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【 CASE REPORT 】

Fulminant Myocarditis and Acute Appendicitis after COVID-19 Vaccination

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Abstract:
A 19-year-old Japanese man was hospitalized for cardiogenic shock 28 days after receiving a second dose of the coronavirus disease 2019 (COVID-19) mRNA-1273 vaccine. He had had a high fever for three days with vomiting and abdominal pain before arriving at our hospital. The patient visited a local hospital and was diagnosed with heart failure and acute appendicitis. An endomyocardial biopsy specimen showed myocarditis. Thereafter, Impella CP left ventricular assist device implantation and venoarterial peripheral extracorporeal membranous oxygenation were initiated immediately along with inotropic support and steroid pulse therapy. Given these findings, he was finally diagnosed with multiple inflammatory syndrome and fulminant myocarditis.

Key words: biopsy, cytokine, inflammation

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Introduction

Several severe acute respiratory coronavirus 2 (SARS-CoV-2) vaccines have proven safe and efficacious in the prevention of its infection (1-3). Although adverse events following immunization (AEFI), including myocarditis and appendicitis, after SARS-CoV-2 vaccination have been reported, they are rare (4-8). Fulminant myocarditis has also been reported in a few histologically confirmed cases (9).

Multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 is rare but leads to a serious and life-threatening hyperinflammatory state 4-6 weeks after SARS-CoV-2 infection in children and adolescents (<21 years old) (10, 11). A similar condition has also been reported as a rare complication of SARS-CoV-2 in adults (MIS-A) (11). Recently, MIS-C/A (MIS-C and MIS-A) was reported as a SARS-CoV-2 vaccine AEFI (11-15).

We herein report a 19-year-old patient who had MIS-C with fulminant myocarditis and acute appendicitis 28 days after receiving the second dose of a coronavirus disease 2019 (COVID-19) mRNA vaccine.

Case Report

A 19-year-old Japanese man was admitted to our hospital with heart failure and cardiogenic shock. He had received the second dose of the COVID-19 mRNA-1273 vaccine 28 days earlier. He had a high fever for three days. After experiencing abdominal pain, vomiting, and appetite loss, he visited a local hospital and was diagnosed with acute appendicitis after computed tomography (CT) revealed a swollen appendix (Fig. 1). The patient was transferred to our hospital because of severe cardiac dysfunction. He had no medical or family history and had no history of smoking or alcohol consumption.

A physical examination on admission revealed the following findings: a blood pressure of 79/50 mmHg; a regular pulse rate of 140 beats per minute; body temperature of 38.6°C; a body mass index of 16.3 kg/m^2; and no abnormal

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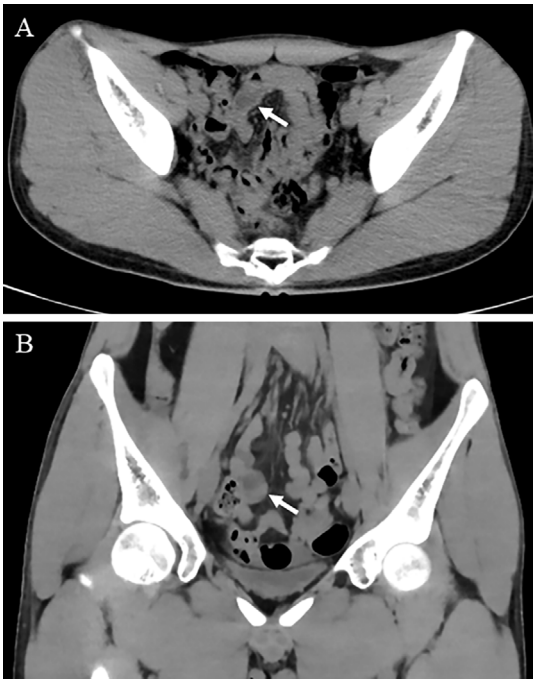

Figure 1. Abdominal computed tomography revealed a swollen appendix (A: transverse view, B: coronal view)

findings except for tenderness of the periumbilical region and a 2-finger-breadth palpable liver.

