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A case of biopsy-proven inflammatory dilated cardiomyopathy following heterologous mRNA-1273 third-dose immunization

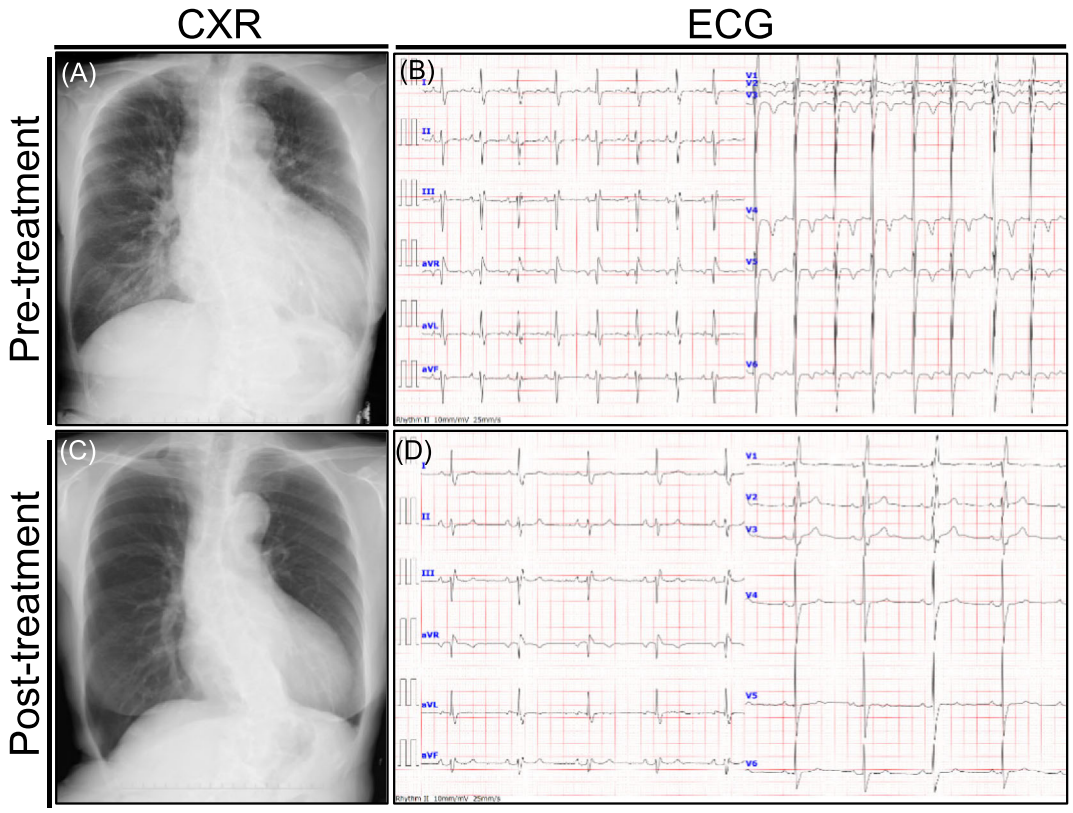
Introduction

Advances in mRNA vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have helped curb the coronavirus disease 2019 (COVID-19) pandemic and prevent disease onset and severity. Growing cases of vaccine-associated myocarditis (VAM) following SARS-CoV-2 immunization have been reported.[1] Although COVID-19 VAM commonly occurs in young males after the second dose of vaccination, most cases are mild.[2] Severe cases can be fatal if left untreated.[3] Early diagnosis remains challenging because of the broad clinical spectrum of phenotypes and pathophysiologies, including minor focal myocarditis, multisystemic inflammatory syndrome and fulminant myocarditis.[4,5] Furthermore, histological evaluation remains to be fully understood.

