressure was 90/67 mmHg, heart rate 101 beats/min, temperature 35.6 °C, and respiratory

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https://doi.org/10.1016/j.jccase.2024.09.008
1878-5409/

Please cite this article as: S. Miura, K. Amemiya, A. Okizaki, et al., Impaired myocardial perfusion and myocardial inflammation of acute myopericarditis associated with COVID-19, Journal of Cardiology Cases, https://doi.org/10.1016/j.jccase.2024.09.008

rate 22/min, with a 99 % oxygen saturation on room air. Electrocardiography (ECG) showed sinus rhythm with low voltage in the limb leads; ST-segment elevation in V3–6, II, III, and F leads; and poor R progression in V2 and V3 (Fig. 1A). No significant radiological findings of pneumonia were observed with chest X-ray computed tomography. Transthoracic echocardiography (TTE) revealed a relatively increased wall thickness and a moderate amount of pericardial effusion at 9 mm at its widest with right ventricular diastolic collapse and a left ventricular (LV) ejection fraction (EF) of 52 % without any valvular abnormalities. Laboratory data revealed elevated creatine kinase (349 U/L; normal value, ≤170 U/L), creatine kinase-myocardial band (15.9 ng/mL; normal value, ≤5.0 ng/mL), and cardiac troponin I (1950.3 pg/mL; normal value, ≤26.2 pg/mL). The coagulation profile was normal except for a slightly elevated D-dimer level of 1.1 μg/mL (normal range, ≤1.0 μg/mL). C-reactive protein (0.06 mg/dL; normal value, ≤0.30 mg/dL) and white blood cell count (4600/μL; normal range, 4000–11,000/μL) were within the normal range. A nasopharyngeal swab for viral respiratory pathogens was negative except for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). She was hospitalized for suspected acute COVID-19-associated myopericarditis.

Oral medications included loxoprofen (180 mg daily), aspirin (200 mg daily), and colchicine (0.5 mg daily). However, the patient did not receive any antiviral medications because 7 days had passed since the initial symptoms. On hospital day 3, cardiac magnetic resonance (CMR) (Fig. 1B-D) was inconclusive, with minimal myocardial edema and diffuse late gadolinium enhancement (LGE) of the entire LV wall with prominence in the subepicardial wall. A moderate amount of pericardial effusion and systolic LV dysfunction were evident with an LVEF of 36 %. On the same day, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) after an 18-h fast with a low-carbohydrate diet revealed diffuse myocardial uptake throughout the LV myocardium (Fig. 2A), suggestive of myocardial inflammation. Initially, the patient did not respond to conservative treatment and required vasopressor support. On hospital day 4, invasive coronary angiography, endomyocardial biopsy, and hemodynamic assessments were performed although pericardiocentesis was deferred because of reduced effusion. Coronary angiography revealed nonobstructive epicardial coronary disease. The endomyocardial biopsy specimen of the right ventricular septum (Fig. 3) showed mild interstitial inflammatory infiltrates and mild interstitial fibrosis without areas of cardiomyocyte necrosis (Fig. 3A-B), composed of sparse T-lymphocytes (Fig. 3C) and increased macrophage infiltration (Fig. 3D). Notably, fine vacuolar degeneration was observed in the cytoplasm of the cardiomyocytes, suggesting acute ischemic changes at the microvascular level. Fresh microthrombi with occlusive changes in the capillaries and plump endothelial cells in small vessels were observed (Fig. 3A-B). These microthrombi and changes in the vessel walls were mostly immunohistochemically positive for C4d and von Willebrand factor (vWF) (Fig. 3E-F). With continued oral medications, her symptoms reduced; but chest pain did not disappear completely despite hemodynamic improvement. On hospital day 13, a ^{13}N-ammonia PET (Fig. 2B-C) to assess CMD showed relatively impaired stress myocardial blood flow and myocardial flow reserve at 2.71 mL/g/min and 2.87, respectively, for her age. The patient was discharged uneventfully on hospital day 14.

