Lymphohistiocytic Myocarditis Possibly Due to Moderna mRNA-1273 Vaccine

A Case Report

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ABSTRACT

Objectives: Despite the clear benefits of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination in mitigating the impact of the coronavirus disease 2019 pandemic, there are emerging reports of postvaccination myocarditis, the majority of which are diagnosed based on the clinical and radiologic findings without biopsy confirmation. We report a case of biopsy-confirmed lymphohistiocytic myocarditis after Moderna mRNA-1273 vaccination.

Methods: We describe a case of a previously healthy 45-year-old woman who had palpitations, exercise intolerance, and syncope 1 week after her first mRNA-1273 vaccine dose. Laboratory tests and cardiac imaging were compatible with myocarditis. Given her unusual clinical presentation, an endomyocardial biopsy was performed to exclude other potential etiologies.

Results: The endomyocardial biopsy specimen showed patchy endocardial and intramyocardial lymphohistiocytic infiltrates with scattered eosinophils and focal myocyte injury. CD3 and CD68 immunostains confirmed the lymphocytic and histiocytic nature of the infiltrate, respectively. A focal histiocytic collection suggestive of an ill-defined granuloma was present. The histologic and immunohistochemical findings of a lymphohistiocytic myocarditis were highly suggestive of a postvaccination hypersensitivity reaction.

Conclusions: Myocarditis following SARS-CoV-2 vaccination is a rare adverse event. The findings of a lymphohistiocytic myocarditis with scattered eosinophils and a possible ill-defined granuloma are highly suggestive of a hypersensitivity reaction. The mechanism by which this inflammation occurs remains uncertain. Despite our findings, the benefits of SARS-CoV-2 vaccination far outweigh the risks.

INTRODUCTION

In December 2020, the US Food and Drug Administration issued Emergency Use Authorization for Pfizer BNT162b2 and Moderna mRNA-1273 vaccinations in response to global urgent need to control the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus and its associated disease, coronavirus disease 2019 (COVID-19), which has killed over 4.9 million people globally. Although vaccination has had a major role in mitigating new cases of COVID-19 in Canada and the United States, there is growing concern over possible side effects of COVID-19 prophylaxis. The Vaccine Adverse Event Reporting System (VAERS)

KEY POINTS

- Few cases of post–coronavirus disease 2019 (COVID-19) vaccination myocarditis have been characterized with biopsy. We report a case of CD3+ and CD68+ lymphohistiocytic myocarditis after Moderna mRNA-1273 vaccination.
- COVID-19 vaccination myocarditis should be considered for patients with palpitations, syncope, or exercise intolerance after vaccination. Most of these patients have a self-limited disease course.
- Histopathologic findings of a patient with myocarditis after COVID-19 vaccination reveal lymphohistiocytic infiltrates with an ill-defined granuloma, suggestive of hypersensitivity reaction.

KEY WORDS

Myocarditis; COVID-19; SARS-CoV-2; Biopsy; Histiocytes

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was established with the purpose of documenting voluntary reports of SARS-CoV-2 vaccination adverse events, either by medical staff or by the public.[1-3] Results of VAERS and several emerging case reports have concluded that one potential adverse effect is SARS-CoV-2 vaccination myocarditis (SC2VM), which typically has a self-limited disease course.

Since fall 2020, there have been several reports of myocarditis or pericarditis after BNT162b2 or mRNA-1273 vaccination.[1,4-7] Most of these cases have been in young, otherwise healthy men, with symptom onset soon after receiving the second dose of BNT162b2 or mRNA-1273.[8,9] Previous case series include 23 young adult men seen by the US Military Health System experiencing symptoms such as acute, severe chest pain after SARS-CoV-2 vaccination[6] and 8 cases of acute myopericarditis in 8 men aged 21 to 56 years.[9]

Although previous cases of SC2VM have been diagnosed through electrocardiogram (ECG), troponin, and cardiac magnetic resonance imaging (cMRI) findings, the exact cause of myocardial inflammation remains uncertain. To clarify the type of inflammatory infiltrate and elucidate aspects of SC2VM pathogenesis, endomyocardial biopsy (EMB) is required. The latter has not been routinely implemented to diagnose SC2VM due to potential risks of cardiac perforation, pericardial tamponade, and bleeding.[10,11] However, it remains the gold standard for definitive diagnosis of myocarditis.

