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

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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.

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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 United States of America (USA) 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 USA. 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 of Japan and His Cabinet 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

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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℃, 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., Durham, NC, 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 (reference range < 0.14 mg/dL), aspartate aminotransferase at 112 U/L (reference range 13-30 U/L), and lactase dehydrogenase at 301 U/L (reference range 124-222 U/L). Notably, elevation of cardiac damage markers (troponin T 1.9 ng/mL, reference range < 0.014; creatine kinase 1,527 U/L, reference range 59-248 U/L; MB isoenzyme of 120 U/L, reference range < 12 U/L) was observed, suggesting the presence of myocarditis. Brain natriuretic peptide (BNP) was mildly elevated at 22.9 pg/mL (reference range < 18.4 pg/mL) (Table 2). Serum antibody showed negative SARS-CoV-2 IgM [titer 0.2 cut off index (C.O.I.), reference range < 1.0 C.O.I.] and positive Anti-S IgG (titer 42.1 AU/mL, reference range < 1.0 AU/mL), 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 1,690 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, D). The patient was discharged eight days after admission without cardiac

Table 1. Results of the FilmArray multiplex polymerase chain reaction of nasopharyngeal swab on admission.

FilmArray	
Viruses	
Adenovirus	N/D
Coronavirus 229E	N/D
Coronavirus HKU1	N/D
Coronavirus NL63	N/D
Coronavirus OC43	N/D
SARS-CoV-2	N/D
Human metapneumovirus	N/D
Human rhinovirus/enterovirus	N/D
Influenza A, B	N/D
Parainfluenza virus 1, 2, 3, 4	N/D
Respiratory syncytial virus	N/D
Bacteria	
Bordetella parapertussis	N/D
Bordetella pertussis	N/D
Chlamydia pneumoniae	N/D
Mycoplasma pneumoniae	N/D

N/D, not detected.

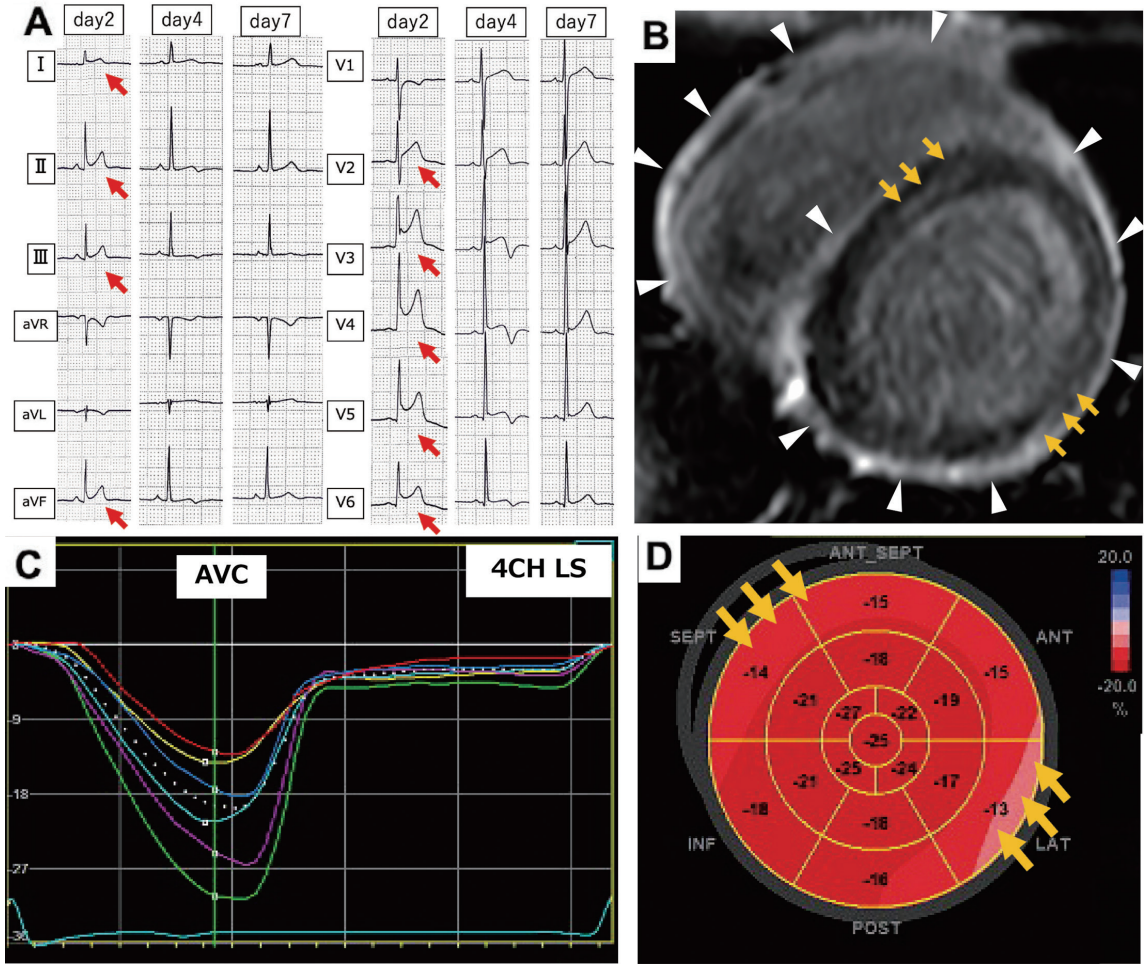

Fig. 1. Electrocardiography, cardiac magnetic resonance imaging (CMR) and speckle-tracking echocardiography.
(A) Electrocardiography shows ST-T elevation in leadsI, II, III, aVF, V2-V6, suggesting the presence of pericarditis (arrows). (B) CMR demonstrates the accepted criteria for perimyocardial inflammation 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.

