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【 CASE REPORT 】

Delayed Acute Perimyocarditis and Bilateral Facial Nerve Palsy in a Patient with COVID-19

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Abstract:
A 41-year-old Japanese man was admitted to our hospital with acute perimyocarditis 4 weeks after coronavirus disease 2019 (COVID-19) infection. Ten days after admission, the patient showed bilateral facial nerve palsy in the course of improvement of perimyocarditis under treatment with aspirin and colchicine. After prednisolone therapy, perimyocarditis completely improved, and the facial nerve palsy gradually improved. Acute perimyocarditis and facial nerve palsy can occur even 4 weeks after contracting COVID-19.

Key words: pathology, viral infection

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Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Myocarditis is a cardiovascular disease that affects patients with COVID-19 (1). However, the pathophysiology of myocarditis caused by COVID-19 is not completely understood.

We herein report a patient with acute myocarditis and bilateral facial nerve palsy approximately one month after contracting COVID-19.

Case Report

A 41-year-old Japanese man was admitted to our hospital with a chief complaint of general fatigue and a high fever. The patient had stayed at home for two weeks after a two-week quarantine at a designated facility because of positive real-time reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 as a close contact with mild symptoms. His medical history was not noteworthy except for hypertension. His mother had colon cancer, and his father had hypertension. He was a non-smoker and had no alcohol intake. He had not been vaccinated against COVID-19 before admission.

A physical examination on admission revealed the following: blood pressure, 124/72 mmHg; pulse rate, 132/min regular; body temperature, 38.2°C; body mass index 24.8 kg/m^2; and no abnormal findings except for mild edema. The main laboratory findings included leukocytosis, liver dysfunction, high levels of N-terminal pro-b-type natriuretic peptide (NT-proBNP), high C-reactive protein and electrolyte abnormality, and dyslipidemia with negative findings for COVID-19 antibody, RT-PCR, and antigen in addition to routine pathogen tests (Table).

Chest X-ray showed mild cardiomegaly (Fig. 1A). Electrocardiography revealed sinus tachycardia and slight ST-segment elevation in leads I, II, aVL, and V2-6 (Fig. 1B). Transthoracic echocardiography (TTE) revealed an impaired left ventricular (LV) systolic function [ejection fraction (LVEF), 53%, end diastolic and systolic dimensions (LVDD and LVDS): 42 and 31 mm, respectively] with thickened walls [interventricular septum (IVS), 12 mm; LV posterior wall (LVPW), 12 mm], and mild pericardial effusion (Fig. 1C and D). Cardiac magnetic resonance imaging re-

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Table. Laboratory Data.

WBC	14,100 /μL	BUN	11 mg/dL
Stab	9 %	Cre	1.14 mg/dL
Seg	80 %	TP	7.4 g/dL
Lymph	7 %	Alb	3.5 g/dL
Mono	3 %	UA	2.5 mg/dL
Eosino	1 %	TG	317 mg/dL
RBC	5.25×10^4 /μL	LDL-C	91 mg/dL
Hb	13.7 g/dL	HDL-C	23 mg/dL
Hct	40.7 %	FPG	91 mg/dL
Plt	117×10^3 /μL	NT-proBNP	4,938 pg/mL
PT-INR	1.16	CRP	24.74 mg/dL
APTT	29.8 s	SARS-CoV-2-Ab	102 COI (<0.1)
D-dimer	1.1 μg/mL	SARS-CoV-2-PCR	(-)
T-Bil	1.1 mg/dL	SARS-CoV-2-Ag	(-)
AST	50 IU/L	Anti-nuclear antibody	<80
ALT	121 IU/L	sIL-2R	520 U/mL (121-613)
ALP	104 IU/L	CMV Ag (C7-HRP)	(-)
LDH	282 IU/L	MPO-ANCA	<1.0 U/mL (<3.5)
γ-GTP	114 IU/L	PR3-ANCA	<1.0 U/mL (<3.5)
CK	685 IU/L	Mycoplasma antibody	<40 (<320)
CKMB	6 IU/L	β-D glucan	5.5 pg/mL (<20)
hs-TnT	0.094 ng/mL	Influenza antigen	(-)
Na	123 mEq/L	Urinary angiten of *Legionella*	(-)
K	3.8 mEq/L	Urinary angiten of *Strept. pneumoniae*	(-)
Cl	86 mEq/L		
Ca	8.8 mg/dL		

WBC: white blood cell, RBC: red blood cell count, 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, 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, sIL-2R: soluble interleukin-2 receptor, CMV Ag: cytomegalovirus antigen, MPO-ANCA: myeloperoxydase-antineutrophil cytoplasmic antibody, PR3-ANCA: proteinase 3-antineutrophil cytoplasmic antibody, urinary angiten of *Strept. pneumoniae*: urinary angiten of *Streptococcus pneumoniae*