Three months after discharge, the patient was asymptomatic. TTE showed no pericardial effusion and the ECG had normalized (Fig. 1E). Repeated CMR demonstrated a marked LVEF improvement of 49 %, with no obvious LGE (Fig. 1F-G) and no abnormality in the T2-weighted images (Fig. 1H). Repeated ^{18}F-FDG-PET images showed no abnormal ^{18}F-FDG uptake (Fig. 2D), and ^{13}N-ammonia PET images

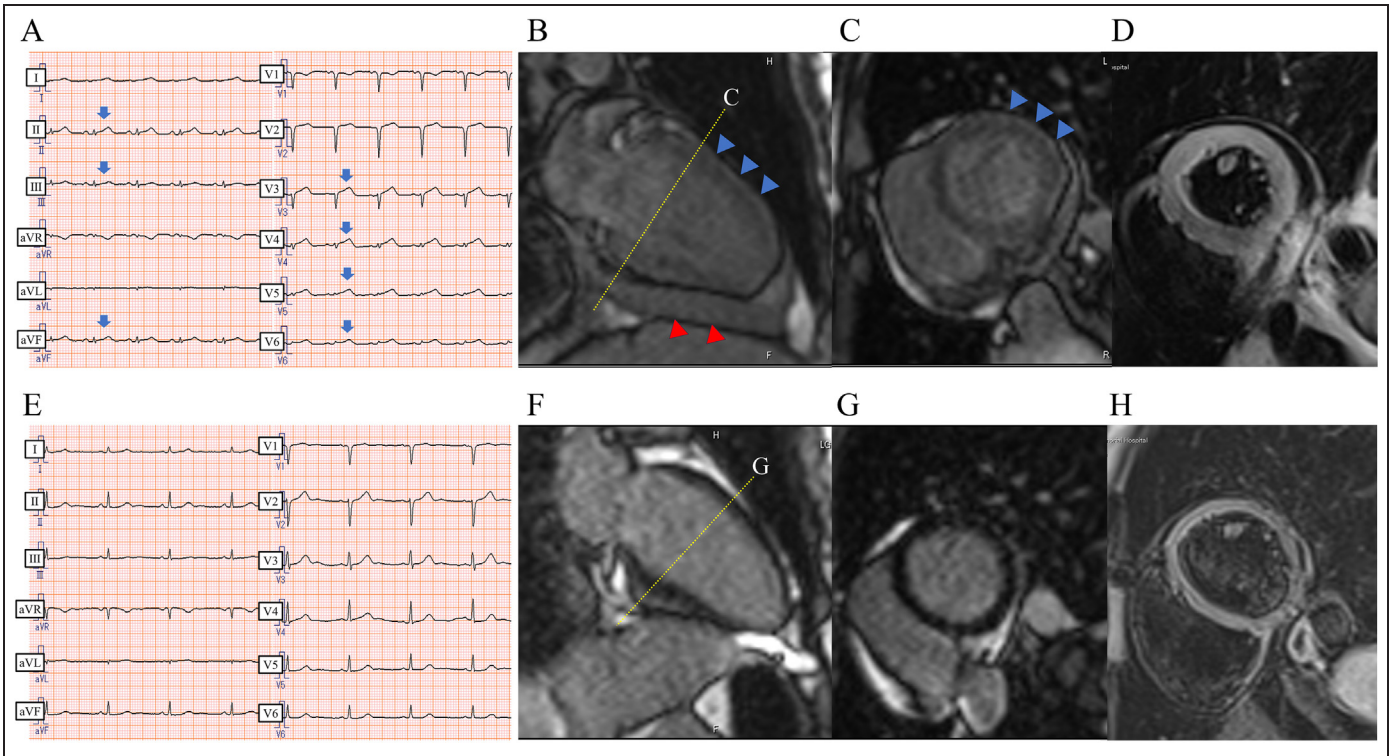
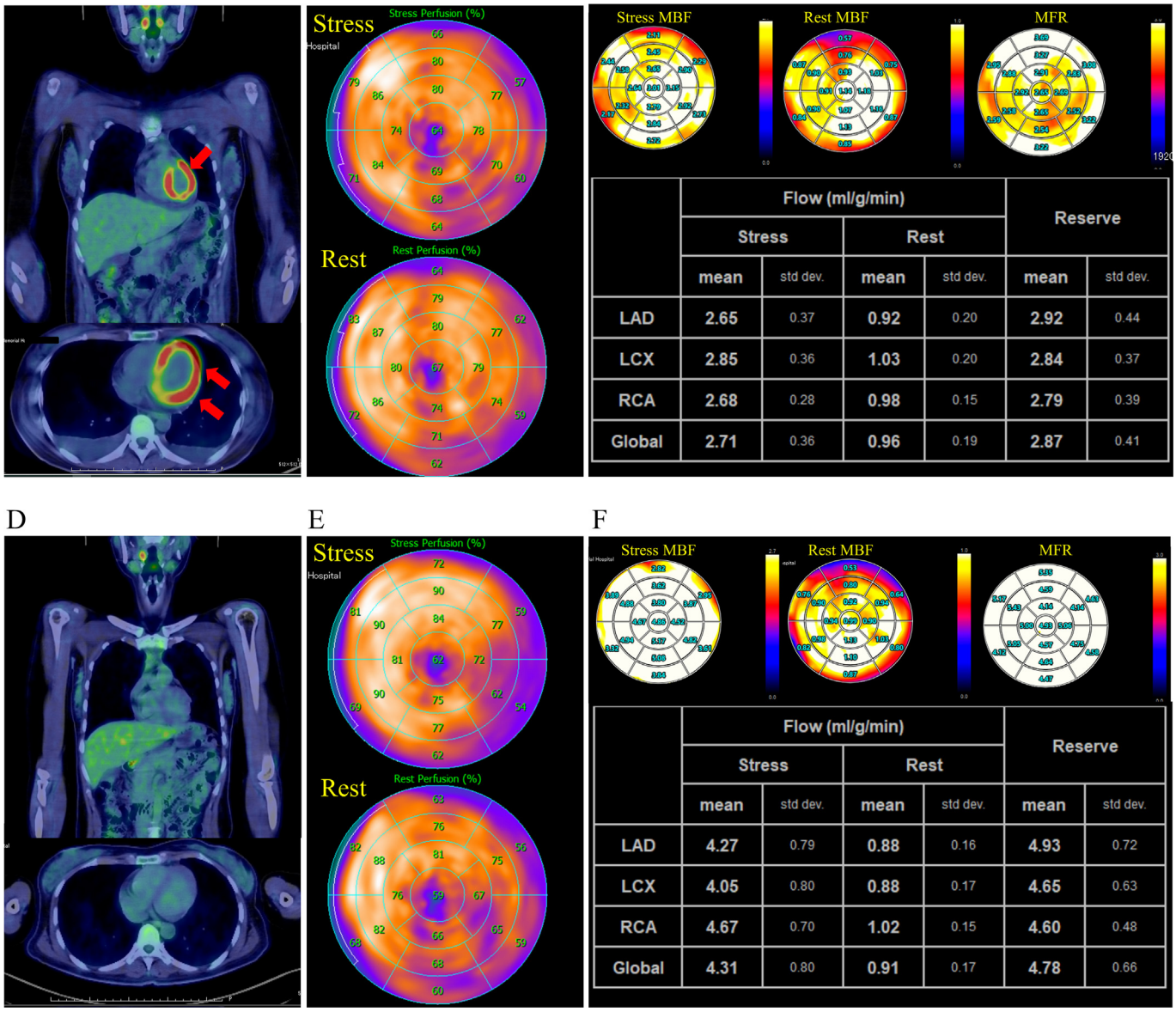


