Acute Perimyocarditis in an Adolescent Japanese Male after a Booster Dose of the BNT162b2 COVID-19 Vaccine

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Running title: Perimyocarditis After COVID-19 Booster Dose

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Abstract
Perimyocarditis is a rare and serious cardiac complication following COVID-19 vaccination. Young males are most at risk after the second dose. With the introduction of the booster (third) dose, some reports have focused on the risk of perimyocarditis after a booster dose. However, no currently available report in Japan has comprehensively described this phenomenon. A healthy 14-year-old Japanese male, who had completed a two-dose primary series of the BNT162b2 (Pfizer-BioNTech) vaccine six months prior, developed fever and chest pain within 24 hours after a homologous booster dose. He was transferred to our institute because of worsening chest pain. A multiplex PCR test showed no evidence of active viral infections, including SARS-CoV-2. Electrocardiography revealed ST-segment elevation in almost all leads, suggesting pericarditis. Echocardiography showed normal systolic function. Laboratory data demonstrated C-reactive protein levels of 8.8 mg/dL and elevated cardiac damage markers (troponin T: 1.9 ng/mL, creatine phosphokinase:1527 U/L, MB isoenzyme: 120 U/L), suggesting myocarditis. He was diagnosed with perimyocarditis associated with the booster dose, which was confirmed by cardiac magnetic resonance imaging four days after initial symptoms. Chest pain improved spontaneously along with a resolution of electrocardiographic findings and laboratory data within several days. He was discharged eight days after admission. Perimyocarditis is less frequent after a booster dose than after primary doses. In this case, the patient with booster-dose-associated perimyocarditis showed favorable clinical course without severe sequelae. The patient’s clinical course was consistent with findings on previous large-scale reports on primary-dose-associated perimyocarditis and case series on booster-dose-associated perimyocarditis.

Keywords: booster dose, COVID-19, first case, perimyocarditis, vaccination
Introduction

There is increased evidence of myocarditis or pericarditis, or both, after completion of the primary set of coronavirus disease 2019 (COVID-19) mRNA vaccination. The most recent large-scale study in the US shows that the risk is highest in young males aged 18 to 25 years, one to seven days after the second dose of the vaccine (Wong et al. 2022). The incidence is rare, with only 411 cases being reported among 15 million people aged 18 to 64 years who received 16,912,716 doses of BNT162b2 (Pfizer-BioNTech) and 10,631,554 doses of mRNA-1273 (Moderna). Most cases presented with a benign short-term clinical course (Oster et al. 2022). Shortly after the COVID-19 booster (third) dose was introduced, a few reports focused on investigating the risk of perimyocarditis after a booster dose. As of February 20, 2022, Centers for Disease Control and Prevention reported 32 confirmed cases of myocarditis among adolescent boys in the United States of America. The study demonstrated that myocarditis was reported less frequently after the booster dose than with primary doses, with similar good short-term clinical outcomes (Hause et al. 2022).

In Japan, people aged over 12 years are eligible for a booster dose, and 78 million people (61.8% of the population) have completed it as of July 1, 2022 (Prime Minister’s Office of Japan 2022). However, no report regarding booster-dose-associated perimyocarditis is currently available in Japan to provide detailed clinical progress and other relevant findings. Herein, we present, to our knowledge, the first report of perimyocarditis after a booster dose of the COVID-19 mRNA vaccine in Japan.

