

A Case of Myopericarditis After the Second Dose of mRNA COVID-19 Vaccine in a Patient With a History of Myopericarditis

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ABSTRACT: Vaccination is important for the prevention of coronavirus-induced disease 2019 (COVID-19) caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) and to protect persons with a high risk for complications. There have been reports of myopericarditis following COVID-19 vaccination, especially in adolescent males and young adults. Breakthrough infections, such as the Delta or Omicron variant of SARS-CoV-2, have raised great concern about the necessity for repeated doses of the vaccine. A case of myopericarditis after the second dose of COVID-19 mRNA-1273 (Moderna) vaccine in a 23-year-old man with a prior episode of viral myopericarditis is presented. He received the second dose of the COVID-19 mRNA vaccine, after which he developed persistent midsternal chest pain and he was subsequently transferred to our emergency department. An echocardiogram showed a trivial inferior pericardial effusion with diffuse left ventricular systolic dysfunction. He was treated with colchicine from the first day of hospitalization with a diagnosis of myopericarditis. His chest pain had resolved by the third day, and left ventricular wall motion was dramatically improved by the seventh day of hospitalization. A strong response to the second vaccination in the present case suggests that the prior history of myopericarditis is evidence of strong congenital or acquired immunological features in this individual. Individuals with such a strong immune response may be more likely to develop myopericarditis after mRNA vaccination. Immunization against COVID-19 is currently recommended from a risk-benefit standpoint. We advised the patient to avoid additional COVID-19 mRNA vaccines because of this episode. The risk of COVID-19 weighed against myopericarditis associated with the mRNA vaccination should be considered on a case-by-case basis. This case may help us better understand the mechanism of myopericarditis following COVID-19 mRNA vaccination.

KEYWORDS: Myocarditis, pericarditis, myopericarditis, COVID-19, SARS-CoV-2, mRNA vaccine, case report

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Introduction

The clinical course of myocarditis varies from mild to fulminant. The onset of myocarditis often follows a viral illness. In addition, certain nonviral infections and autoimmune syndromes remain important causes of myocarditis.¹ Postvaccination myocarditis, which may result from vaccine-related autoimmunity, has been reported as a rare adverse event after especially smallpox vaccination.² However, in many cases, the underlying cause has not been identified. The currently available vaccines have been shown to be highly effective against severe coronavirus induced disease 2019 (COVID-19).³ There are some reports of myopericarditis as a rare complication of mRNA COVID-19 vaccination, especially in adolescent males.^{4–6} Breakthrough infections, such as the Delta or Omicron variant of SARS-CoV-2, have raised great concern about the necessity for repeated dose of the vaccine.⁷ Especially, the Omicron variant, a highly mutated virus of SARS-CoV-2, poses a very high risk of infection and has been designated as a variance of concern by the World Health Organization (WHO) with recommendations for continued vaccination.⁸

A case of myopericarditis after the second dose of COVID-19 mRNA-1273 vaccine in a 23-year-old man with a prior event of myopericarditis is described. In this case, we focused on the mechanism of myopericarditis after COVID-19 vaccination using mRNA vaccine, and discussed the indication of

repeated administration of mRNA vaccine against the risk of myopericarditis.

Case Report

The patient was a 23-year-old Japanese man with a history of myopericarditis 3 years earlier, which resolved after 1 week of hospitalization. Despite the lack of serological evidence, he was tentatively diagnosed as having had viral myopericarditis due to his clinical course, new chest pain, changes in ECG (ST segment elevation at inferior leads), left ventricular wall motion abnormalities in echocardiogram with a trivial inferior pericardial effusion, and transient changes in laboratory results (creatinine kinase 473 U/L, creatine kinase-isoenzyme MB 42.3 U/L elevation, etc.). There were no other identifiable causes of the symptoms and findings. This diagnosis corresponded to the possible case of myopericarditis according to the CDC's definition of myopericarditis.⁹ These abnormalities improved 5 days after admission without medication. Ever since his cardiac function returned to normal, he had not taken any medication. Due to the COVID-19 pandemic, vaccination was made available to and recommended even for healthy young people in Japan. He received his first dose of the COVID-19 mRNA-1273 (Moderna) vaccine without any particular symptoms. Four weeks later, he received the second dose, after which he had a high fever of 38.9°C the next day. At midnight 2 days