Fig. 1. Electrocardiogram (ECG) and cardiovascular magnetic resonance (CMR) findings. Twelve-lead ECG at initial presentation (A) showing ST-segment elevation in V3–6, II, III, and F leads (blue arrows) without any prolonged QT (323 ms) and QTc (420 ms), and one at a 3-month follow-up from hospital discharge (E) showing normalized ST-segments. CMR in the long-axis (B) and short-axis (C) views on hospital day 3 showing diffuse late gadolinium enhancement (LGE) in the entire left ventricular (LV) myocardium from the anterolateral to inferolateral walls (blue arrowheads) with more prominence in the subepicardial layers. Moderate pericardial effusion is observed (red arrowheads). Dark-blood T2-weighted imaging reveals no abnormally high signals in the LV myocardium (D). At a 3-month follow-up, LGE is negative in the long-axis (F) and short-axis (G) views, and pericardial effusion is absent; dark-blood T2-weighted images show no abnormal intensity in the entire LV myocardium (H). The short-axis images in panels (C) and (G) are indicated by dotted yellow lines in panels (B) and (F), respectively.



	Flow (ml/g/min)				Reserve	
	Stress		Rest			
	mean	std dev.	mean	std dev.	mean	std dev.
LAD	2.65	0.37	0.92	0.20	2.92	0.44
LCX	2.85	0.36	1.03	0.20	2.84	0.37
RCA	2.68	0.28	0.98	0.15	2.79	0.39
Global	2.71	0.36	0.96	0.19	2.87	0.41

	Flow (ml/g/min)				Reserve	
	Stress		Rest			
	mean	std dev.	mean	std dev.	mean	std dev.
LAD	4.27	0.79	0.88	0.16	4.93	0.72
LCX	4.05	0.80	0.88	0.17	4.65	0.63
RCA	4.67	0.70	1.02	0.15	4.60	0.48
Global	4.31	0.80	0.91	0.17	4.78	0.66

Fig. 2. Myocardial inflammation and perfusion positron emission tomography (PET) imaging assessed using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) and ^{13}N-ammonia. The initial ^{18}F-FDG PET/computed tomography (upper, coronal view; lower, axial view) showing abnormal FDG uptake (white arrowheads) in the left ventricular (LV) myocardium on hospital day 3 (A), highlighting complete resolution of the abnormal findings at the 3-month follow-up (D). Polar maps of qualitative myocardial perfusion imaging from stress (upper panel) /rest (lower panel) ^{13}N-ammonia PET demonstrating almost irreversible impaired myocardial perfusion in the lateral and posterior basal walls on hospital day 13 (B) and at the 3-month follow-up (E). Quantitative assessment of myocardial perfusion ^{13}N-ammonia PET [upper left, stress myocardial blood flow (MBF); upper middle, rest MBF; upper right, myocardial flow reserve (MFR)] on hospital day 13 (C) and at the 3-month follow-up (F) with PET-derived flow indices in each coronary artery territory (presented at the bottom). LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

(Fig. 2E-F) revealed remarkable improvements in stress myocardial blood flow and myocardial flow reserve to 4.31 mL/g/min and 4.78, respectively.

Discussion

The association between CMD and COVID-19-associated myopericarditis is not fully understood. Our case indicates that CMD appears to have a crucial role in COVID-19-associated myopericarditis because the patient's clinical improvement coincided with the improvement in myocardial flow reserve on ^{13}N-ammonia PET and myocardial inflammation on ^{18}F-FDG-PET. The relevant explanation might be related to the pathophysiology of myocardial injury and subsequent myocarditis. First, CMD is a potential mechanism for myocardial injury in COVID-19 patients [4–6]. Microvascular impairment can be a consequence of the exaggerated systemic inflammatory response and endothelial dysfunction found to be responsible for microthrombi formation in addition to a direct action of SARS-CoV-2 on the microcirculation by expressing the cellular host receptor angiotensin-converting enzyme 2 on the surface of endothelial cells [3,7]. Second, myocardial injury could be a consequence of myocardial involvement in the inflammatory processes, potentially leading to acute myocarditis. The degeneration of cardiomyocytes and inflammatory infiltrates in the myocardial interstitium has been described together with vascular de-epithelization, vasculitis, and microthrombi formation [6].

