Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9800-22
Intern Med 61: 2319-2325, 2022
http://internmed.jp

【 CASE REPORT 】

Fulminant Myocarditis 24 Days after Coronavirus Disease Messenger Ribonucleic Acid Vaccination

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Abstract:

A 60-year-old Japanese woman was hospitalized for cardiogenic shock 24 days after receiving the second dose of the coronavirus disease 2019 BNT162b2 vaccine. Impella CP left ventricular assist device implantation and venoarterial peripheral extracorporeal membranous oxygenation were immediately initiated along with inotropic support and steroid pulse therapy, as an endomyocardial biopsy specimen showed myocarditis. Three weeks later, her cardiac function had recovered, and she was discharged. An immune response associated with the presence of spike protein in cardiac myocytes may be related to myocarditis in the present case because of positive immunostaining for severe acute respiratory syndrome coronavirus 2 spike protein and C4d in the myocardium.

Key words: biopsy, pathology, inflammation

(Intern Med 61: 2319-2325, 2022)
(DOI: 10.2169/internalmedicine.9800-22)

Introduction

The overall incidence of coronavirus disease 2019 (COVID-19) messenger ribonucleic acid (mRNA)-vaccine-related myocarditis is low (0.3-5.0 cases per 100,000 vaccinated people as reported in case-series studies). This condition mostly occurs in young adults, and in most cases, it appears in the mild form several days after the administration of the second dose of vaccination (1-4). However, fulminant myocarditis due to COVID-19 mRNA vaccination has been reported to occur 10-14 days after the second dose of vaccination in a few cases, and the precise mechanisms are unknown (5).

We herein report a patient who had fulminant myocarditis due to an immune response related to COVID-19 vaccination as suggested by a myocardial biopsy 24 days after receiving the second dose of a COVID-19 mRNA vaccine.

Case Report

A 60-year-old Japanese woman was admitted to our hospital due to heart failure and cardiogenic shock. She had received the second dose of the COVID-19 BNT162b2 mRNA vaccine 24 days earlier. She had had a high fever for three days before visiting our hospital. After suffering palpitations, she visited a local hospital first and was then transferred to our hospital because of severe cardiac dysfunction. Her medical history included breast cancer surgery at 40 years old, with no remarkable family history. She also had no history of smoking or alcohol consumption.

A physical examination on admission revealed the following findings: blood pressure, 97/72 mmHg; pulse rate, 91 beats per minute regular; body temperature, 37.0°C; body mass index, 22.8 kg/m^2; and no abnormal findings except for abnormal heart sounds in S3.

Data of laboratory parameters were as follows: white blood cell count, 6,700/mm^3; C-reactive protein, 1.42 mg/dL; D-dimer, 2.7 μg/mL; high-sensitivity troponin T, 2.01 ng/mL; creatinine kinase (CK), 548 IU/L; and N-terminal pro-brain natriuretic peptide (NT-proBNP), 6,999 pg/mL. In addition to these findings, we noted liver and renal dysfunction with negative results for COVID-19 antibody, real-time reverse transcription polymerase chain reaction (RT-PCR)

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Received: March 22, 2022; Accepted: April 18, 2022; Advance Publication by J-STAGE: May 31, 2022
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Table 1. Laboratory Data.