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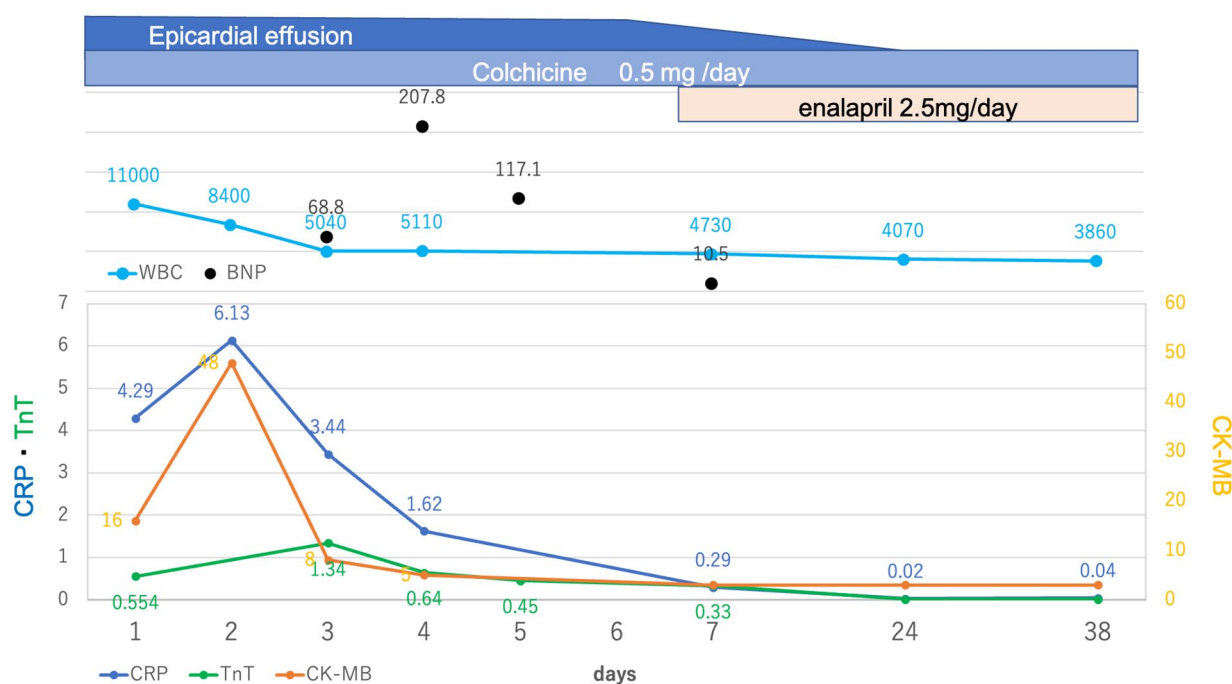


Figure 1. Clinical course. Myocardial enzymes (TnT, CK-MB) and inflammatory markers (WBC, CRP) were transiently elevated. These findings, including pericardial effusion, improved over the clinical course. BNP transiently increased several days after these changes, and returned to the normal range at discharge. Colchicine was continued for 1 month after discharge and ACE-I for 6 months. WBC, white blood cell (cell count/ μ L, normal range 3300–8600/ μ L); CRP, C-reactive protein (mg/dL, normal ≤ 0.14 mg/dL); TnT, high-sensitivity troponin T (ng/mL, normal ≤ 0.1 ng/mL); BNP, B-type natriuretic peptide (pg/mL, normal ≤ 18.4 pg/mL); CK-MB, creatine kinase-isoenzyme MB (U/L, normal ≤ 12 U/L).

following his second vaccination, he developed persistent mid-sternal chest pain. The pain had not subsided by early morning the following day, and he was subsequently transferred to our emergency department and admitted to our hospital.

The following vital signs were recorded: temperature of 36.9°C, blood pressure of 112/72 mmHg, pulse rate was 86/min, respiratory rate of 30/min, and oxygen saturation of 100% on room air. Physical examination was unremarkable, with no pericardial friction rub on auscultation. His initial electrocardiogram showed sinus rhythm with atrial premature complexes in a pattern of bigeminy and right axis deviation, ST segment elevations in leads II, aVf, V4–6, and tall T waves in leads V3–6. An echocardiogram showed a trivial inferior pericardial effusion with diffuse left ventricular systolic dysfunction, the ejection fraction was less than 50% (Supplemental Video1–6).

His initial laboratory tests showed a high white blood cell count of 11000/ μ L (normal range 3300–8600/ μ L), neutrophil-dominant (75.7%). The C-reactive protein (CRP) level was 4.29 mg/dL (normal ≤ 0.14 mg/dL), high-sensitivity troponin T (TnT) was 0.554 ng/mL (normal ≤ 0.1 ng/mL), and B-type natriuretic peptide (BNP) was 68.8 pg/mL (normal ≤ 18.4 pg/mL). A SARS-CoV-2 antigen test of specimen obtained from nasal mucosa was negative. Serology of various viruses known as causes of myopericarditis were all negative.