To date, there have been a few reports of patients with SC2VM undergoing EMB after Janssen, Pfizer, and Moderna SARS-CoV-2 vaccinations, and results from these studies have been mixed.[12-14] Among reported biopsy results, 3 cases revealed no abnormality,[9,15] 2 cases revealed an admixture of T cells and macrophages,[13] 1 case revealed lymphohistiocytic myocarditis,[12] and 1 case revealed lymphocytic myocarditis.[14] We report a case of biopsy-confirmed lymphohistiocytic myocarditis after the first dose of the Moderna mRNA-1273 vaccine. The nature of the inflammatory infiltrate suggested a likely hypersensitivity reaction, although the causative etiology of SC2VM remains poorly understood.[1,4,7,16-20] Endomyocardial biopsy findings in our patient, in addition to previous and future cases, will be an asset in characterizing the pathogenesis of SC2VM, as well as its future prevention and treatment.

CASE REPORT

A 45-year-old healthy woman with no significant medical history noticed a progressive decline in her exercise capacity in the beginning of April 2021, approximately 1 week after her first mRNA-1273 vaccine dose. Prior to her vaccination, she was very physically active with moderate to strenuous physical activity five to six times per week. She denied any recent symptoms of a viral illness and relevant medication/illicit drug/alcohol use. Other than a prior cutaneous rash to amoxicillin, she has no other known allergies. There was no family history of premature coronary artery disease, sudden cardiac death, or other heart conditions.

Subsequently, she experienced multiple, intermittent episodes of palpitations lasting seconds to minutes and new generalized fatigue with exertional dyspnea. An ECG performed 1 month after her first vaccine dose showed T-wave inversions (TWIs) in leads III and augmented vector foot. In the beginning of July (3 months after her first vaccine dose and 1 month after her second dose), she suddenly felt profoundly unwell at rest with a spontaneous intense bout of palpitations, acute shortness of breath, and loss of consciousness for 5 minutes. During this episode, her husband noticed increased muscle tone, foaming at the mouth, apparent tonic-clonic movements, and urinary incontinence. However, there was no postictal state, tongue biting, or history of seizures. Her syncopal episode was initially deemed to be a seizure after she went to the emergency room (ER). During assessment, ECG revealed frequent premature ventricular contractions (PVCs) and abnormal QRS complexes. No ECG changes of myocardial ischemia/infarction, including TWIs, were noted. She was diagnosed with likely symptomatic ventricular tachycardia (VT) and given a Holter monitor for further outpatient assessment. CBC with automated differential, electrolytes, creatinine, urea, glucose, hemoglobin A_{1c}, and blood gases were within normal limits. A limited toxicology screen (acetaminophen, ethanol, and salicylates) was negative. No peripheral eosinophilia was observed. Troponin levels were not measured at that time. Head computed tomography (CT) and magnetic resonance imaging revealed no significant findings to account for the patient's loss of consciousness.

Two weeks following the patient's initial ER presentation (3.5 months after the first vaccine dose), the patient was called back to the ER following her outpatient Holter monitor showing multiple runs of sustained VT, the longest of which lasted 8 minutes. CBC with automated differential, electrolytes, creatinine, urea, and liver function tests were within normal limits; however, troponin I (high sensitivity) was dramatically elevated at 8,461 ng/L, and N-terminal pro-B-type natriuretic peptide (ntBNP) was elevated at 1,379 ng/L. A comprehensive autoimmune workup was negative. An ECG showed inferior TWIs and frequent PVCs. She was prescribed amiodarone, ramipril, metoprolol, aspirin, ticagrelor, and fondaparinux.

