ABSTRACT
A 48-year-old woman suffered from cardiogenic shock with fulminant myocarditis following the second dose of COVID-19 vaccine (mRNA-1273). Venoarterial extracorporeal membrane oxygenation and Impella support were essential in achieving hemodynamic stability. Endomyocardial biopsy revealed lymphocytic infiltration with predominant immunostaining for CD8- and CD68-positive cells. The left ventricular ejection fraction improved significantly after treatment with mechanical circulatory support. Myocarditis following COVID-19 mRNA vaccination may also occur in middle-aged women; it may be fulminating and require mechanical circulatory support. Although our results suggest the involvement of cytotoxic T lymphocytes and macrophages, further investigation is needed before these can be established as pathogenetic mechanisms.

Vaccination is being widely implemented due to the COVID-19 pandemic. Some cases of myocarditis following COVID-19 mRNA vaccination have been reported; however, the histopathologic and immunologic mechanisms by which this occurs remain unclear. We present a rare case of fulminating myocarditis in a middle-aged woman who received the second dose of a COVID-19 mRNA vaccine, and we consider the histopathologic findings of this case.

Case
A 48-year-old woman experienced persistent malaise for 1 week after receiving the second dose of the Moderna COVID-19 (mRNA-1273) vaccine; dyspnea appeared on the 7th day following vaccination. Her symptoms did not improve, and she was taken to the emergency department of her local hospital on the 9th day after vaccination. The second dose was administered 28 days after the first, and she had also experienced malaise after the first dose, which had resolved spontaneously. She had no significant past medical history and was postmenopausal. She had never experienced any previous side effects to the vaccine, and there was no history of autoimmune disorders in the patient or her family. She had been taking acetaminophen since vaccination, but she had not used any other drug. She presented with the following: body temperature 36.1°C; blood pressure of 83/60 mm Hg; pulse rate of 113 beats/min; respiratory rate of 24 breaths/min; and saturation of 88% on 6L of oxygen. She was pale, with cold, clammy
Novel Teaching Points

- Fulminant myocarditis following COVID-19 mRNA vaccination may occur in middle-aged women.
- Early introduction of MCS is important in fulminant myocarditis.
- Cellular immunity may be involved in the pathogenesis of this disease.

extremities. Laboratory tests showed multiple-organ damage and the following: lactate at 10.8 mmol/L (normal: 0.4-0.8 mmol/L); aspartate aminotransferase at 5358 U/L (normal: 13-30 U/L); alanine aminotransferase at 3079 U/L (normal: 7-23 U/L); lactate dehydrogenase at 4453 U/L (normal: 124-222 U/L); creatine kinase (CK) at 15,962 U/L (normal: 41-153 U/L); CK-myocardial band of 349 ng/mL (normal: < 5 ng/mL); and creatinine at 1.64 mg/dL (normal: 0.46-0.79 mg/dL). Troponin I and brain natriuretic peptide levels increased to 25.2 ng/mL (normal: 0.46-0.79 mg/dL). Therefore, to unload the left ventricle and relieve pulmonary congestion, the IABP was changed to an intra-aortic balloon pump (IABP) and an intra-aortic balloon pump (IABP) was immediately introduced with ventilatory support, owing to cardiogenic shock. The VA-ECMO cannula was inserted through the right femoral artery and vein, and the IABP was inserted through the left femoral artery. After establishing mechanical circulatory support (MCS), coronary angiography was performed, which demonstrated no significant stenosis. An endomyocardial biopsy (EMB) of the right ventricular septum was performed with the right jugular vein approach. A polymerase chain reaction test result for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was negative. The merase chain reaction test result for severe acute respiratory virus. Paired serology also showed no significant increase in the levels of the antibodies of the abovementioned viruses. The patient underwent rehabilitation and was discharged on day 23 with no residual symptoms.