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 USA, 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

Table 2. Laboratory data on admission and discharge.

Laboratory data	Admission	Discharge
Blood cell count		
White blood cells ($\times 10^3/\mu L$) [reference range 3.3-8.6]	10.1	3.8
Neutrophils (%) [40-71]	84.2	57.2
Lymphocytes (%) [26.2-46.6]	5.8	31.8
Hemoglobin (g/dL) [13.7-16.8]	15.5	16.8
Platelets ($\times 10^4/\mu L$) [15.8-34.8]	16	24
Coagulation test		
Prothrombin time-INR [0.85-1.15]	1.3	1.09
Fibrinogen (mg/dL) [200-400]	385	315
D-dimer (μg/mL) [< 1]	< 0.5	< 0.5
Blood biochemistry		
Ferritin (ng/mL) [13-277]	141.9	90.3
C-reactive protein (mg/dL) [< 0.14]	8.83	0.53
Brain natriuretic peptide (pg/mL) [< 18.4]	22.9	8.7
Creatinine kinase (U/L) [59-248]	1,527	98
Creatine kinase-myoglobin binding (U/L) [≦ 12]	120	4
Aspartate aminotransferase (U/L) [13-30]	112	32
Alanine aminotransferase (U/L) [10-42]	41	48
Lactate dehydrogenase (U/L) [124-222]	301	274
Troponin T (ng/mL) [< 0.014]	1.900	0.037

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 sexes. 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 out-

Table 3. Literature review on the case series of COVID-19 third dose/booster-associated myocarditis.

Case series	Hause et al. (2022)	Aviram et al. (2022)	Friedensohn et al. (2022)	Sharff et al. (2022)	Shiyovich et al. (2022)	Simone et al. (2022)	Present case
Cases, n	32	4	8	6	4	9	1
Case source	Vaccine Adverse Event Reporting System, CDC, USA	Hospitalized, Israel	Hospitalized, military personnel, Israel	Inpatient and outpatient, 18-39 years, USA	Members of Clalit Health Services, referral for Cardiac MRI, Israel	Kaiser Permanente Southern California members, Hospitalized ≥ 18 years, USA	Hospitalized, Japan
Male, %	100	100	100	67	75	89	Male
Age range, years	adolescent	21-38	18-24	18-24 (n = 3) 25-29 (n = 1) 30-39 (n = 2)	18-44	18-40 (n = 5)	14
Boost vaccine	Pfizer	Pfizer	Pfizer	Pfizer	Pfizer	N/A	Pfizer
Estimated prevalence per 100,000 shot (95% Confidence Interval)	1.1 (12-17 boys)	0.03%	< 1week: 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)	N/A	Incidence rate ratio < 1week: 6.08 (2.34-13.3) 1-2 week: 1.74 (0.21-6.56)	-
Onset after booster shot, days	N/A	2-11	< 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.	100	Diagnosis was based on laboratory, ECG, echocardiography, and cardiac MRI findings. All reports were reaffirmed by an independent cardiologist.	67	100	100	Yes
Peak troponin, median (range), ng/mL		2.8		(2.9-17.8)	(0.08-4.9)	N/A	1.9
% Patients with abnormal ECG		50 (ST elevation)		83 (ST elevation)	75 (ST elevation)		ST elevation
% Patients with abnormal cardiac MRI		100 (LGE and edema on T2 imaging)		N/A	100 (all met Updated Lake Louise Criteria)	At least one of these: ・ECG findings ・New wall motion abnormalities ・Cardiac MRI findings	Subepicardial LGE
% Patients with abnormal echocardiography, decreased LVEF		50 (EF 50-55%, n = 2)		17 (EF 35-40%, n = 1)	N/A		Normal (EF 59%)
Other modalities		Cardiac CT (n = 4)		N/A	Coronary angiography (n = 1) Coronary CT (n = 2)	N/A	STE
Outcome							
% Patients with symptoms resolved	100	100	100	N/A	N/A	100	Yes
hospitalization LOS, days	N/A	Several days	N/A	1-4	N/A	N/A	8

CDC, Centers for Disease Control and Prevention; CT, computed tomography; ECG, electrocardiography; LGE, late gadolinium enhancement; LOS, length of stay; EF, ejection fraction; LVEF, left ventricle ejection fraction; MRI, magnetic resonance imaging; N/A, not available; STE, speckle-tracking echocardiography.

comes, which are necessary to strike a favorable balance between benefit-risk assessment for COVID-19 vaccination.

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Author Contributions

Y.M., D.M., M.S. managed the patient, contributed to the conception of the study, and drafted the manuscript. D.T. reviewed the manuscript from the infection perspective. T.T. critically reviewed the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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