Case report

A 78-year-old previously healthy female was referred by her family physician and admitted to our hospital for management of dyspnoea 11 days after receiving the third mRNA-1273 vaccine dose. The patient underwent a primary two-dose BNT162b2 series. On the fourth day after vaccination, the patient experienced palpitations and dyspnoea, which gradually worsened. The patient had a history of mild dementia but no risk factors for coronary artery disease. She had no recent travel history, contact with patients with confirmed COVID-19, recent infectious prodrome or any history of alcohol consumption, cigarette smoking or illicit drug use. On admission, her vital signs were as follows: body temperature, 36.7°C; blood pressure, 139/98 mmHg; heart rate, 120 b.p.m.; and oxygen saturation of 90% in ambient air. Jugular vein distention and bilateral leg oedema were also noted. Cardiovascular auscultation revealed a cardiac gallop rhythm, a diastolic cardiac murmur and bilateral crackles. Chest radiography revealed cardiomegaly and lung congestion (Figure 1A). Electrocardiography (ECG) revealed sinus tachycardia with complete right bundle branch block and left anterior hemiblock; high QRS voltage and broad T-wave inversions in the precordial leads were noted (Figure 1B). Compared with the results of the previous ECG performed the day before admission (Figure S1), the current ECG revealed a similar type of tachycardia but with deeper T-wave inversions and a prolonged QT interval, suggesting progressive myocardial damage. Laboratory test results revealed a white blood cell count of 7600/μL, elevated levels of cardiac troponin I (156 pg/mL, reference: <26.2 pg/mL) and brain natriuretic peptide (1367 pg/mL, reference: <18.4 pg/mL). Repeated nasopharyngeal swab specimens tested negative for SARS-CoV-2. Echocardiography revealed diffuse severe hypokinesis with left ventricular (LV) enlargement and moderate pulmonary hypertension (LV diastolic diameter, 65 mm; LV ejection fraction, 20%; and estimated right ventricular systolic pressure, 56 mmHg) (Figure 2A,B and Videos S1 and S2). Speckle-tracking echocardiography revealed a reduced baseline LV global longitudinal strain of −5.7% (Figure 2C). Doppler echocardiography revealed moderate aortic regurgitation (Figure 2D). The coronary angiography findings were unremarkable. The patient was diagnosed with acute heart failure and treated with administration of oxygen at 4 L/min, intravenous nitroglycerine infusion (2 μg/kg/min) and intravenous loop diuretics (furosemide 20 mg twice daily). Thereafter, anti-heart failure therapy was initiated (enalapril, 2.5 mg/day; spironolactone, 25 mg/day; and dapagliflozin, 10 mg/day). Cardiac magnetic resonance (CMR) imaging revealed diffuse severe LV dysfunction with cavity enlargement on cine imaging and a septal midwall abnormality with late gadolinium enhancement (LGE). The T2-weighted image revealed the absence of remarkable myocardial oedema, suggestive of dilated cardiomyopathy (DCM) (Figure 3). However, the DCM phenotype following COVID-19 immunization prompted us to perform an endomyocardial biopsy (EMB) (Figure 4A–E). Photomicrographs showed moderate myocyte hypertrophy, interstitial fibrosis and scattered interstitial inflammatory

Figure 1 Chest X-ray (CXR) and electrocardiography (ECG) before and after corticosteroid treatment. A CXR on admission reveals marked cardiomegaly and lung congestion (A), which resolve completely on the 6 month follow-up CXR after treatment (C). ECG reveals sinus tachycardia and prolonged QT interval with complete right bundle branch block and left anterior hemiblock (B). High QRS voltage and broad T-wave inversions in the precordial leads are noted (heart rate, 98 b.p.m.; QRS axis, −63°; corrected QT interval, 470 ms; and R-wave amplitude in the V4 lead, 3.3 mV). The above changes observed on the initial ECG (B) resolve at the 6 month follow-up ECG after treatment (D) (heart rate, 56 b.p.m.; QRS axis, −35°; corrected QT interval, 433 ms; and R-wave amplitude in the V4 lead, 1.7 mV).