Data of laboratory parameters were as follows: white blood cell count, 12,200/mm^3 with lymphopenia (9.4%); C-reactive protein (CRP), 10.27 mg/dL; D-dimer, 1.6 μg/mL; high-sensitivity troponin T, 3.67 ng/mL; creatinine kinase (CK), 476 IU/L; and N-terminal pro-brain natriuretic peptide (NT-proBNP), 24,112 pg/mL. In addition to these findings, we noted liver and renal dysfunction with negative results for COVID-19 antibodies, a real-time reverse transcription polymerase chain reaction assay (RT-PCR), antigens, and routine pathogen tests (Table 1).

Chest radiography showed normal findings, with a cardiothoracic ratio of 49.7% (Fig. 2A). Electrocardiography (ECG) revealed sinus tachycardia; abnormal Q waves in leads V1-3; and slight ST-segment elevation in leads I, II, aVF, and V2-6 (Fig. 2B). Echocardiography revealed diffuse left ventricular hypokinesis [left ventricular ejection fraction (LVEF), 34%], thickened interventricular septal wall (12 mm), and LV posterior wall (12 mm) with normal LV dimensions and pericardial effusion (Fig. 2C, D). Coronary angiography revealed no remarkable findings.

He received tracheal intubation because of respiratory alkalosis (pH, 7.503; PCO_2, 26.1 mmHg; PO_2, 90.1 mmHg; HCO_3^-, 20.3 mEq/L; base excess, -1.0 mEq/L); and an increased lactic acid level (2.2 mmol/L) with nasal oxygen inhalation (3 L/min).

Cardiac catheterization on admission revealed normal coronary arteries. The results of a pressure study were as follows: pulmonary capillary wedge pressure (a wave/v wave/mean), 31/27/26 mmHg; pulmonary artery pressure (systolic/diastolic/mean), 35/26/31 mmHg; right ventricular pressure (systolic/diastolic/end-diastolic pressure), 38/9/12 mmHg; right atrial pressure (a wave/v wave/mean), 15/11/11 mmHg; left ventricular pressure (systolic/diastolic/end-diastolic pressure), 84/19/28 mmHg; cardiac output, 3.01 L/min; cardiac index, 1.85 L/min/m^2.

Implantation of an Impella CP left ventricular assist device and veno-arterial peripheral extracorporeal membrane oxygenation (VA ECMO) were immediately initiated along with inotropic support [noradrenalin (0.05 μg/kg/min)]. He also received methylprednisolone (1 g/day for 3 days) and immunoglobulin (5 g/day for 3 days), along with azithromycin (500 mg/day for 3 days). An endomyocardial biopsy specimen showed mild myocyte damage and cell infiltration (Fig. 3A) with T cells (Fig. 3B) [both CD4+ (Fig. 3C) and CD8+ cells (Fig. 3D)], an increased number of macrophages (Fig. 3E), and a decreased number of B cells (Fig. 3F). Based on these findings, he was diagnosed with fulminant myocarditis.

We also performed immunostaining for the myocardium biopsy specimen using antibodies against angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 spike S protein, and C4d to evaluate the relationship between myocarditis and COVID-19 vaccination. The myocytes were negative for these antibodies (Fig. 4).

His cardiac function gradually improved, and he was weaned from VA ECMO and Impella CP eight days and nine days after admission, respectively. CT revealed no swelling of the appendix seven days after admission. After treatment for heart failure with furosemide (40 mg/day), enalapril (1.25 mg/day), and carvedilol (2.5 mg/day), his condition gradually improved. Two weeks after admission, his cardiac function had recovered to an almost normal systolic function with an LVEF of 56%, normal LV wall thickness on echocardiography, and normal CK levels. The patient experienced liver dysfunction due to enalapril (1.25 mg/day), which was changed to losartan (12.5 mg/day). The patient was discharged with a serum NT-proBNP level of 694 pg/mL and normal ECG findings (Fig. 5) 5 weeks after admission and was prescribed losartan (12.5 mg/day) and carvedilol (5 mg/day).