Whether COVID-19-associated myocarditis is caused by direct infection of the cardiac tissue by SARS-CoV-2 or infection-related systemic inflammatory response (cytokine storm) remains debatable. To date,

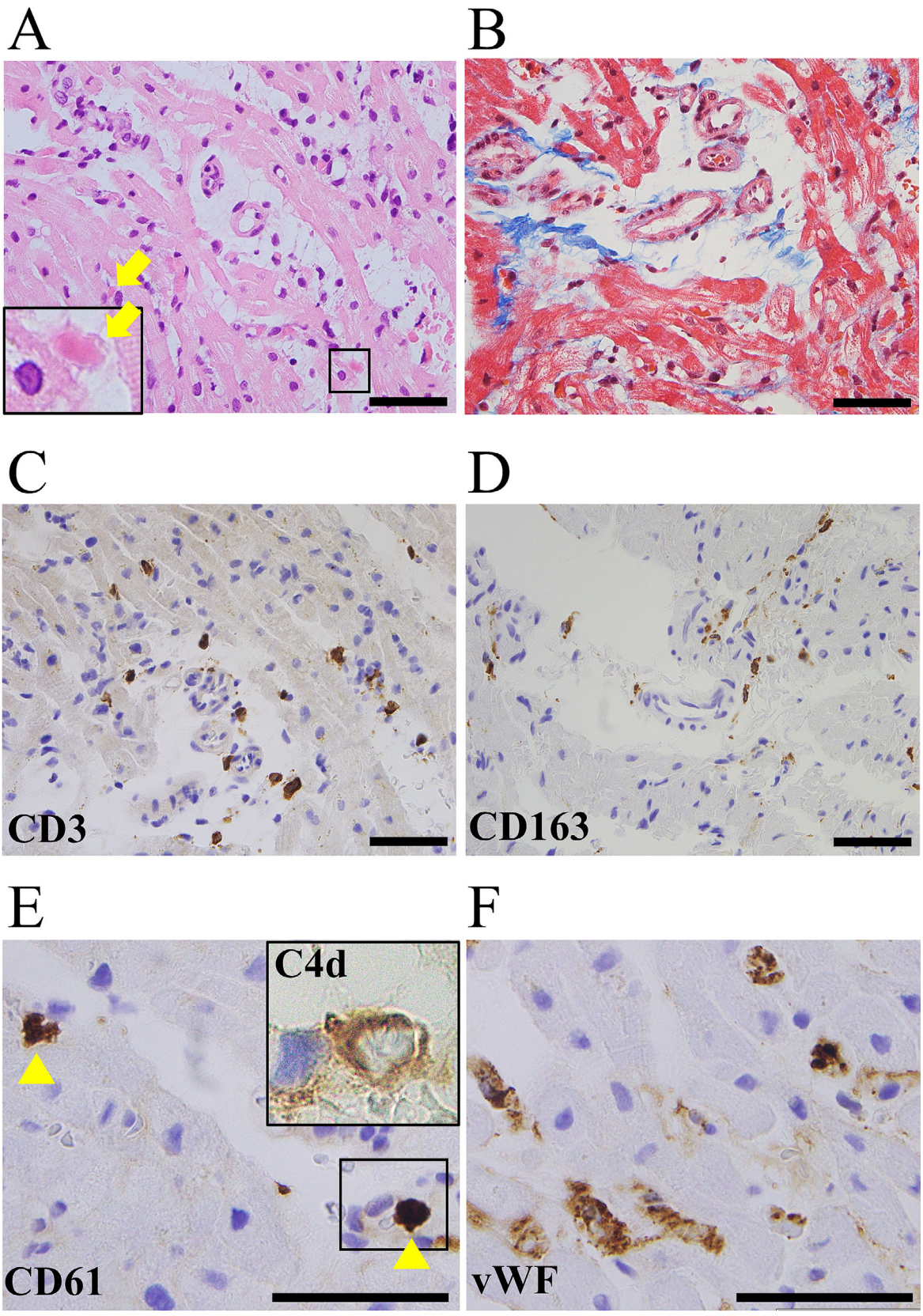


Fig. 3. Histology and immunohistology of the endomyocardial biopsy sample. (A, B) Mild inflammation without adjacency to cardiomyocyte necrosis accompanied by interstitial edema with mild interstitial fibrosis (A, hematoxylin and eosin stain; B, Masson's trichrome stain). Non-necrotic myocytes in the vicinity showed cytoplasmic vacuolization with microthrombi (yellow arrows and inset in Panel A). (C, D) Sparse T lymphocytes (C, immunostaining with CD3 antibody) and increased macrophages (D, immunostaining with CD163 antibody) were observed in the interstitium. (E) Platelet aggregates are observed filled in some capillaries (yellow arrowhead, immunostaining with CD61 antibody). (E, F) Microthrombi and the vessel wall are mostly positive for C4d (inset in Panel E) and vWF, respectively. Black bars indicate 50 μm.
vWF, von Willebrand factor.

little evidence supports the direct destruction of cardiomyocytes through virus-mediated lysis, resulting in myocyte injury and cardiac dysfunction because SARS-CoV-2 has not been isolated in the myocardium [7]. In line with previous reports [8,9], we also found some myocardial injury accompanied by prominent microthrombi and endothelial injury in the myocardium; microthrombi were mostly immunohistochemically positive for vWF with some platelet aggregates. These findings could reflect the early features of myocardial injury at biopsy a few days after onset. In the late stage, fibrin-rich microthrombi and organized mural thrombi within small vessels should be detected. Increased complement activation and elevated vWF levels have been reported in patients with COVID-19 [8]. Thus, we speculate that SARS-CoV-2 infection triggered a dysregulated cytokine response, induced endothelial injury, complement activation, macrophage activation, and diffuse microthrombosis in the myocardium, which led to transient myocardial ischemia (impaired microcirculation), resulting in severe cardiac dysfunction. Additionally, our case added noteworthy findings that the myocardial inflammation assessed with ^{18}F-FDG-PET improved within 3 months along with the LGE resolution. Most patients with COVID-19-associated