Case Presentation

A healthy 14-year-old Japanese male, who had completed a two-dose primary series of the BNT162b2 (Pfizer-BioNTech) mRNA vaccine six months prior without any side effects, developed low grade fever and chest pain within 24 hours after a homologous third booster
dose. He was consequently transferred to our institute due to worsening chest pain. On admission, his vital signs were stable, with a body temperature of 37.7 °C, respiratory rate of 18/ minute, heart rate of 100 bpm, blood pressure of 114/78 mmHg, and oxygen saturation of 98% on ambient air. Physical examination was unremarkable, although inspiration aggravated the patient’s chest pain. A FilmArray multiplex PCR test (bioMérieux Inc., USA) of nasopharyngeal swab showed no evidence of active viral infections, including that of SARS-CoV-2, as well as other viral or bacterial pathogens known to cause upper respiratory tract infection (Table 1). Electrocardiography revealed ST-T segment elevation with upward concavity in leads I, II, III, aVF, and V2-V6, suggesting pericarditis (Fig. 1A). Echocardiography showed normal systolic function with a left ventricular ejection fraction (LVEF) of 59%. Coronary arteries were normal, and pericardial effusion was not evident. Laboratory data demonstrated serum levels of C-reactive protein at 8.8 mg/dL (range: < 0.14), aspartate aminotransferase at 112 U/L (range: 13-30), and lactase dehydrogenase at 301 U/L (range: 124-222). Notably, elevation of cardiac damage markers (troponin T: 1.9 ng/mL, range: < 0.014) and creatine kinase of 1527 U/L (range: 59-248) with an MB isoenzyme of 120 U/L (range: <12)) were observed, suggesting the presence of myocarditis. Brain natriuretic peptide (BNP) was mildly elevated at 22.9 pg/mL (range: < 18.4) (Table 2). Serum antibody showed negative SARS-CoV-2 IgM (titer: 0.2 C.O.I (range: < 1.0)) and positive Anti-S IgG (titer: 42.1 AU/mL (range: < 1.0)), confirming recent vaccination. Consequently, the patient was diagnosed with perimyocarditis associated with the booster dose of the BNT162b2 mRNA vaccine. This was confirmed by cardiac magnetic resonance imaging (CMR) four days after the initial symptoms, indicating perimyocardial inflammation, which presented as late gadolinium enhancement on the pericardium and focal myocardium (Fig. 1B). Chest pain improved spontaneously with only bed rest, along with the subsequent normalization of the electrocardiographic findings, seven days after initial symptoms. Troponin T peaked on
admission and returned to normal after seven days. Other laboratory data also normalized by
day seven post-admission (Table 2). Two weeks post-admission, serum antibody against
SARS-CoV-2 IgM remained negative (titer: 0.5 C.O.I) but Anti-S IgG increased to 1690
AU/mL. Speckle-tracking echocardiography, six days after initial symptoms, showed no
ventricular dyssynchrony in any LV segments, suggesting no abnormal LV wall motion delay
(Fig. 1C and D). The patient was discharged eight days after admission without cardiac
sequelae.

Ethical review and approval was not required for the study on human participants in accordance
with local legislation and institutional requirements. The patient and the patient’s family
provided written informed consent for the publication of this case report.

Discussion

Literature regarding perimyocarditis after a booster dose is limited to a few reports, suggesting
that it is less frequent than with primary doses (Hause et al. 2022). The smaller number of
booster vaccinations than that of primary first and second doses, may partly explain the absence
of reports of perimyocarditis after booster vaccinations in Japan. In this present case, the patient
with booster-dose-associated perimyocarditis showed favorable clinical course without severe
sequelae with no need for any specialized treatments. This was consistent with a recent large-
scale study in the US, which reported no fatalities among 826 cases with primary-dose-
associated myocarditis in people younger than 30 years of age treated with nonsteroidal anti-
inflammatory drugs (87.1%) and glucocorticoids (12.0%) (Oster et al. 2022). A few case series
of booster-associated myocarditis also demonstrated benign clinical courses. Literature on the
case series for COVID-19 booster-associated myocarditis are summarized in Table 3 (Hause
et al. 2022; Aviram et al. 2022; Friedensohn et al. 2022; Sharff et al. 2022; Shiyovich et al. 2022; Simone et al. 2022).

The present case showed a significant elevation of troponin levels, which was observed in 97.9% of primary- (Oster et al. 2022) and 100% of booster-associated myocarditis (Table 3). Therefore, troponin could be useful in screening for vaccine-associated myocarditis, although false negatives could be possible, especially within a few days after vaccination (Awaya et al. 2022). Considering the benign clinical course, however, the prognostic value of troponin in patients with vaccine-associated myocarditis is unclear, which is not the case in COVID-19-related cardiac injury (Sandoval et al. 2020).