WBC	6,700 /μL	UA	4.1 mg/dL
Seg	75 %	TG	93 mg/dL
Lymph	21.2 %	LDL-C	82 mg/dL
Mono	3.6 %	HDL-C	44 mg/dL
RBC	4.62×10^4 /μL	FPG	121 mg/dL
Hb	12.9 g/dL	HbA1c	5.7 %
Hct	39.0 %	NT-proBNP	6,999 pg/mL
Plt	251×10^3 /μL	CRP	1.41 mg/dL
PT-INR	1.12	SARS-CoV-2-Ab	102 COI (<0.1)
APTT	34.4 s	SARS-CoV-2-PCR	(-)
D-dimer	2.7 μg/mL	SARS-CoV-2-Ag	(-)
T-Bil	0.5 mg/dL	RF	9.8 IU/mL (<15)
AST	192 IU/L	Anti-nuclear antibody	160
ALT	257 IU/L	Anti-dsDNA antibody	<10 IU/mL (<12.0)
ALP	210 IU/L	Anti-ssDNA antibody	<10 IU/mL (<25.0)
LDH	542 IU/L	CH50	30.0 /mL (30-46)
γ-GTP	230 IU/L	MPO-ANCA	<1.0 U/mL (<3.5)
CK	548 IU/L	PR3-ANCA	<1.0 U/mL (<3.5)
CKMB	46 IU/L	Anti-SS-A antibody	1.4 U/mL (<10.0)
hs-TnT	2.01 ng/mL	Anti-SS-B antibody	<1.0 U/mL (<10.0)
Na	135 mEq/L	β-D glucan	5.5 pg/mL (<20)
K	3.8 mEq/L	Influenza antigen	(-)
Cl	99 mEq/L	Urinary angiten of *Legionella*	(-)
Ca	8.2 mg/dL	Urinary angiten of *Strept. pneumoniae*	(-)
BUN	11 mg/dL	CMV antibody IgG	24.2 (<2.0)
Cre	1.14 mg/dL	CMV antibody IgM	0.64 (<0.80)
TP	6.1 g/dL	EBV VCA IgG	20 (<10)
Alb	3.1 g/dL	EBV VCA IgM	<10 (<10)

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Hct: hematocrit, Plt: platelet, 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-CoV-2-PCR: SARS-CoV-2-polymerase chain reaction, SARS-CoV-2-Ag: SARS-CoV-2-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 viral capsid antigen

assay, and antigens as well as for routine pathogen tests (Table 1).

Electrocardiography indicated abnormal Q waves in leads II, III, aVF, and V1-3 (Fig. 1A). Echocardiography revealed diffuse left ventricular hypokinesis [left ventricular ejection fraction (LVEF), 23%] with a normal left ventricular dimension and pericardial effusion (Fig. 1B, C). Coronary angiography suggested unremarkable findings.

She received tracheal intubation because of respiratory alkalosis (pH, 7.476; PCO_2, 30.0 mmHg; PO_2, 106 mmHg; HCO_3^-, 21.9 mEq/L; base excess, -0.4 mEq/L) and an increased lactic acid level (2.1 mmol/L) with nasal oxygen inhalation (2 L/min).

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 (0.1 μg/kg/min) and olprinone (0.05 μg/kg/min)] because of gradual blood pressure reduction. She also received methylprednisolone (1 g/day for 3 days) because an endomyocardial biopsy specimen showed myocyte damage, increased interstitial fibrosis, and cell infiltration (Fig. 2A) with more T cells (Fig. 2B) [both CD4+ cells (Fig. 2C) and CD8+ cells (Fig. 2D)], more macrophages (Fig. 2E) and fewer decreased numbers of B cells (Fig. 2F). Based on these findings, she was diagnosed with fulminant myocarditis.

Her cardiac function gradually improved, and she was weaned from VA ECMO and Impella CP three days after admission. After treatment, her condition gradually improved. Three weeks later, her cardiac function had recovered to a normal systolic function with an LVEF of 68% on echocardiography and a serum NT-proBNP level of 313 pg/