Tests performed for infections showed negative results for the following: two sets of blood cultures taken before administration of antibiotics; PCR for COVID-19; IgM antibody for cytomegalovirus and Epstein-Barr virus-viral capsid antigen; influenza A and B kits; and viral antibodies (paired serum samples) against adenovirus, Coxsackie virus (A16, A7, B1, B2, B3, B4, B5, and B6), echovirus (3, 6, 7, 11, and 12), and parainfluenza virus (1, 2, and 3). Immunology screening results for antinuclear antigen (ANA) and antineutrophil cytoplasmic antibodies (ANCA) were normal (Table 1). Given these results, he was finally diagnosed with fulminant myocarditis and acute appendicitis related to the COVID-19 vaccine. In addition, this patient also met the level 1 diagnostic criteria (definitive case) of vaccine-induced MIS-C according to the Brighton Collaboration Network definition (11). The criteria are as follows: age <21

Table 1. Laboratory Data.

WBC	12,200 /μL	RF	<5.0 IU/mL (<15)
Seg	69.9 %	Anti-nuclear antibody	<80
Lymph	9.4 %	Anti-dsDNA antibody	<10 IU/mL (<12.0)
Mono	19.5 %	Anti-ssDNA antibody	<10 IU/mL (<25.0)
RBC	4.89×10^4 /μL	CH50	30.5 /mL (30-46)
Hb	14.2 g/dL	MPO-ANCA	<1.0 U/mL (<3.5)
Hct	40.9 %	PR3-ANCA	<1.0 U/mL (<3.5)
Plt	163×10^3 /μL	Anti-SS-A antibody	<1.0 U/mL (<10.0)
PT-INR	1.22	Anti-SS-B antibody	<1.0 U/mL (<10.0)
APTT	28.5 s	NTproBNP	24,112 pg/mL
D-dimer	1.6 μg/mL	CRP	10.27 mg/dL
T-Bil	0.7 mg/dL	SARS-CoV-2-Ab	<0.1 COI (<0.1)
AST	51 IU/L	SARS-CoV2-PCR	(-)
ALT	43 IU/L	SARS-CoV2-Ag	(-)
ALP	36 IU/L	Procalcitonin	0.156 ng/mL (<0.046)
LDH	347 IU/L	β-D glucan	5.0 pg/mL (<20)
γ-GTP	33 IU/L	Influenza antigen	(-)
CK	476 IU/L	Urinary antigen of *Legionella*	(-)
CKMB	17 IU/L	*Legionella* nucleic acid (sputum)	(-)
hs-TnT	3.67 ng/mL	*Mycoplasma* nucleic acid (sputum)	(-)
Na	135 mEq/L	HSV IgG	12.5 (<2.0)
K	4.0 mEq/L	HSV IgM	0.29 (<0.80)
Cl	97 mEq/L	HSV DNA PCR	(-)
Ca	8.7 mg/dL	*Chlamydia pneumoniae* IgG	27 (<30)
BUN	23 mg/dL	*Chlamydia pneumoniae* IgA	5 (<8.0)
Cre	1.07 mg/dL	CMV antibody IgG	12.9 (<2.0)
TP	6.1 g/dL	CMV antibody IgM	0.04 (<0.80)
Alb	3.3 g/dL	CMV nucleic acid	(-)
UA	6.3 mg/dL	Urinary antigen of *Strept. pneumoniae*	(-)
TG	64 mg/dL	EBV VCA IgG	40 (<1.0)
LDL-C	49 mg/dL	EBV VCA IgM	<10 (<10)
HDL-C	39 mg/dL		
FPG	130 mg/dL	EBV EBNA IgG	2.6 (<1.0)
HbA1c	5.3 %	T-SPOT. TB	(-)

WBC: white blood cell count, RBC: red blood cell count, Hb: hemoglobin, Hct: hematocrit, Plt: platelet count, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, T-bil: total bilirubin , AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, γ-GTP: γ-glutamyl transpeptidase, CK: creatine kinase, hs-TnT: high sensitive-troponin T, BUN: blood urea nitrogen, Cre: creatinine, TP: total protein, Alb: albumin, UA: uric acid, TG: triglyceride, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, FPG: fasting plasma glucose, HbA1c: hemoglobin A1c, NT-pro BNP: N terminal-pro brain natriuretic peptide, CRP: C-reactive protein, SARS-CoV-2-Ab: SARS-CoV-2-antibody, SARS-CoV2-PCR: SARS-CoV2-polymerase chain reaction, SARS-CoV2-Ag: SARS-CoV2-antigen, MPO-ANCA: myeloperoxydase-antineutrophil cytoplasmic antibody, PR3-ANCA: proteinase 3-antineutrophil cytoplasmic antibody, urinary antigen of *Strept. pneumoniae*: urinary antigen of *Streptococcus pneumoniae*, CMV: cytomegalovirus, EBV VCA: Epstein-Barr virus virus capsid antigen

years old; a fever for 3 days; ≥2 clinical features of multiple organ involvement [gastrointestinal (abdominal pain, vomiting), and shock/hypotension]; laboratory evidence of inflammation (elevated CRP levels), ≥2 measures of disease activity (elevated NT-proBNP and troponin, lymphopenia, low LVEF on echocardiography, and ECG changes consistent with myocarditis), and SARS-CoV-2 vaccination.