Since vaccine-associated myocarditis is a rare entity, it is essential to consider alternative pathogenesis before making a definite diagnosis. Differential diagnosis includes other non-COVID-19-related viral myocarditis such as enterovirus; however, with negative result of FilmArray multiplex PCR test on admission, this was not the case in the present patient. Multisystem inflammatory syndrome in children associated with COVID-19 is a hyperinflammatory disorder frequently involving the cardiac system; however, it usually occurs 2-6 weeks after infection (Feldstein et al. 2021). Other non-infectious disorders, such as coronary artery disease, also have to be considered. We decided not to perform coronary angiography since the patient showed a quick resolution of his chest pain after admission and clear echocardiographic images with normal coronary arteries. Serological evidence related to COVID-19 as well as other relevant findings guided us in the direction of vaccine-associated perimyocarditis.
In addition, multimodality imaging such as CMR and longitudinal strain measurements by echocardiography, should be considered, if available, to make a definitive diagnosis in patients with suspicious vaccine-associated myocarditis, considering that a majority of primary-dose-associated myocarditis show normal systolic function by echocardiography (only 11.7% exhibited decreased LVEF) and mild or absent BNP elevation (two-thirds showed mild elevation) (Bozkurt et al. 2021). CMR could become a useful modality to detect perimyocardial inflammation in vaccine-associated myocarditis, recognizing that 72% of primary- (Oster et al. 2022) and 100% of booster-associated myocarditis (Table 3) resulted in abnormal CMR findings, suggestive of myocarditis such as late gadolinium enhancement and myocardial edema, which were both noted in the present case. However, its prognostic value should be investigated further. Longitudinal strain measurements by echocardiography could provide additional functional information on myocardial status such as wall motion abnormality and decreased magnitude of myocardial systolic motion in primary-associated myocarditis (Bews et al. 2022).

It is apparent that COVID-19 vaccination provides public health benefits for all ages and genders. However, it also poses certain risks for a specific population. The present case of a young Japanese male contracting perimyocarditis after an mRNA vaccine booster dose displayed a clinical course similar to that of patients contracting myocarditis after a primary dose. As it is a rare incidence, we employed diagnostic multimodalities such as troponin T, electrocardiography, echocardiography including strain measurements and CMR to make a definitive diagnosis. We need to amass more cases of vaccine-associated perimyocarditis to better understand its clinical characteristics and long-term outcomes, which are necessary to strike a favorable balance between benefit-risk assessment for COVID-19 vaccination.
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Author Contributions

YM, DM, MS managed the patient, contributed to the conception of the study, and drafted the manuscript. DT reviewed the manuscript from the infection perspective. TT critically reviewed the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

References


Figure 1 legend

(A) Electrocardiography shows ST-T elevation in leads I, II, III, aVF, V2-V6, suggesting the presence of pericarditis (arrows). (B) Cardiac magnetic resonance imaging (CMR) demonstrates the accepted criteria for perimyocardial inflammation as late gadolinium enhancement (LGE) on the pericardium (white arrow heads) and focal myocardium in basal septal and basal lateral lesions (yellow arrows). (C) Speckle-tracking echocardiography demonstrates no ventricular dyssynchrony in any left ventricle (LV) segments, suggesting no abnormal LV wall motion delay. Each color represents longitudinal strain curve in each LV segment during one cardiac cycle. (D) Bull’s eye mapping of longitudinal strain values in all LV segments. Basal septal and basal lateral lesions (yellow arrows) present reduced strains, which correspond to focal myocardial inflammation lesions on LGE by CMR, mentioned above. AVC, aortic valve closure; 4CH LS, 4-chamber longitudinal strain.
Table 1. Results of the FilmArray multiplex polymerase chain reaction of nasopharyngeal swab on admission.

<table>
<thead>
<tr>
<th></th>
<th>Viruses</th>
<th>Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adenovirus</td>
<td><em>Bordetella parapertussis</em></td>
</tr>
<tr>
<td></td>
<td>Coronavirus 229E</td>
<td><em>Bordetella pertussis</em></td>
</tr>
<tr>
<td></td>
<td>Coronavirus HKU1</td>
<td><em>Chlamydia pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td>Coronavirus NL63</td>
<td><em>Mycoplasma pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td>Coronavirus OC43</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SARS-CoV-2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Human metapneumovirus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Human Rhinovirus/Enterovirus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Influenza A, B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Parainfluenza Virus 1, 2, 3, 4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Respiratory Syncytial Virus</td>
<td></td>
</tr>
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</table>

N/D, not detected.
Table 2. Laboratory data on admission and discharge.