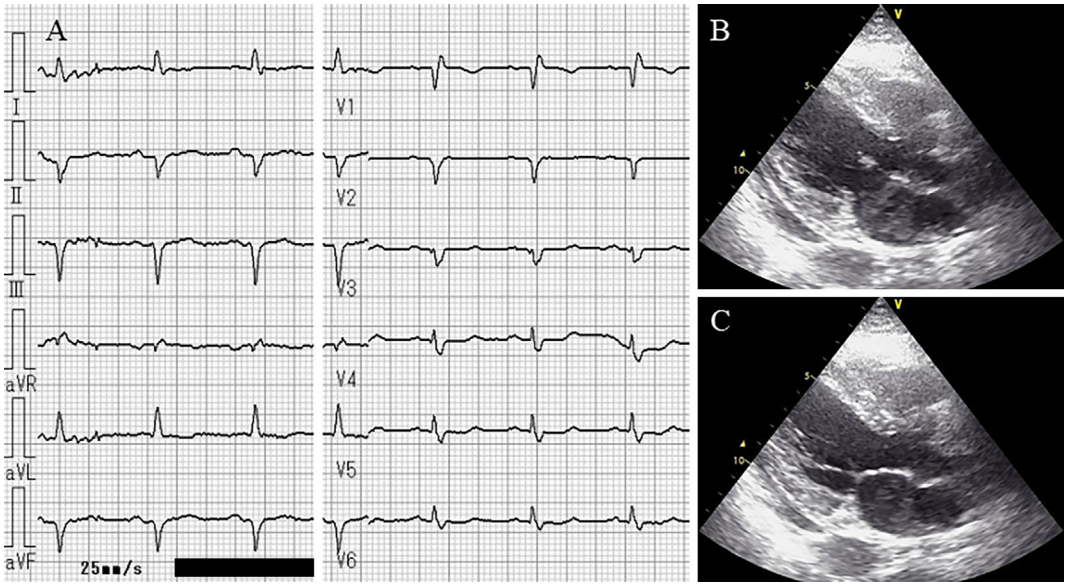

Figure 1. **A: Electrocardiography performed on admission showing abnormal Q waves in leads II, III, aVF, and V1 to 3. Transthoracic echocardiography showing left ventricular hypokinesis with mild pericardial effusion (B, end-diastolic phase of parasternal long-axis view; C, end-systolic phase of the parasternal long-axis view).**

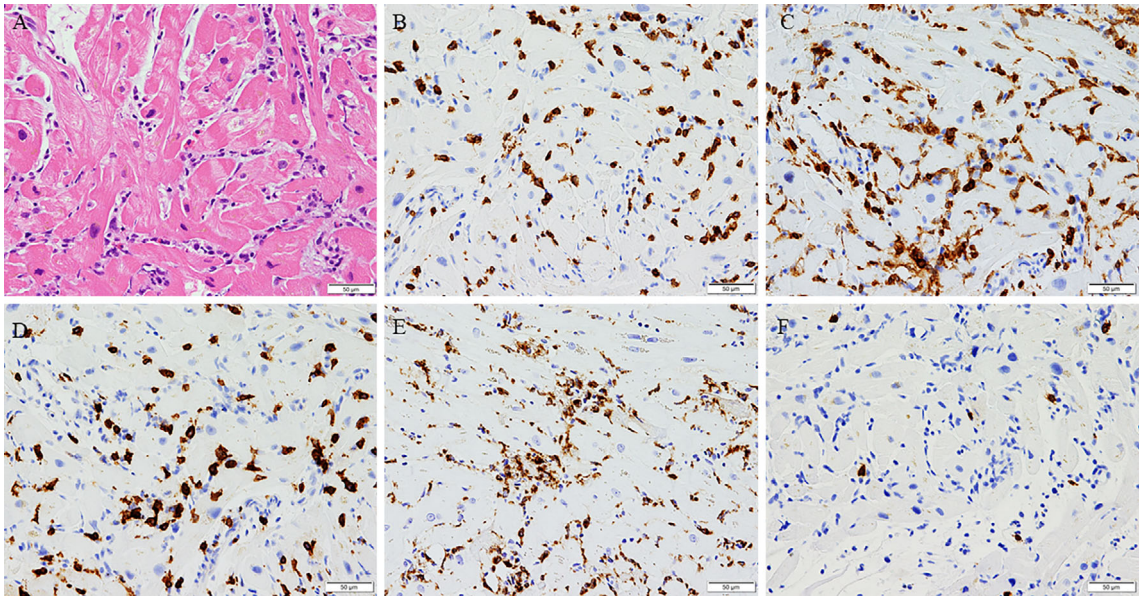

Figure 2. **Endomyocardial biopsy specimen showing myocyte damage, increased interstitial fibrosis, and cell infiltration (A, Hematoxylin and Eosin staining) with more CD3+ cells [B (both CD4+ cells (C) and CD8+ cells (D))] and more CD68+ cells (E) and less CD20+ cells (F) (×200).**

mL and normal CK level, and she was discharged (Fig. 3).