Discussion

We encountered a patient with MIS-C with fulminant myocarditis and acute appendicitis 28 days after receiving the second dose of a COVID-19 mRNA vaccine. He recovered after treatment with steroids and antibiotics, in addition to Impella CP implantation and VA ECMO support.

There have been no reports of patients with myocarditis and appendicitis at the same time after COVID-19 mRNA

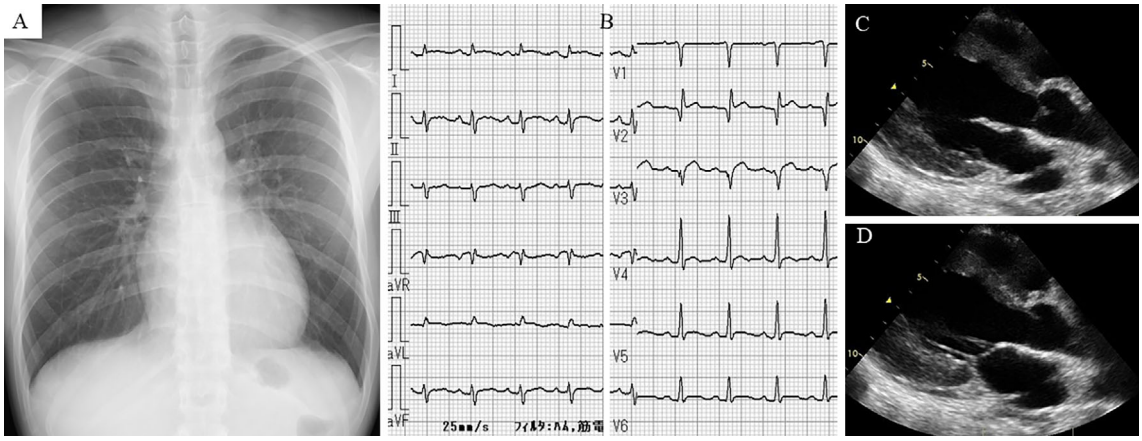

Figure 2. **Chest radiography showed normal findings with a cardiothoracic ratio of 49.7% (A). Electrocardiography revealed sinus tachycardia, abnormal Q waves in leads V1-3, and slight ST-segment elevation in leads I, II, aVF, and V2-6 (B). Transthoracic echocardiography showing left ventricular hypokinesis with mild pericardial effusion (C: end-diastolic phase of parasternal long-axis view, D: end-systolic phase of the parasternal long-axis view).**