The patient underwent further testing to assess the underlying etiology of her palpitations, VT, and syncope. Transthoracic echocardiography (TTE) revealed a reduced left ventricular ejection fraction (LVEF) of 40%, akinesis of most of the inferior wall and basal to mid-inferolateral segments, compensatory hyperdynamic contractility of the apex, dyssynchronous septal wall motion abnormality, and mild mitral regurgitation. A cMRI revealed severe global hypokinesia with regional variability of wall motion but no dominant regional wall motion abnormalities. There were multiple areas of abnormal delayed gadolinium enhancement (DGE) in a nonischemic pattern of distribution (subepicardial DGE without convincing subendocardial involvement) involving portions of the inferior/inferoseptal, basal septum, and anterior/anteroseptal walls of the left ventricle. In addition, there was severe right ventricular systolic functional impairment observed without focal regional motion wall abnormalities. These findings were overall consistent with the 2018 Lake Louise criteria for cMRI-established myocarditis. Coronary angiogram revealed a 50% occlusive plaque of the posterior descending artery and 90% stenosis of 1 of 2 right posterolateral artery branches in its terminal 1 to 2 cm. The rest of the coronary

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arterial tree was completely normal. Carotid Doppler ultrasound was unremarkable.

Given the patient's unusual clinical presentation, right heart catheterization and EMB were performed a week after being recalled to the ER to exclude other potential etiologies. It showed 3 small fragments of endomyocardial tissue containing patchy endocardial and intramyocardial lymphohistiocytic infiltrates, including scattered eosinophils with accompanying focal myocyte injury, consistent with lymphohistiocytic myocarditis FIGURE 1A and FIGURE 1B. A focal histiocytic collection suggestive of an ill-defined granuloma was observed FIGURE 1C. No definite multinucleated giant cells were identified. CD3 FIGURE 1D and CD68 FIGURE 1E confirmed the presence of an admixture of T lymphocytes and histiocytes, respectively. Sirius red stain showed possible early collagen deposition. While no established myocardial scarring was noted, this may not be represented on the biopsy specimen due to the limited sample. In view of the EMB findings and given the temporal relationship of the patient's onset of symptoms relative to her first mRNA-1273 vaccine dose and worsening of symptoms after her second dose, postvaccination hypersensitivity myocarditis was believed to be the most likely diagnosis.

Subsequently, the patient was treated with prednisone and showed dramatic improvement in troponin I to 218 ng/L from a peak of 8,800 ng/L. Both cMRI and positron emission tomography/CT showed residual inflammatory changes in the inferior and inferior septal distribution. She improved clinically without complications and was discharged from the hospital.

DISCUSSION

Patients with myopericarditis after SARS-CoV-2 vaccination have generally followed a consistent clinical presentation. Nonpleuritic chest pain and fever were the most consistent complaints,[1,2,4,11,16] with other less frequent complaints including dyspnea, cough, and headache.[11] Most of the cases adhered to the recommended Immunize British Columbia vaccination dose interval of 6 to 8 weeks, reduced to 4 weeks in urgent outbreak situations. Symptomatic onset was typically 6 hours to 4 days after the second vaccination dose,[1,9] although onset up to 7 days and beyond has been reported.[11] Notable exceptions to these presentations include a male who experienced symptom onset 16 days after his first BNT162b2 dose[5] and a male who experienced symptoms 6 hours after his second BNT162b2 dose, which was 3 weeks after his first dose.[1]

There are some intriguing distinctions between the demographics and clinical history of our reported patient in comparison with previous documented cases of SC2VM. Our case is consistent with previous reports in that most cases of SC2VM occur in young, previously healthy patients. In contrast to male predominance in new cases, we report an otherwise healthy woman with SC2VM. Interestingly, our patient's symptoms were progressive decline in exercise tolerance, exertional dyspnea, and palpitations after her first mRNA-1273 dose, as well as a syncopal episode approximately 1 month after her second dose. During her ER visits, she did not report any prolonged fever or chest pain.