infiltrates, largely composed of $CD68^+$ macrophages admixed with $CD3^+$ T-lymphocytes, without associated myocyte necrosis. No $CD20^+$ B-lymphocytes or eosinophils were detected. The counts of $CD68^+$ macrophages and $CD3^+$ T-lymphocytes were 64 and 16 cells/mm^2, respectively, meeting the quantitative criteria of EMB in myocarditis, including the Marburg criteria (≥14 leucocytes/mm^2, including up to 4 monocytes/mm^2, and $CD3^+$ T-lymphocytes ≥ 7 cells/mm^2), which were adopted in a position statement by the World Heart Federation and European Society of Cardiology experts, leading to the pathological diagnosis of chronic myocarditis and inflammatory cardiomyopathy, including DCM (iDCM). Immunohistochemical analyses further characterized the inflammatory infiltrates. CD61 positivity, suggestive of platelet aggregation, was partially observed in the interstitium and endocardium. Simultaneously, human leucocyte antigen-DR was strongly induced in the capillary endothelial cells. Notably, diffuse expression of tenascin-C (TNC) was increased in the endocardium and interstitium, suggesting an active disease stage. A thorough aetiological workup for iDCM was performed. Autoimmune profiles and blood cultures yielded negative results. SARS-CoV-2 polymerase chain reaction (PCR) and serological tests for potential cardiotropic viruses using paired sera confirmed the absence of acute infection (Table S1). Therefore, the temporal relationship between the preceding COVID-19 immunization and the occurrence of iDCM with no other identifiable cause led to the final diagnosis of COVID-19 VAM. The patient's condition steadily improved with oral prednisolone (30 mg/day). On Day 16, the patient was discharged with a reduced dose of prednisolone (20 mg/day). At the 6 month follow-up, the cardiac structural and functional abnormalities observed on admission had recovered considerably, supporting the diagnosis of active inflammatory disease (Figures 1C and 2E–H and Videos S3 and S4). The follow-up ECG also showed the resolution of all abnormalities on the initial ECG (Figure 1D). In addition, the post-treatment CMR confirmed reverse LV remodelling (Figure S2). As the enlarged left ventricle was close to the chest wall before treatment and the normalized left ventricle was located away from the chest wall after

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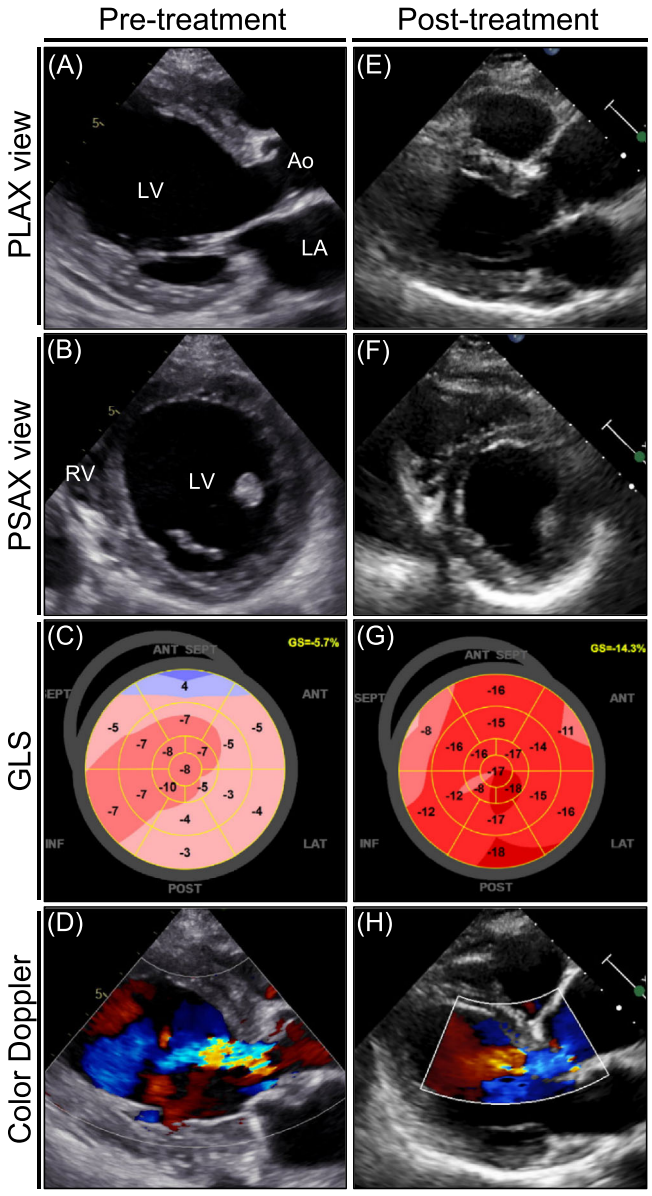
Figure 2 Effects of corticosteroid treatment on transthoracic echocardiographic parameters. Initial echocardiography reveals diffuse severe left ventricular systolic dysfunction with increased cavity size and reduced global longitudinal strain (GLS) values of the LV [left ventricular diastolic diameter (LVDd), 65 mm; left ventricular ejection fraction (LVEF), 20%; and GLS, −5.7%] (A–C). A preserved left ventricular wall thickness out of proportion to LVDd is observed [interventricular septal end-diastolic thickness (IVSd), 9 mm; left ventricular posterior wall end-diastolic thickness (LVPWd), 10 mm]. Follow-up echocardiography at 6 months after corticosteroid treatment reveals significant improvements in cavity size, wall thickness, ventricular function and GLS values of the LV (LVDd, 55 mm; IVSd, 7 mm; LVPWd, 8 mm; LVEF, 56%; and GLS, −14.3%; respectively) (E–G). Continuous-wave Doppler revealed a peak tricuspid regurgitation velocity of 3.2 m/s and an estimated right ventricular systolic pressure of 56 mmHg, which improved to 28 mmHg after corticosteroid treatment. Colour Doppler echocardiography in the PLAX view reveals that the mild-to-moderate aortic regurgitation observed on the initial echocardiography improves to mild after corticosteroid treatment (D, H). Ao, aorta; LA, left atrium; LV, left ventricle; PLAX, parasternal long axis; PSAX, parasternal short axis; RV, right ventricle.