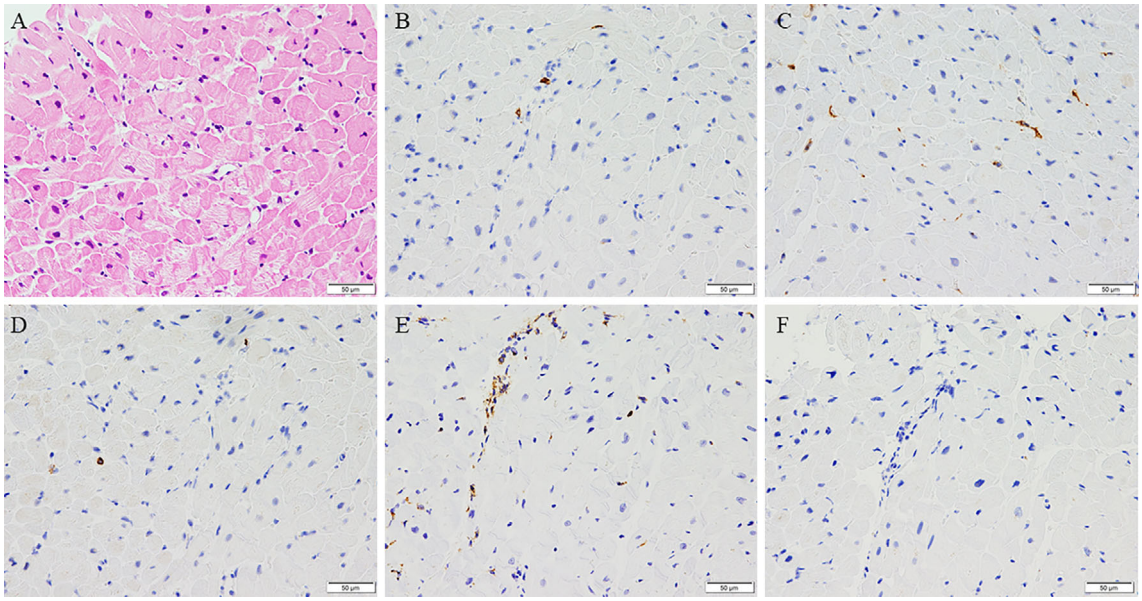

Figure 3. **Cell infiltration in the myocardium (A, Hematoxylin and Eosin staining) with CD3+ cells (B), both CD4+ cells (C), CD8+ cells (D), more CD68+ cells (E), and fewer CD20+ cells (F) (×200).**

vaccination, although COVID-19 mRNA vaccination is associated with an elevated risk of both myocarditis and appendicitis (8).

We searched for previous reports on MIS and the COVID-19 vaccine and identified 67. Patients with evidence of COVID-19 infection were excluded from the study. Finally, we reviewed 19 cases of myocarditis and evaluated the vaccine type, duration between vaccination and the first sign of symptoms, presence of hypotension/shock, and treatments including medication and VA ECMO, in addition to those in our case (Table 2) (13, 14, 16-26). The vaccine dose and duration between vaccination and the MIS-C/A onset varied among the reports, indicating that the occurrence of MIS-C/A after COVID-19 mRNA vaccination is heterogeneous, and the underlying mechanisms may differ among cases.

Of the 20 patients, including our own, 9 had hypotension/shock, and 3 [case 12 (our case), 16, and 17] were treated with VA ECMO in addition to other medical treatments (Tab 2). A myocardial biopsy was performed in only 2 of the 20 patients: in our patient (case 12) and case 17. Case 17 underwent a myocardial biopsy on day 13 of hospital admission that showed cardiomyocytes with focal cytoplasmic vacuolization and rare interstitial lymphocytic infiltration, suggesting healing myocarditis. Our myocardial biopsy showed cell infiltration (more macrophages than T and B cells) without ACE2, spike protein, or C4d expression in myocytes, which differed from our previously reported case