myocarditis recover from myocardial inflammation within weeks of acute infection and do not suffer long-term consequences; however, others with cardiac involvement have poor clinical outcomes with long-term structural and functional changes [3]. We believe that these complications might be related to prolonged impaired microcirculation and/or inflammation. Of note, our case may show remarkable, but not complete, recovery from acute myocarditis because the CMR-derived LVEF at the 3-month visit was subnormal, requiring careful follow-up.

Accurately diagnosing COVID-19-associated myopericarditis is challenging. The histopathological findings in our case demonstrated borderline myocarditis according to the Dallas criteria [10], characterized by few inflammatory cells but no definitive myocardial damage. These results were concordant with previous reports [8], suggesting that the pathogenesis of COVID-19-associated myocarditis would be different from that of lymphocytic myocarditis [2,7–9]—immune dysregulation and cytokine storm rather than direct myocardial injury. Although the Lake Louise Criteria [10] are proposed using CMR in diagnosing myocarditis non-invasively, there are limitations to the criteria, primarily because of the highly heterogeneous distribution of LGE [9]. Diffuse forms of myocardial inflammation can be inconclusive, as seen in our case. COVID-19-associated myocarditis often occurs without necrosis; therefore, the absence of an elevated troponin or negative LGE does not rule out the presence of myocarditis, even severe myocarditis [2]. Beyond conventional CMR sequences, T1 and T2 mapping are promising with enhanced sensitivity in detecting and qualifying myocardial fibrosis and edema; however, there is a lack of standardization [10]. As a novel complementary tool, ^{18}F-FDG-PET has high diagnostic accuracy for acute myocarditis by distinguishing between fibrosis and active inflammation [3]. In our case, the combined use of CMR and ^{18}F-FDG-PET was highly diagnostic in that myocardial inflammation, not fibrosis, presented and improved over time when the histopathological findings were not conclusive.

Funding

None.

Patient permission/consent statement

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Declaration of competing interest

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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