treatment, the higher QRS voltage observed on the pre-treatment ECG was likely attributable to geometric alterations in the left ventricle caused by VAM. The follow-up EMB confirmed the beneficial effects of corticosteroid treatment on the abnormal findings observed in the initial EMB (Figure 4F–J). Thereafter, prednisolone was tapered off over the next 6 months. The patient remained clinically stable without any recurrence during the 1 year follow-up period.

The authors confirm that written consent for the submission and publication of this case report, including the images and videos, was obtained from the patient.

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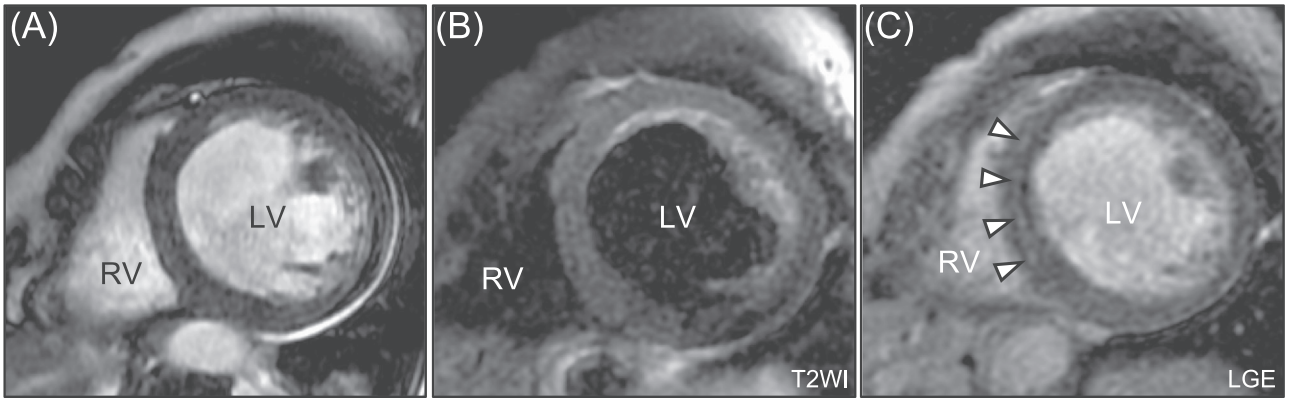
Figure 3 Short axial cardiac magnetic resonance (CMR) findings on admission (A–C). Cine-mode CMR reveals a dilated LV with diffuse severe systolic dysfunction. It analyses the left ventricular end-diastolic volume index, 175.7 mL/m^2; the left ventricular ejection fraction, 9%; and the left ventricular systolic index, 15.3 mL/m^2. (A) Negative findings on fat-suppressed T2-weighted imaging (T2WI) (B) but slight late gadolinium enhancement (LGE) in the septal midwall on enhanced CMR imaging (arrowheads) (C). LV, left ventricle; RV, right ventricle.



Discussion

Herein, we report a unique case of iDCM following a heterologous SARS-CoV-2 vaccination that was successfully treated with steroids. Our study provides several valuable insights.