Tests performed for infections showed negative results: polymerase chain reaction for COVID-19; IgM antibody of 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).

As eosinophilic infiltration was also observed in the myocardium biopsy (Fig. 4), a drug-induced lymphocyte stimulation test (DLST) was performed using residual volumes of the BNT162b2 vaccine donated after usage by a clinic and before discarding, and it was negative in 131 stimulation index (%) (positive: >181).

Subsequently, we performed immunostaining for the myocardium biopsy using antibodies against angiotensin-converting enzyme 2 (ACE2) (HPA000288; Sigma, USA), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike S protein (GTX632604; GenTex, USA), and C 4d (A213; Quidel, USA) to evaluate the relationship be-

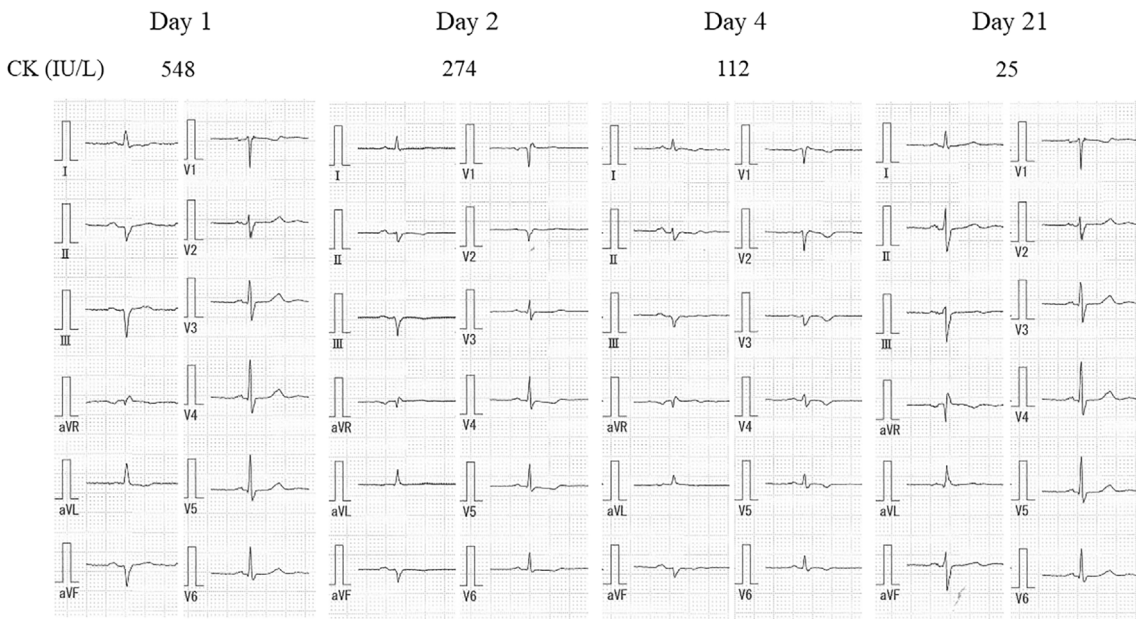

Figure 3. **Time course of electrocardiography and serum creatinine kinase.**

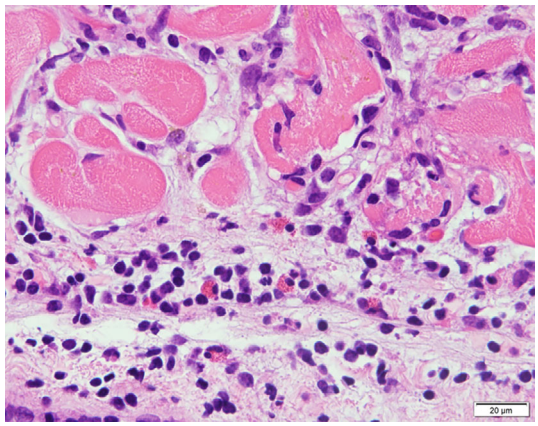

Figure 4. **Eosinophils are seen in the myocardium biopsy sample (Hematoxylin and Eosin staining, ×400).**

tween myocarditis and COVID-19 vaccination. The myocytes were positive for these antibodies (Fig. 5).

Discussion

We encountered a patient who had fulminant myocarditis 24 days after receiving the second dose of the COVID-19 mRNA vaccine and in whom findings of a histological examination showed infiltration of more T cells and macrophages, few B cells, and ACE2, SARS-CoV-2 (COVID-19) spike protein, and C4d positivity in the myocardium biopsy specimen.

We searched for previous reports on myocarditis, the COVID-19 vaccine, and biopsy or histology findings and identified 40 reports. Among them, we reviewed 18 cases with the vaccine type defined and evaluated the histopathology of the myocardium, including biopsy and autopsy findings, in addition to those in our case (Table 2) (5-20). The vaccine dose and duration between vaccination and myocarditis onset varied among the reports, indicating that the occurrence of myocarditis after COVID-19 mRNA vaccination is heterogeneous, and the underlying mechanisms may differ among cases.