<table>
<thead>
<tr>
<th>Laboratory data</th>
<th>Admission</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood cell count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell ($\times 10^3/\mu L$) [normal: 3.3-8.6]</td>
<td>10.1</td>
<td>3.8</td>
</tr>
<tr>
<td>Neutrophil (%) [40-71]</td>
<td>84.2</td>
<td>57.2</td>
</tr>
<tr>
<td>Lymphocyte (%) [26.2-46.6]</td>
<td>5.8</td>
<td>31.8</td>
</tr>
<tr>
<td>Hemoglobin (g/dL) [13.7-16.8]</td>
<td>15.5</td>
<td>16.8</td>
</tr>
<tr>
<td>Platelets ($\times 10^4/uL$) [15.8-34.8]</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td><strong>Coagulation test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin Time-INR [0.85-1.15]</td>
<td>1.30</td>
<td>1.09</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL) [200-400]</td>
<td>385</td>
<td>315</td>
</tr>
<tr>
<td>D-dimer (ug/mL) [&lt;1]</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td><strong>Blood biochemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin (ng/mL) [13-277]</td>
<td>141.9</td>
<td>90.3</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL) [&lt;0.14]</td>
<td>8.83</td>
<td>0.53</td>
</tr>
<tr>
<td>Brain natriuretic peptide (pg/mL) [&lt;18.4]</td>
<td>22.9</td>
<td>8.7</td>
</tr>
<tr>
<td>Creatinine kinase (U/L) [59-248]</td>
<td>1527</td>
<td>98</td>
</tr>
<tr>
<td>Creatine kinase-myoglobin binding (U/L) [≤12]</td>
<td>120</td>
<td>4</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/L) [13-30]</td>
<td>112</td>
<td>32</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L) [10-42]</td>
<td>41</td>
<td>48</td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/L) [124-222]</td>
<td>301</td>
<td>274</td>
</tr>
<tr>
<td>Troponin T (ng/mL) [&lt;0.014]</td>
<td>1.900</td>
<td>0.037</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Cases, n</td>
<td>32</td>
<td>4</td>
</tr>
</tbody>
</table>

**Case source**

- Vaccine Adverse Event Reporting System, CDC, US
- Hospitalized, military personnel, Israel
- Inpatient and outpatient, 18-39 years, US
- Members of Clalit Health Services, referral for Cardiac MRI, Israel
- Kaiser Permanente Southern California members, Hospitalized >18 years, US
- Hospitalized, Japan

**Male, %**

- 100
- 100
- 100
- 67
- 75
- 89
- Male

**Age range, years**

- Adolescent: 21-38
- 18-24 (n=3)
- 25-29 (n=1)
- 30-39 (n=2)
- 18-44
- 18-40 (n=5)
- 18-40 (n=5)
- 14

**Boost vaccine**

- Pfizer
- Pfizer
- Pfizer
- Pfizer
- Pfizer
- N/A
- Pfizer

**Estimated prevalence per 100,000 shot (95% Confidence Interval)**

- 12-17 boys: 1.1
- <1 week: 6.43 (0.13-12.73)
- <2 weeks: 11.25 (2.92-19.59)
- Overall: 9.1 (3.4-19.9)
- Men: 14.8 (4.0-37.6)
- Incidence rate ratio
  - <1 week: 6.08 (2.34-13.3)
  - 1-2 week: 1.74 (0.21-6.56)

**Onset after booster shot, days**

- N/A
- <7 (n=4)
- 8-10 (n=3)
- >14 (n=1)
- <4 (n=5)
- <8 (n=1)
- 2-14
- <7 (n=7)
- 8-14 (n=2)
- Within 1 day

**Diagnostic evaluation**

- % Patients with troponin elevation
  - Reports were confirmed by provider interview or medical record review to meet the CDC working definition of myocarditis.
  - Peak troponin, median (range), ng/mL
    - 2.8 (2.9-17.8) (0.08-4.9)
  - % Patients with abnormal ECG
    - 50 (ST elevation)
    - 83 (ST elevation)
    - At least one of these:
      - ECG findings
      - New wall motion abnormalities
      - Cardiac MRI findings
    - Normal (EF 59%)
  - Subepicardial LGE
  - ST elevation
- % Patients with abnormal cardiac MRI
  - 100 (LGE and edema on T2 imaging)
  - 100 (all met Updated Lake Louise Criteria)
  - N/A
  - Normal (EF 59%)
- % Patients with abnormal echocardiography, decreased LVEF
  - 50 (EF 50-55% (n=2))
  - 17 (EF 35-40% (n=1))
  - All reports were reaffirmed by an independent cardiologist.
  - Coronary angiography (n=1)
  - N/A
- Cardiac CT (n=4)
- Coronary CT (n=2)
- N/A
- STE

**Outcome**

- % Patients with symptoms resolved hospitalization LOS, days
  - 100
  - 100
  - 100
  - N/A
  - N/A
  - 8

CT, computed tomography; ECG, electrocardiography; LGE, late gadolinium enhancement; LOS, length of stay; EF, ejection fraction; MRI, Magnetic Resonance Imaging; N/A, not available; STE, speckle-tracking echocardiography.