To the best of our knowledge, this is the first reported case of biopsy-proven iDCM following mRNA-1273 immunization. The histology of most cases with COVID-19 VAM includes lymphocyte-predominant inflammatory cell infiltrates, which are distinct from those of previously reported VAMs with other causes, mainly composed of eosinophilic cell infiltration.[6] Generally, COVID-19 VAM includes the following characteristic histological findings: (i) lymphohistiocytic myocarditis, characterized by CD68$^+$ macrophage and CD3$^+$ T-lymphocyte infiltration[5]; (ii) cardiac microthrombi that primarily comprise CD61$^+$ platelets[7]; and (iii) focal cardiac necrosis with C4d-positive staining.[8] Our patient exhibits similar histological features. The proposed mechanisms underlying COVID-19 VAM include an aberrant immune response, cross-reactivity of antibodies against the SARS-CoV-2 spike protein with structurally similar cardiac antigens and differences in sex hormone signaling.[9] However, its exact mechanism of action remains unclear. As in our case, myocardial macrophages and lymphocytes, mainly observed in COVID-19 VAM, are essential key players in myocardial inflammation processes.[10] Considering that VAMs commonly develop within 7 days of COVID-19 vaccine exposure (3–5 days),[11] it is highly likely that innate immunity might play a more important role in COVID-19 VAM than adaptive immunity. Furthermore, a study analysing the immune profile revealed that circulating levels of interleukin (IL)-18, a Th1-type immune response trigger mainly produced by monocytes and macrophages, were considerably elevated in patients with mRNA-1273 VAM compared with those in the control group. Another study confirmed IL-18-induced cardiomyocyte injury in experimental models,[12] supporting this notion. Another histopathological study analysing nine patients with iDCM after various SARS-CoV-2 vaccinations, except for mRNA-1273, revealed the presence of SARS-CoV-2 spike protein and CD4$^+$ T-cell-dominant inflammatory infiltrates in EMB samples, suggesting an autoimmune response.[13] Cases of acute necrotizing eosinophilic myocarditis, acute eosinophilic myocarditis and fulminant giant cell myocarditis following the SARS-CoV-2 vaccination have been reported.[14] Therefore, these facts suggest heterogeneous mechanisms for COVID-19 VAMs. Further detailed histological analyses of each clinical phenotype and vaccine type are required.

Second, our patient with VAM exhibited a DCM phenotype with septal midwall LGE on CMR. As septal midwall LGE is a characteristic finding in non-ischaemic DCM,[15,16] the patient's case was not initially predictive of VAM and required differentiation from classic DCM. However, in a recent multicentre observational study analysing patients with an LV ejection fraction $<$ 50% on CMR, septal midwall LGE was observed in 34% and 10% of patients with DCM and ischaemic cardiomyopathy, respectively.[17] This finding suggests that septal midwall LGE is not specific to DCM. Another multicentre study evaluating patients with stable acute myocarditis showed that LGE patterns are divided into four categories according to the inflammation distribution patterns: subepicardial and lateral myocardial walls, 41%; septal wall, 36%; other segments, 16%; and no LGE, 7%.[18] This finding underscores the heterogeneity in the pattern of acute myocardial inflammation. Moreover, patients with iDCM examined in previous studies exhibited inflammatory patterns with various LGE distributions, including septal midwall LGE.[19,20] In the current patient, EMB was performed, leading to the definitive diagnosis of iDCM. Therefore, all clinicians should consider iDCM and perform an EMB in patients with suspected VAM who present with a DCM phenotype.