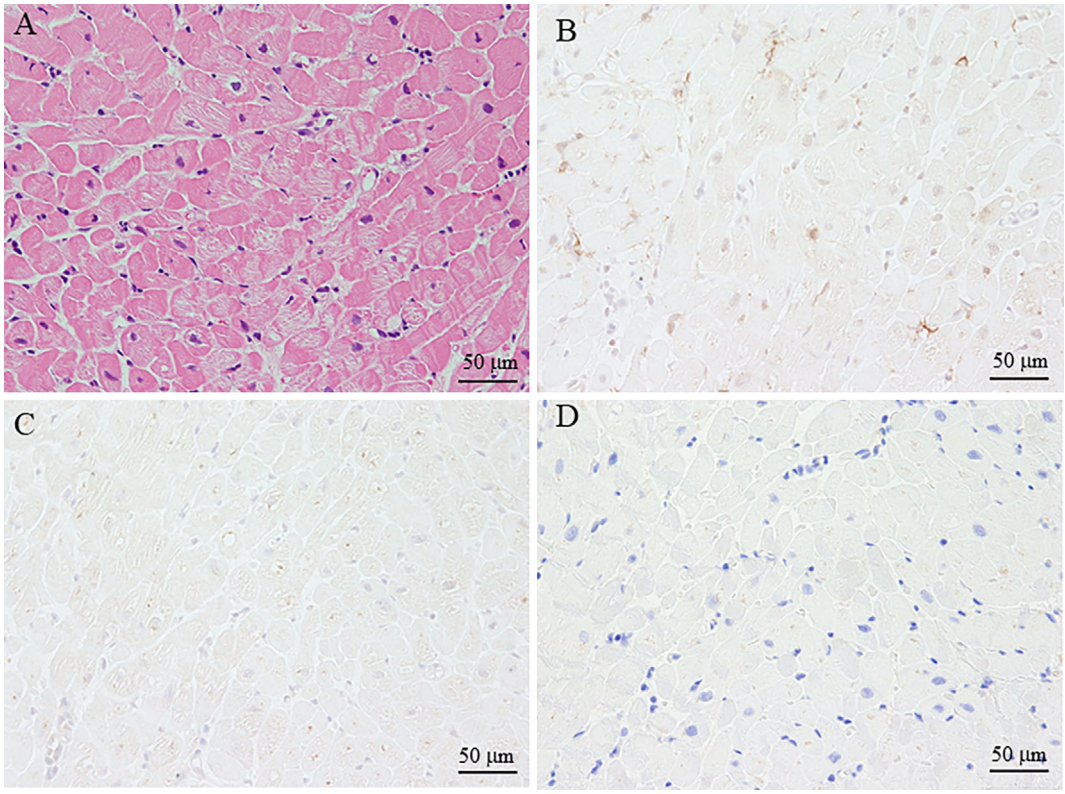

Figure 4. **Immunostaining of the myocardium biopsy sample using antibodies for ACE2, SARS-CoV-2 (COVID-19) spike protein, and C4d. In the myocardium biopsy sample with myocarditis (A, Hematoxylin and Eosin staining, ×200), ACE2 (B, ×200), SARS-CoV-2 (COVID-19) spike protein (C, ×200), and C4d (D) were negative in myocytes. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, COVID-19: coronavirus disease 2019, ACE2: angiotensin-converting enzyme 2**

	Day 1	Day 14	Day 35
CRP (mg/dL)	10.27	0.15	0.08
CK (IU/L)	476	161	78
NT-pro BNP (pg/dL)	24112	2787	694
LVEF (%)	34	56	56
IVST (mm)	12	8	6
LVPWT (mm)	12	11	8

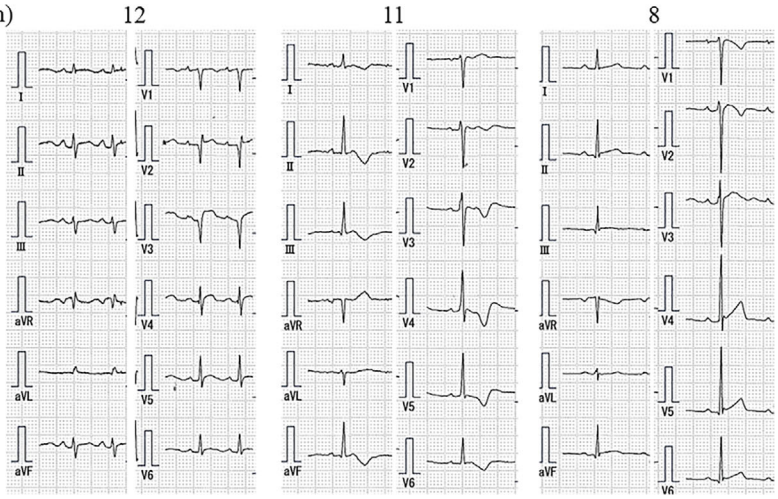

Figure 5. **Time course of electrocardiography, echocardiographic data, and laboratory data. CRP: C-reactive protein, CK: creatinine kinase, NT-proBNP: N-terminal pro-brain natriuretic peptide, LVEF: left ventricular ejection fraction, IVST: interventricular septal thickness, LVPW: left ventricular posterior wall thickness**

Table 2. Multisysten Inflammatory Syndrome with Myocarditis after COVID-19 Vaccination in the Previous Reports and Our Report.