Workup for possible SARS-CoV-2 vaccination myopericarditis requires exclusion of other etiologies and assessment of cardiac inflammation by ECG, troponin, C-reactive protein (CRP), echocardiogram, cMRI, coronary angiography, and EMB. Previous case reports have involved patients negative for cardiotropic viruses and SARS-CoV-2 infection by polymerase chain reaction.[1,2,4,5,9,16] ECG findings have included ST elevation,[1,4] T-wave inversions,[6,11] nonspecific ST changes,[6,11] ST depression,[2,11] or diffuse ST changes.[11] Troponin I, troponin T, and CRP measurements were acutely elevated in most presentations.[4-7,9,11,16-18,20] TTE findings have been inconsistent, with several unremarkable examinations,[1,5,16] with some cases of borderline or low LVEF[7,9,16] and occasional studies revealing hypokinesis of the left ventricular walls.[4,9] Coronary angiography has generally been within normal limits. cMRI findings have confirmed acute myocarditis, with subepicardial DGE as well as myocardial edema, consistent with the 2018 Lake Louise criteria.[5,7,9,11,20]

The investigations and imaging findings of our patient are largely consistent with previous reports of SC2VM. Our patient's troponin I values were consistently elevated, peaking at 8,800 mg/L, and were at their maximum during the timeframe she was most symptomatic. Simultaneous elevation of ntBNP at 1,553 pg/mL strongly suggests that myocardial injury was the cause of her presentation. In-hospital ECG and Holter monitor for our patient revealed sustained and nonsustained runs of VT, frequent PVCs, and inferior T-wave abnormality.

TTE of our patient revealed reduced LVEF, akinesis of the inferior wall and of the basal to mid-inferolateral segments, compensatory hyperdynamic apical contractility, and dyssynchronous septal motion. Reduced LVEF in combination with segmental wall motion abnormalities supported her imaging diagnosis of myocarditis. The large areas of abnormal DGE on cMRI are very consistent with previously reported cases of SC2VM and with the 2018 Lake Louise criteria for acute myocarditis. Interestingly, coronary angiography of our patient revealed 50% occlusive plaque of the posterior descending artery (PDA) and 90% stenosis of one of two right posterolateral artery branches in its terminal 1 to 2 cm, which appears inconsistent with entirely patent coronary angiographic findings in most SC2VM cases. However, the narrowing in the right posterolateral branch appears to be out of keeping with the rest of the coronary angiographic findings, which were largely normal except for the 50% occlusive plaque in the PDA. The etiology of this focal narrowing is unknown, but it is not necessarily due to atherosclerosis. Other clinical considerations at the time included coronary vasospasm, vasculitis, spontaneous coronary artery dissection, and fibromuscular dysplasia. Further radiologic investigations were unrevealing. After retrospective review of the coronary angiogram, one proposed cause was myocarditis-related extrinsic compression.

The significant narrowing of the right posterolateral branch does raise the possibility of myocardial ischemia as a potential cause for the patient's cardiac dysfunction. However, the absence of a dominant regional wall motion abnormality and subepicardial without convincing subendocardial DGE would argue against myocardial ischemia. In addition, the significant biventricular hypokinesia appears out of keeping with such limited narrowing of the coronary