Of the 19 total patients including our own, 9 had fulminant myocarditis. All of these cases of fulminant myocarditis, except for 1 case of fulminant necrotizing eosinophilic myocarditis, occurred 7-28 days after receiving the first or second dose of the BNT162b or mRNA-1273 vaccine, which was later than that of non-fulminant myocarditis, which occurred 1-6 days after the first or second dose of the BNT162b or mRNA-1273 vaccine. However, there was no significant difference in the pathological findings of infiltrating cells in patients with fulminant and non-fulminant myocarditis, which mainly comprised T-cells and macrophages. Thus, the mechanisms underlying myocarditis after COVID-19 vaccination were not determined by the histological findings of the myocardium in many cases, although only one patient (case 15) had neutrophil infiltration and natural killer cells, suggesting maladaptive innate immune response activation triggered by mRNA vaccination against SARS-CoV-2.

The proposed potential mechanisms include hypersensitivity reaction, immune cross-reactivity, sex-related factors (including testosterone), and genetic variants (variants in genes encoding human leukocyte antigen, desmosomal, cytoskeletal, or sarcomeric proteins) (21). There was one case of biopsy-proven eosinophilic myocarditis related to tetanus toxoid immunization (22), wherein the DLST was positive, and a type IV delayed hypersensitivity reaction was suspected. Although there have been no reports of DLST using a COVID-19 vaccine, we performed a DLST in our patient