Discussion

With the widespread use of COVID-19 mRNA vaccines, postvaccination myocarditis is attracting attention. This condition is conventionally known to be more common in young males under 30 years of age, and it is more common after the second dose than after the first; in many cases, these complications occur within a week of vaccination. Moreover, disease severity has been reported to be mild in most cases, and cases requiring MCS are very rare. Although the Lake Louise Criteria of cardiac MRI are often used as a noninvasive method of diagnosing myocarditis, the 2020 American Heart Association guidelines recommend EMB for diagnosing suspected cases of fulminant myocarditis requiring MCS, such as ours. Most of the reported cases of myocarditis following COVID-19 mRNA vaccination have been mild, and diagnosis is confirmed by cardiac MRI accordingly, but there are several histopathologic studies on myocarditis following COVID-19 mRNA vaccination. In a large Israeli cohort of approximately 5.1 million people given the COVID-19 vaccine, 142 people were diagnosed with myocarditis after receipt of the BNT162b2-mRNA vaccine. EMB samples obtained from only 2 people showed foci of endo-interstitial edema and neutrophils, along with macrophages and lymphocytes with no giant cells. In the histopathologic pictures of 2 recently reported cases of post—COVID-19 vaccination myocarditis, infiltration by T lymphocytes and macrophages was visible, and B lymphocytes and plasma cells were also seen. Lim et al. reported fulminant myocarditis requiring VA-ECMO following the first dose of the BNT162b2-mRNA vaccine, in a woman; in this case, histopathologic examination of EMB samples revealed marked and diffuse lymphocytic infiltration of the myocardium. Additionally, in a case report of fulminant myocarditis with systemic hyperinflammation after COVID-19 vaccination, an EMB showed cardiomyocytes with minute foci of cytoplasmic vacuolization and rare interstitial lymphocytic infiltrates. Histopathology of the myocardium in our case
showed inflammatory cell infiltration, mainly lymphocytes, with some cytotoxicity. Immunostaining showed that the staining for CD8 was more positive than that for CD4; moreover, the staining for CD68 was positive, suggesting that cytotoxic T lymphocytes and macrophages may be largely involved in myocardial inflammation. In a case report showing the histopathology of fulminant lymphocytic myocarditis (not following COVID-19 vaccination), the myocardium was infiltrated with CD8-dominant T lymphocytes and macrophages, similar to our case.\textsuperscript{6} CD3 and CD68 positive findings are one of the hallmarks of immunostaining for lymphocytic myocarditis, but they are not disease-specific. However, T lymphocytes and macrophages are presumed to be involved in the pathogenic mechanisms. To date, no histopathologic findings have been established to distinguish myocarditis associated with COVID-19 vaccine from myocarditis that is not associated with COVID-19 vaccine.

Many reports have been made on COVID-19 infection and myocardial injury. In previous reports, the proposed mechanisms of myocardial injury are direct damage to the cardiomyocytes, systemic inflammation, myocardial interstitial fibrosis, interferon-mediated immune response, coronary plaque destabilization, and hypoxia. Whether
myocardial injury has a common mechanism via the mRNA vaccine vs via COVID-19 infection is currently unclear. A recent meta-analysis speculated that myocarditis may develop when the immune system detects genes in the vaccine as antigens, thereby activating proinflammatory cascades and immune pathways. Other possible mechanisms include induction of cytokine expression via anti-idiotypic cross-reactive antibodies in the myocardium and abnormal induction of apoptosis leading to inflammation of the myocardium and pericardium. In addition to age and gender, certain genetic predispositions have been speculated to be risk factors for the development of myocarditis, but the details are unknown. Furthermore, the clinical course of fulminant myocarditis following COVID-19 vaccination also has not been established. The patient in this case was able to be weaned off MCS in a relatively short period of time, even though the patient’s condition was initially lethal. Previous reports have suggested that left ventricular unloading with an Impella suppresses inflammatory cell infiltration in fulminant myocarditis. We speculated that, also in this case, left ventricular unloading by early introduction of an Impella CP may have suppressed inflammatory cell infiltration, and improved left ventricular contraction in a relatively short period. Therefore, early introduction of MCS with left ventricular unloading is important in fulminant myocarditis. The exact mechanism is still unclear, and more cases need to be accumulated; however, this report helps confirm that classic lymphocytic fulminant myocarditis can be triggered by a COVID-19 mRNA vaccine.

Conclusions

Fulminant myocarditis following COVID-19 mRNA vaccination may occur in middle-aged women, and early introduction of MCS is important in severe cases. Although cellular immune mechanisms may be involved in the pathogenesis, further investigations are needed before establishing the pathogenetic mechanisms of COVID-19 vaccine–related myocarditis.

Funding Sources

Japan Society for the Promotion of Science (JSPS) KAKENHI, grant number JP21K08025 (to T.O.).

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA vaccines. Circulation 2021;144:471-84.
2. Mevorach D, Anis E, Cedar N, et al. Myocarditis after BNT162b2 mRNA vaccine against Covid-19 in Israel. N Engl J Med 2021;385:2140-9.
3. Verma AK, Lavine KJ, Lin CY. Myocarditis after Covid-19 mRNA vaccination. N Engl J Med 2021;385:1332-4.

4. Lim Y, Kim MC, Kim KH, et al. Case report: acute fulminant myocarditis and cardiogenic shock after messenger RNA coronavirus disease 2019 vaccination requiring extracorporeal cardiopulmonary resuscitation. Front Cardiovasc Med 2021;8:758996.

5. Abbate A, Gavin J, Madanchi N, et al. Fulminant myocarditis and systemic hyperinflammation temporally associated with BNT162b2 mRNA COVID-19 vaccination in two patients. Int J Cardiol 2021;340:119-21.

6. Jurcova I, Roczek J, Bracamonte-Baran W, et al. Complete recovery of fulminant cytotoxic CD8 T-cell-mediated myocarditis after ECMELLA unloading and immunosuppression. ESC Heart Fail 2020;7:1976-81.

7. Wang M, Wen W, Zhou M, Wang C, Feng ZH. Meta-analysis of risk of myocarditis after messenger RNA COVID-19 vaccine. Am J Cardiol 2022;167:155-7.

8. Spillmann F, Van Linthout S, Schmidt G, et al. Mode-of-action of the PROPELLA concept in fulminant myocarditis. Eur Heart J 2019;40:2164-9.

Supplementary Material

To access the supplementary material accompanying this article, visit CJC Open at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2022.02.004.