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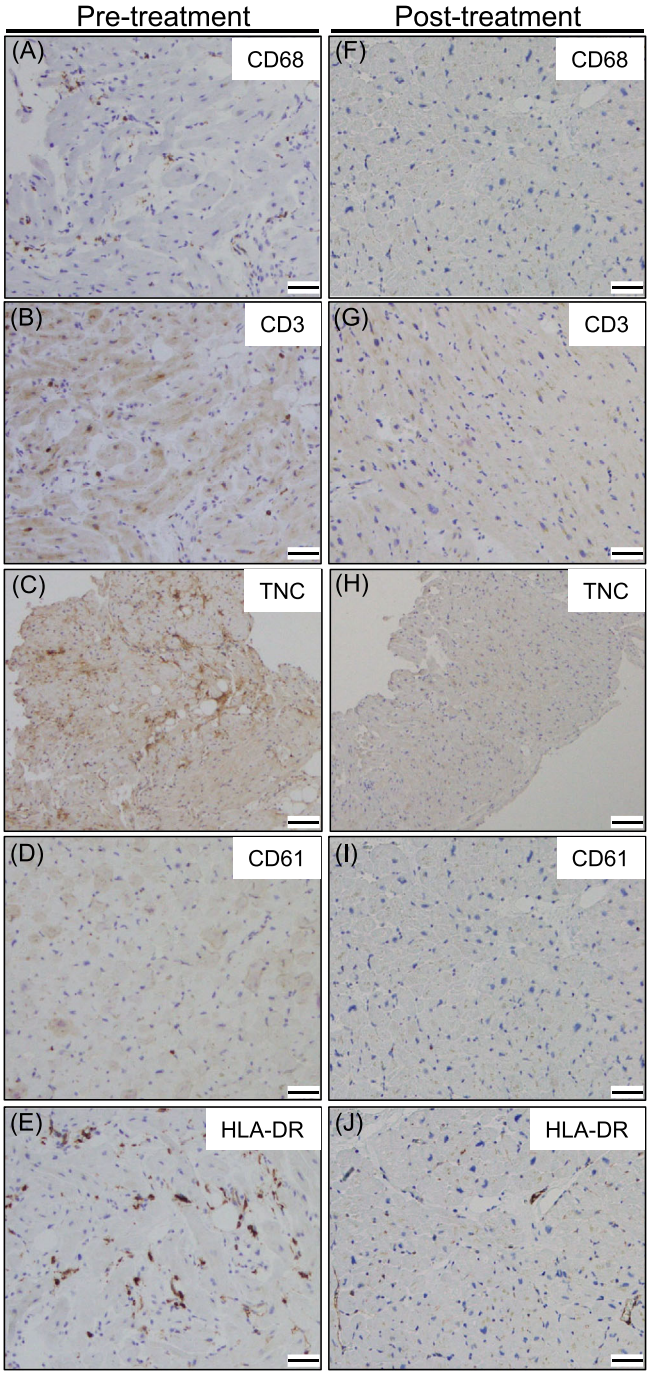
Figure 4 Effects of corticosteroid treatment on endomyocardial biopsy (EMB) findings of the right ventricle. Photomicrographs showing immunostaining against CD68 (A, F), CD3 (B, G), tenascin-C (TNC, 4C8) (C, H), CD61 (D, I) and human leucocyte antigen (HLA)-DR (E, J). Initial EMB histology reveals moderate myocyte hypertrophy with partial interstitial inflammatory infiltrates without associated myocyte necrosis. EMB immunohistochemistry shows CD68-positive macrophages (A) and CD3-positive T-cells (B) sporadically in the interstitium. Notably, the endocardium and interstitium are diffusely positive for TNCs (C). CD61 expression is partially positive in the endocardium and interstitium (D). HLA-DR is strongly expressed in capillary endothelial cells within the interstitium (E). Follow-up EMBs after corticosteroid treatment show significant improvement in the abnormal histological and immunohistochemical findings of the EMBs described above (F–J). Scale bars: 50 μm (A, B, D–G, I, J) and 100 μm (C, H).



Third, TNC was a useful indicator of disease activity in mRNA-1273-related iDCM in our case. As the expression of TNC, an extracellular matrix protein, is induced by cardiac injury or inflammation in response to various stimuli, TNC (4C8) has been used as an indicator of active myocarditis.[21] Similarly, in our case, cardiac dysfunction and LV remodelling recovered after corticosteroid treatment, and TNC expression disappeared concurrently. Therefore, TNC (4C8) may be valuable for both activity and therapeutic monitoring of VAM-related iDCM.

Fourth, this was a unique case of an older female patient with VAM following heterologous mRNA-1273 third-dose immunization after a primary two-dose BNT162b2 series. A large cohort study of approximately 23 million residents receiving two doses of the COVID-19 vaccine revealed 5.6 excess myocarditis events in 28 days per 100 000 vaccinees after BNT162b2/BNT162b2, 18.4 excess events per 100 000 vaccinees after mRNA-1273/mRNA-1273 and 27.5 excess events per 100 000 vaccinees after BNT162b2/mRNA-1273 among young males (ages 16–24). This evidence suggests that heterologous vaccination may be associated with a much higher risk of VAM compared with homologous vaccination among young males.[1] Furthermore, a prospective study conducted in Japan revealed that a heterologous mRNA-1273 third-dose booster following the primary two-dose BNT162b2 series induced a significantly higher titre of antibodies against the SARS-CoV-2 spike protein than a homologous booster, irrespective of age or sex.[22] Therefore, the greater immunogenicity induced by heterologous vaccination might have been involved in the development of VAM in our older female patient.