He was treated with colchicine (0.5 mg once daily) from the first day of hospitalization with a presumptive diagnosis of myopericarditis. For follow-up, we performed bedside

echocardiography daily until discharge and electrocardiogram was performed several times.

CRP peaked on the second day of hospitalization (6.13 mg/dL), TnT peaked on the third day (1.34 ng/mL), and BNP peaked on the fourth day (207.8 pg/mL) (Figure 1).

Contrast-enhanced cardiac magnetic resonance imaging (MRI) performed on day 5 showed linear midmyocardial late gadolinium enhancement in the septal and apical walls of the left ventricle, consistent with acute myocarditis (Figure 2).

Coronary angiography and endomyocardial biopsy were performed on day 6. Angiography showed normal coronary arteries, and neither obvious lymphocytic infiltration of the myocardium nor cardiomyocyte damage were observed on myocardial biopsy specimens (Figure 3).

His chest pain had resolved by the third day, and left ventricular wall motion was dramatically improved by the seventh day of hospitalization with the ejection fraction of 70%. He was discharged on colchicine and an angiotensin-converting enzyme inhibitor (ACE-I; enalapril 2.5 mg once daily) to prevent subsequent cardiac dysfunction. Colchicine was continued for 1 month after discharge and ACE-I for 6 months. This patient had no recurrence of chest pain for more than 6 months after discharge, and serial echocardiography confirmed the disappearance of the remaining pericardial fluid 1 month after discharge. Although this episode was not fatal and there was no residual cardiac dysfunction, we advised the patient to avoid additional COVID-19 mRNA vaccines because of this episode.

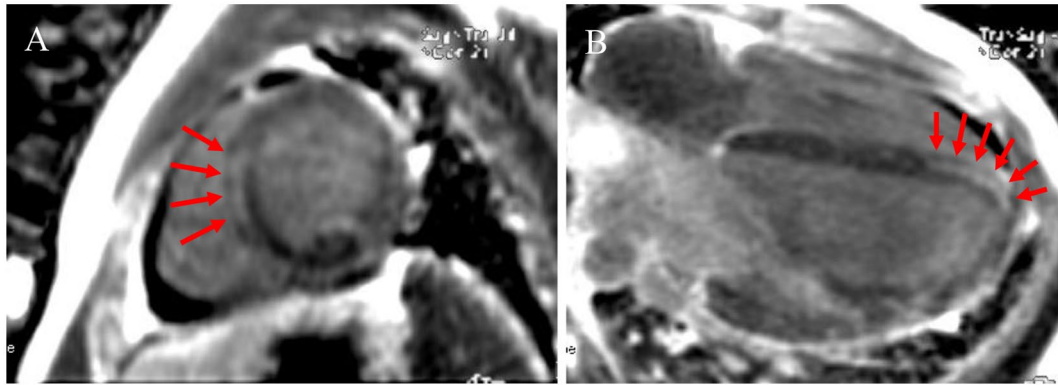


Figure 2. Contrast-enhanced cardiac magnetic resonance imaging performed on day 5, short-axis views (A), 4-chamber views (B). Linear midmyocardial late gadolinium enhancement is seen in the septal and apical walls of the left ventricle (red arrow).

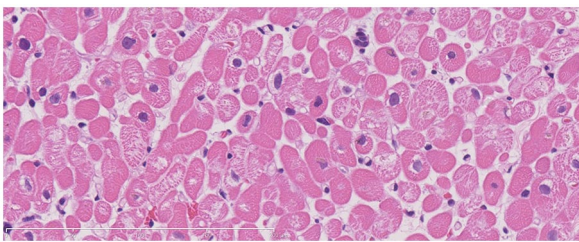


Figure 3. Endomyocardial biopsy specimens show no obvious lymphocytic infiltration of the myocardium and no cardiomyocyte damage. (Hematoxylin and eosin staining, original magnification $\times 40$, The white bar indicates 200 μm).