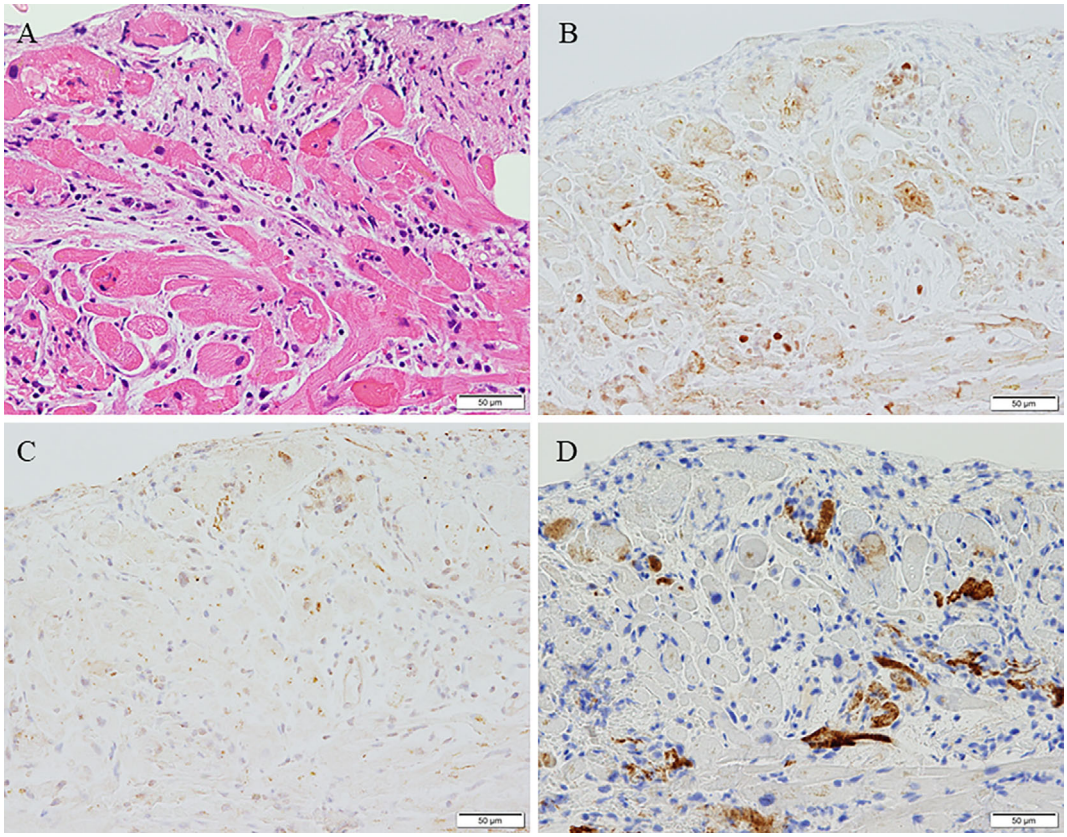

Figure 5. **Immunostaining of the myocardium biopsy sample using antibodies for ACE2, SARS-CoV-2 (COVID-19) spike protein, and C4d. In the myocardium biopsy sample with myocarditis (A, Hematoxylin and Eosin staining, ×200), ACE2 (B, ×200) and SARS-CoV-2 (COVID-19) spike protein (C, ×200) were positive in some myocytes, while C4d (D) was positive in some myocytes and interstitial cells. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, COVID-19: coronavirus disease 2019, ACE2: angiotensin-converting enzyme 2**

because eosinophils were detected among the infiltrating cells in the myocardium, and the time delay after vaccination was compatible with a type IV delayed hypersensitivity reaction. However, the DLST result was negative, suggesting a mechanism other than hypersensitivity reaction was involved in the present case.

Immune cross-reactivity is controversial, as one recent report did not support the notion that the increased occurrence of myocarditis after SARS-CoV-2-spike vaccination is mediated by a cross-reactive adaptive immune response (23). The COVID-19 virus uses the spike S protein to attain entry into the target cell receptor, ACE2 (24). ACE2 is expressed in the lungs, heart, gut smooth muscle, liver, kidney, neurons, and immune cells (24). Zou et al. (25) linked ACE2 expression in different organs to the potential risk of SARS-CoV-2 infection. High-risk tissues have cell types with >1% ACE2 expression, which includes the heart (>7.5%).

Recently, it was reported that circulating exosomes with the COVID-19 spike S protein are detectable on day 14 following the first dose of the BNT162b2 (Pfizer-BioNTech) vaccine, with a significant increase being noted on day 14 after the second dose; in addition, antibodies specific to the SARS-CoV-2 spike S protein are also increased on day 14 after the second dose (26). Furthermore, BNT162b2 (Pfizer-BioNTech) vaccination was also shown to stimulate spike-specific T cell responses, which were readily detectable seven days after and increased three to four weeks after the second dose (27). It was postulated that these exosomes were taken up by antigen-presenting cells, resulting in both humoral and cellular immune responses (26, 27).