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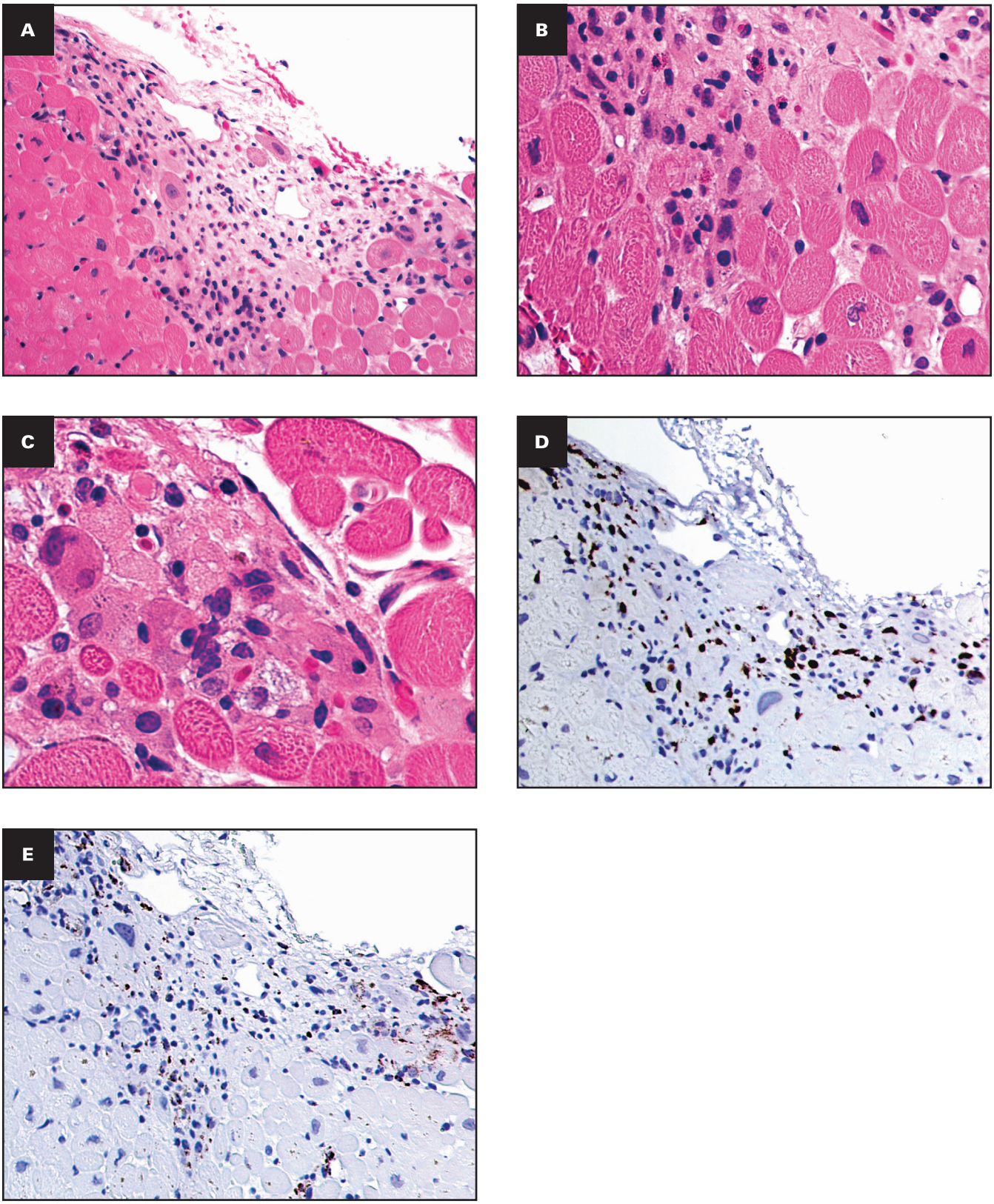

FIGURE 1 **A**, H&E-stained section of the endomyocardial biopsy specimen showing primarily endocardial-based inflammatory infiltrate with extension into subendocardial myocardium and associated myocyte injury (×200). **B**, At high power, the inflammatory infiltrate comprises lymphocytes, histiocytes, and scattered eosinophils (H&E, ×400). **C**, Focally, a vague histiocytic collection suggestive of an ill-defined granuloma is seen (H&E, ×600). The CD3 (**D**) and CD68 (**E**) immunostains highlight, respectively, T lymphocytes and histiocytes (×200).

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arterial tree, which is mostly normal otherwise. There was no notable myocytolysis, myocardial coagulative necrosis, or replacement fibrosis suggestive of ischemic injury on the biopsy specimen, although it is a limited sample and from the right ventricle. While the presence of TWIs on the ECG may suggest myocardial ischemia, TWIs may also be seen in other conditions, including cerebrovascular insults, pulmonary embolism, and perimyocarditis. They may also be normal variants. Certainly, their presence, especially when identified in more than one lead, should warrant further investigations.