Discussion

A phase 3, randomized, clinical study reportedly showed the safety and efficacy of the mRNA-1273 vaccine describing no safety concerns besides transient local and systemic reactions.³ However, the CDC recently reported cases of a possible association between the COVID-19 mRNA vaccine and myocarditis/pericarditis.¹⁰

Data from the US Vaccine Adverse Event Reporting System (VAERS) up to June 11, 2021, show reports of 1784 possible cases of myocarditis after approximately 300 million doses of COVID-19 mRNA vaccine, 67% of which were observed after the second vaccination. Males accounted for 79% of these reports, the majority of whom were under 30 years of age and the median age was 24 years. The median time from vaccination to onset of symptoms was 3 days, and the estimated rate of myocarditis was 12.6 cases per million doses of the second mRNA vaccine in persons between the ages of 12 and 39 years.^{4,10} Most of these patients had elevated levels of troponin T and CRP, none had eosinophilia, and most who underwent magnetic resonance imaging showed late myocardial gadolinium enhancement. Regarding treatment, there are reports of the use of non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, prednisone, etc., and most cases were reported to improve within approximately 1 week.⁴⁻⁶ However, since fulminant myocarditis was reported in several cases, careful observation is required.^{11,12}

In the present case, the course from mRNA vaccination to symptom onset was consistent with these previous reports, and

transient elevations of biochemical parameters and left ventricular dysfunction on echocardiogram were observed. In addition, as in previous reports, endomyocardial biopsy showed no obvious myocardial infiltration,^{5,6} but magnetic resonance imaging revealed late myocardial gadolinium enhancement.^{4,5,11-14} Based on these findings, we diagnosed our case as confirmed myocarditis according to the CDC's definition of myocarditis.⁹

The mRNA-1273 vaccine is an mRNA-based vaccine that encodes the full-length spike glycoprotein of SARS-CoV-2. Vaccine mRNA stimulates host cells to synthesize spike glycoproteins and the host immune response produces antibodies against the target virus. There are several possible mechanisms by which this mRNA vaccine may cause myocarditis.

First, a molecular mimicry mechanism between synthesized spike glycoproteins and unknown cardiac proteins has been suggested.^{4,6,15} Antibodies to the SARS-CoV-2 spike glycoprotein have been reported to cross-react with human peptide protein sequences.¹⁶ This could explain the high incidence of myocarditis after the second vaccination. However, since cases of myocarditis have been reported even after the first vaccination, multiple mechanisms need to be considered.^{4,6}

Another potential mechanism is an immune response or hyperimmunity to the mRNA vaccine. The mRNA molecule is immunogenic and can be attacked before it reaches the target cell. However, the nucleoside-modified mRNA contained in the vaccine has its immunogenicity reduced.^{4,17} In the presence of a genetic predisposition, the immune response to mRNA does not decrease after nucleoside modification, and the immune system may detect the mRNA in the vaccine as an antigen, leading to a pro-inflammatory cascade and activation of the immune pathway, resulting in myocarditis. In addition, the high prevalence of myocarditis after mRNA vaccination among adolescents may be explained by innate and hyperimmune mechanisms.^{4,18} If repeated antigen exposure enhances the immune response, this can also explain why myocarditis has been more prevalent after the second vaccination.

Interestingly, the present case had a history of suspected viral myocarditis, and this, therefore, plays an important

role in our consideration of the possible mechanisms of myopericarditis after mRNA vaccination. The history of myocarditis, in this case, does not seem to indicate a past coronavirus infection. If past coronavirus infection sensitization had induced an immune response to the vaccine, a stronger immune response would have been observed after the first vaccination. Therefore, the prior history of myopericarditis in the present case is considered to indicate strong congenital or acquired immunological features in the individual. Such individuals may be more likely to develop myopericarditis after mRNA vaccination. However, the limitation of this argument is that it cannot be said that the current event is not a relapse of the initial event.

Kojima et al reported the case of mRNA vaccine-related myocarditis with prior history of myocarditis associated with *Campylobacter jejuni*.¹⁹ In this case, they described that the mechanism of myocarditis induced by mRNA vaccination remains unclear, and that there may be something more in addition to the common pathogenesis mechanism if there is a history of myocarditis. They advised the patient to avoid the booster COVID-19 mRNA vaccine because of the episode.

Vaccination against COVID-19 infection is currently recommended as the benefit outweighs the risk and shows a favorable balance for people over 12 years of age. When considering the indications for repeated vaccination, the present case will help us in discussing the pros and cons of vaccination in each case. The risk of COVID-19 weighed against myopericarditis associated with the mRNA vaccination should be considered on a case-by-case basis. Accumulation of cases with a similar course may elucidate the potential mechanism of myopericarditis following mRNA vaccination.


Author Contributions

KF: principle investigator, patient management, manuscript preparation. KK: overall direction of the patient management and manuscript preparation.

Ethics Statement

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. The patient's informed written consent was obtained; patient confidentiality and data were protected and encrypted.

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Supplemental Material

Supplemental material for this article is available online.

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