	Age (years)	Sex	Type of vaccine	Vaccine dose	Days from vaccination to onset	Hypotension/ shock	Treatment	VA-ECMO	Outcome	Ref.
1	12-15, 3 cases 18-20, 3 cases	M, 3	BNT162b	1st	NA	2 cases	IVIG,4 cases steroid, 4 cases	-	Recovered	13
2			BNT162b	2nd	21 days			-	Recovered	13
3			BNT162b	2nd	14 days			-	Recovered	13
4			BNT162b	2nd	84 days			-	Recovered	13
5			BNT162b	2nd	5 day			-	Recovered	13
6			BNT162b	2nd	0 days			-	Recovered	13
7	12	M	mRNA-1273	2nd	35 days	+	IVIG	-	Recovered	16
8	12	M	BNT162b	2nd	2 days	-	-	-	Recovered	17
9	14	F	BNT162b	2nd	60 days	+	IVIG+steroid	-	Recovered	18
10	16	M	BNT162b	1st	12 days	-	IVIG+steroid	-	Recovered	19
11	17	F	BNT162b	1st	7 days	-	IVIG+steroid	-	Recovered	20
12	19	M	mRNA-1273	2nd	28 days	+	IVIG+steroid	+	Recovered	Our
13	Late teens	F	BNT162b	2nd	20 days	-	IVIG+steroid	-	Recovered	21
14	22	F	ChAdOX1	1st	10 days	+	IVIG+steroid+tocilizmab	-	Recovered	22
15	24	M	BNT162b	2nd	14 days	-	Steroid	-	Recovered	23
16	27	M	BNT162b	2nd	2 days	+	IVIG+steroid+anakinra	+	Dead	24
17	34	F	BNT162b	1st	9 days	+	IVIG+steroid+anakinra	+	Recovered	24
18	44	F	BNT162b	NA	2 days	+	Steroid	-	Recovered	14
19	46	M	Ad26.COV2.S	NA	12 days	-	Steroid	-	Recovered	25
20	67	M	ChAdOX1	1st	6 days	-	Steroid	-	Recovered	26

F: female, IVIG: human immunoglobulin, M: male, NA: not applicable, Ref.: reference, VA-ECMO: veno-arterial peripheral extracorporeal membrane oxygenation

of fulminant myocarditis after COVID-19 vaccination without MIS (27). These findings suggest that the pathophysiology of myocarditis following COVID-19 vaccination may be multifactorial.

Several reports have shown histopathological features of MIS following SARS-Cov-2 infection (28-32). Cardiac injury in MIS following viral infection may occur either because of direct cardiac invasion of the virus or inflammatory response by cytokine release (cytokine storm) (29). The presence of more macrophages and less T cell infiltration (29) or mild T cell (31) without substantial myocyte necrosis suggested an inflammatory response by cytokine release but not direct cardiac damage due to viral invasion. As these histopathological features were similar to those of our patient, myocarditis in MIS following COVID-19 vaccination may be due to hyperinflammation induced by cytokine release, although the precise mechanism that leads to hyperinflammation in MIS is unknown.

There have been several case reports of MIS-C associated with SARS-CoV-2 infection and acute appendicitis (33-37). These previous findings suggested that it may be difficult to make the differential diagnosis between acute appendicitis and MIS-C, as some patients may have both acute appendicitis and MIS-C, and others may have appendix inflammation (mimicking appendicitis) as gastrointestinal involvement due to MIS-C. However, there have been no reports of MIS-C after COVID-19 mRNA vaccination along with acute appendicitis. Our patient was clinically diagnosed with acute appendicitis based on his symptoms, laboratory data, and CT findings, and he had no appendectomy because his condition was ameliorated with treatment including steroid pulse therapy for fulminant myocarditis in addition to antibiotics. We should therefore consider MIS-C in patients with multisystem organ involvement, including suspected acute appendicitis, after COVID-19 mRNA vaccination because the treatment may differ among patients with acute appendicitis and MIS-C.

Almost all patients recovered by treatment with steroids and/or intravenous immune globulin (IVIG); anakinra, an interleukin (IL)-1 receptor antagonist; or tocilizumab, an IL-6 receptor antagonist. However, one patient without hypotension/shock (case 8) recovered without these treatments, and one patient (case 16) with fulminant myocarditis died despite treatment with IVIG, steroids, and anakinra (Table 2). Although there are no prospective studies, immunomodulatory therapy may be effective for myocarditis associated with MIS-C. Further studies are required to determine the optimal treatment for this condition.

In conclusion, myocarditis associated with MIS-C should be considered in patients even after COVID-19 mRNA vaccination for timely and proper treatment, although this is very rare.

The authors state that they have no Conflict of Interest (COI).

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