Our patient's EMB findings were consistent with previously observed inflammatory infiltrates accompanying focal myocyte damage. To our knowledge, this is the second confirmed case of lymphohistiocytic myocarditis following Moderna mRNA-1273 vaccination. There exists a previous case report of lymphohistiocytic myocarditis after Janssen SARS-CoV-2 vaccination[12] and a case report of macrophages and T-cell infiltrate after Moderna mRNA-1273 vaccination.[13]

Although no causal relationship has been established between SARS-CoV-2 vaccination and myocarditis, SARS-CoV-2 vaccination does appear to increase the risk of myocardial inflammation. Several case reports have observed clusters of these diagnoses since introduction of the vaccine, including a near sixfold increase over background incidence in Israel.[5] There are several proposed mechanisms causing myocarditis after SARS-CoV-2 vaccination. These include autoimmune dysregulation resulting in lymphocytic and eosinophilic infiltration of the myocardium,[1,5,7,11,16,17] autoimmune targeting of an unnamed cardiac protein due to its molecular mimicry of the SARS-CoV-2 spike protein,[4,9,11] nonspecific systemic inflammatory response, and vaccine mRNA activation of cytokine storm.[5,11,17] Proposed factors leading to SARS-CoV-2 vaccination adverse effects include genetic predisposition to immune reaction[7] and previous subacute infections such as *Mycoplasma* or asymptomatic SARS-CoV-2.[4] There is a possibility that the lipid nanoparticle vaccine component of mRNA-1273 may be implicated in myocardial inflammation, as there have been reports of possible hypersensitivity-type reactions in patients receiving Moderna, Pfizer, and Janssen vaccines.[21] Although histologic findings of lymphocytic and eosinophilic infiltration appear to contribute to myocardial inflammation and damage in these cases, it remains unclear what is driving this targeted immune response to cardiac tissues.

With some notable exceptions,[13] most patients with SC2VM have a mild disease course with few or no complications. Administered medications included nonsteroidal anti-inflammatory drugs, steroids, and intravenous immune globulin,[11,20] and patients were discharged 2 to 8 days after admission.[5,8,11,18] Due to these reassuring findings, numerous authorities have concluded that the risk-benefit profile still clearly favors SARS-CoV-2 vaccination over refusal of prophylaxis.

Our study does have some limitations. Unfortunately, our patient was not subjected to cardiotropic viral testing or SARS-CoV-2 testing at the time of both her ER presentations. Thus, symptomatic myocarditis due to SARS-CoV-2 or other infections cannot be definitively ruled out. However, the patient did not report any symptoms of a recent upper respiratory infection and showed subjective improvement in symptoms and significant reduction in troponin I after initiation of corticosteroid therapy. While the timing of our patient's symptomatic onset and investigative findings are consistent with likely vaccine-induced myocarditis, we cannot confirm our patient's Moderna mRNA-1273 vaccination caused her myocarditis. There has yet to be a definitive causative mechanism of SC2VM established in the literature. Moreover, the possibility of a drug-induced hypersensitivity myocarditis could not be definitively excluded, as the EMB was performed 1 week following administration of various medications such as amiodarone, ramipril, ticagrelor, and metoprolol. While this possibility cannot be excluded, the patient's presentation and clinical course, as well as absence of other hypersensitivity reaction manifestations, such as angioedema and rash, suggest against a drug reaction. The temporal association of the patient's symptoms 1 week after her first vaccine dose; intensification of symptoms in the subsequent months, including the syncopal episode 3 months after the first dose resulting in her ER presentation; and radiographic findings preceded the start of any medications that may have caused drug-related hypersensitivity myocarditis. Furthermore, the patient's troponin levels have continued to decline consistently alongside clinical improvement despite being on these medications.

CONCLUSIONS

In summary, we report the case of a previous healthy 45-year-old woman who had palpitations, exercise intolerance, and syncope. The symptoms were associated chronologically with two doses of the Moderna mRNA-1273 vaccine. Laboratory tests, imaging, and EMB were consistent with lymphohistiocytic myocarditis. Ultimately, she was diagnosed with possible SARS-CoV-2 vaccination-induced myocarditis. Her recovery was uncomplicated, and she was discharged from the hospital with no long-term sequelae. Few patients with suspected SC2VM have had EMB to date, and histopathologic findings have been inconsistent with no abnormalities in some cases and lymphocytic or lymphohistiocytic abnormalities in others. Proof of a definitive mechanism causing SC2VM has not yet been established, although hypersensitivity reaction has been postulated. Despite our findings, we would like to emphasize that the benefits of SARS-CoV-2 vaccination continue to outweigh the risks of SC2VM or of contracting COVID-19.

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