This case report has three limitations. First, the possibility of latent SARS-CoV-2 infection could not be completely ruled out as the SARS-CoV-2 viral genome was not analysed in the EMB. However, the patient had no recent travel history nor any contact with patients with confirmed COVID-19, including family members, and maintained social distancing. Hence, the patient was unlikely to have acute COVID-19. Second, the diagnostic accuracy of serological screening testing for myocarditis is limited. A prospective comparative study evaluating 124 patients with suspected myocarditis demonstrated that the viral serological test results were not always consistent with the detection of the viral genome in myocardial biopsy tissues by PCR.[23] In the present patient, viral infection was not completely ruled out as the viral genome was not examined during EMB. Generally, the levels of serologic viral antibody titres increase four-fold or more during acute infection.[24–26] As no significant increase was observed in the levels of paired viral antibody titres and no clinical signs and symptoms suggestive of acute viral infection were present, the patient was unlikely to have acute or active viral myocarditis. Lastly, the T1/T2 mapping method on CMR was not available at our institution. Although EMB remains the gold standard for diagnosing myocarditis, concerns such as sampling errors, low diagnostic yield and procedure-related complications have prompted increased interest in CMR as an alternative approach.[27] With the progress of imaging technologies, the T1/T2 mapping method, which can evaluate the signals specific to native cardiomyocytes, and extracellular volume fractions, which can determine myocardial damage, allow the accurate diagnosis of acute myocarditis. Compared with the conventional CMR diagnostic criteria, mainly based on T2-weighted and LGE images, the revised version can increase diagnostic sensitivity.[28] These modalities might have aided the diagnostic accuracy of iDCM in our case.

Conclusions

Herein, we describe the first case of biopsy-proven iDCM following heterologous mRNA-1273 immunization that was successfully treated with corticosteroids. Vaccine-related iDCM is rare but treatable if diagnosed early. Therefore, clinicians should not hesitate to perform EMB on patients presenting with the DCM phenotype following SARS-CoV-2 immunization.

Funding

None.

Conflict of interest statement

The authors declare no conflicts of interest.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Electrocardiography (ECG) performed at the referring hospital the day before admission. ECG reveals sinus tachycardia with complete right bundle branch block and left anterior hemiblock. High QRS voltage and broad T-wave inversions in the precordial leads are observed (heart rate, 118 bpm; QRS axis, −67 degrees; corrected QT interval, 436 ms; and R-wave amplitude in V4 lead, 3.0 mV).

Figure S2. Effects of corticosteroid treatment on the left ventricular morphology observed on cardiac magnetic resonance (CMR). Short axial view (A, C) and long-axis two-chamber view (B, D). A CMR performed upon admission reveals a marked enlarged left ventricle (A, B), which completely resolves as shown on the 6-month follow-up CMR after treatment (C, D). The figure shows the anatomic positioning of the left ventricle and chest wall before and after treatment.

Table S1. Serological tests for viral infections.
Video S1. Transthoracic echocardiography at pre-treatment: parasternal long-axis view.
Video S2. Transthoracic echocardiography at pre-treatment: parasternal short-axis view.
Video S3. The 6-month follow-up transthoracic echocardiography and post-treatment: parasternal long-axis view.
Video S4. The 6-month follow-up transthoracic echocardiography and post-treatment: parasternal short-axis view.

Katsuya Hashimoto
Department of Cardiovascular Medicine, Narita-Tomisato Tokushukai Hospital, Chiba, Japan

Hiroyuki Yamamoto
Department of Cardiovascular Medicine, Narita-Tomisato Tokushukai Hospital, Chiba, Japan
Department of Cardiology, Tokyo Medical University Hospital, Tokyo, Japan
E-mail: hyamamoto19700908@gmail.com

Yoshihiko Ikeda
Department of Pathology, National Cerebral and Cardiovascular Center, Suita, Japan

Jun Isogai
Department of Radiology, Asahi General Hospital, Asahi, Japan

Toru Hashimoto
Department of Cardiovascular Medicine, Narita-Tomisato Tokushukai Hospital, Chiba, Japan

Katsuya Hashimoto and Hiroyuki Yamamoto equally contributed to this work.

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