Using immunohistochemistry, we confirmed ACE2 and spike protein expression in the myocytes in the present case. In addition, C4d was also positive in some myocytes and interstitial cells. These findings suggest that the immune response associated with the presence of spike S protein in cardiac myocytes and antibody induced by COVID-19 vaccination may be related to myocarditis in the present patient who developed fulminant myocarditis 24 days after receiving the second dose of the BNT162b2 vaccine.

However, there have been no reports concerning the expression of spike protein in cardiac myocytes in patients with myocarditis after COVID-19 vaccination, and the precise mechanisms underlying the presence of spike proteins in the myocytes in the present patient are unclear. Further studies are thus needed to elucidate the mechanisms underlying the development of myocarditis after COVID-19 vaccination with different vaccines and in different phases after vaccination.

Table 2. Histological Findings of Myocarditis after COVID-19 Vaccination in the Previous Reports and Our Report.

	Age	Sex	Type of vaccine	Vaccine dose	Days from vaccination to onset	Diagnosis	Eosinophil	T cell (CD3)	Macro-phage (CD68)	B cell (CD20)	Others	Ref.
1	22	M	BNT162b	1st	5 days	Myocarditis	-	+	++	ne	Neutrophil C4d (+)	(15)
2	40	M	BNT162b	1st	6 days	Lymphocytic myocarditis	-	++	++	ne	ne	(19)
3	45	F	BNT162b	1st	10 days	Fulminant myocarditis	+	++	++	+	CD4, CD8, CD138	(5)
4	57	F	BNT162b	1st	2 days	Fulminant necrotizing eosinophilic myocarditis	++	ne	ne	ne	ne	(14)
5	65	M	BNT162b	1st	1 day	Lymphocytic myocarditis	-	ne	ne	ne	ne	(16)
6	80	F	BNT162b	1st	12 days	Fulminant myocarditis	-	++	++	+	CD138 rare	(9)
7	18	M	BNT162b	2nd	3 days	Lymphocytic myocarditis	-	++	++	ne	ne	(6)
8	23	M	BNT162b	2nd	3 days	Acute myocarditis	-	-	+	ne	ne	(10)
9	38	M	BNT162b	2nd	4 days	Lymphocytic myocarditis	-	+	+	ne	ne	(6)
10	50	M	BNT162b	2nd	10 days	Fulminant myocarditis	+	++	++	+	ne	(8)
11	60	F	BNT162b	2nd	24 days	Fulminant lymphocytic myocarditis	+	++	++	+	C4d (+)	Our case
12	20	M	mRNA-1273	1st	3 days	Acute myocarditis	-	+	+	ne	ne	(17)
13	38	M	mRNA-1273	1st	8 days	Fulminant lymphocytic myocarditis	-	++	++	+	C4d (-)	(12)
14	48	F	mRNA-1273	1st	28 days	Fulminant lymphocytic myocarditis	-	++	++	+	CD4<CD8	(7)
15	20	M	mRNA-1273	2nd	2 days	Non-infectious endocarditis and myocarditis	-	-	-	ne	NK cell, neutrophil	(11)
16	42	M	mRNA-1273	2nd	14 days	Fulminant myocarditis	+	++	++	+	CD4, CD8, less CD138	(5)
17	29	M	Sputnik V	2nd	2 days	Lymphocytic myocarditis	-	ne	ne	ne	ne	(20)
18	38	F	BNT162b	?	7 days	Fulminant lymphocytic myocarditis	-	ne	ne	ne	ne	(13)
19	62	F	Ad26.COV2.S	?	4 days	Lymphohistocytic myocarditis	+	+	ne	ne	CD168	(18)

F: female, M: male, ne: not examined, Ref.: reference

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

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