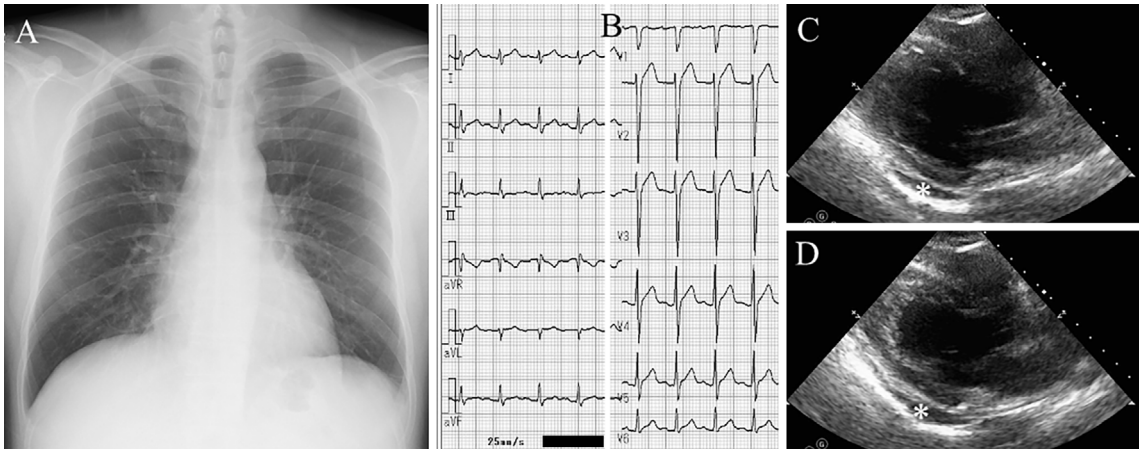

Figure 1. Chest radiography showed a cardiothoracic ratio of 51% (A); electrocardiography showed sinus tachycardia and slight ST segment elevation in leads I, II, aVL, and V2-6 (B); and transthoracic echocardiography demonstrated an impaired left ventricular systolic function (ejection fraction: 53%) with mild pericardial effusion (*) (parasternal long-axis view) (C, end-diastolic phase; D, end-systolic phase).

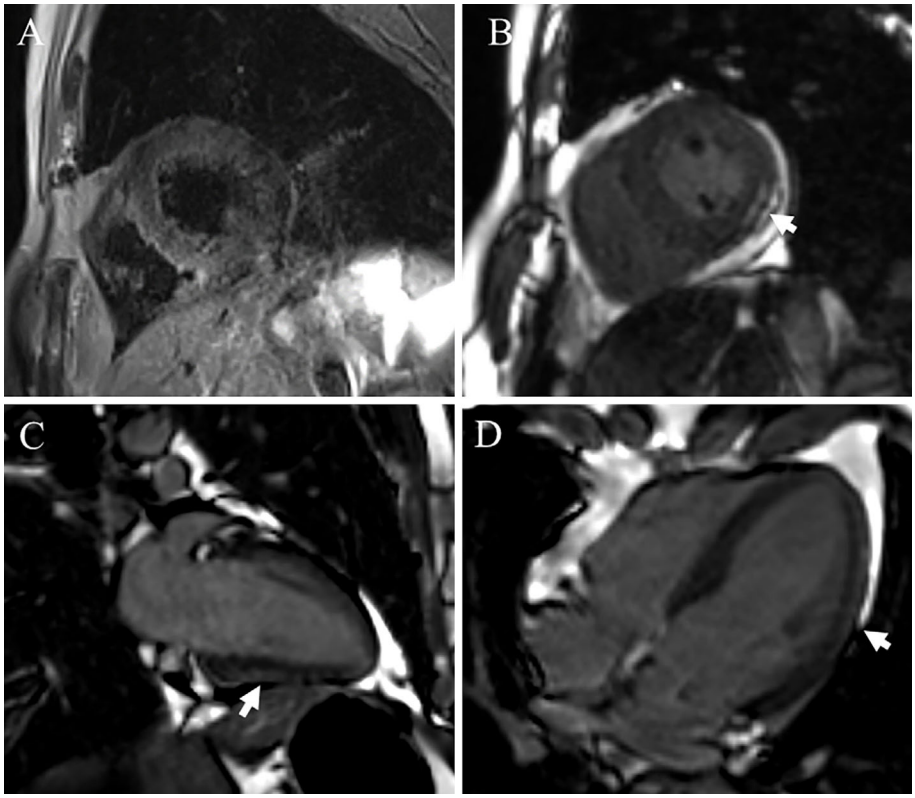

Figure 2. **Cardiac magnetic resonance imaging showed a high signal of T2-weighted black blood in the anterior, interventricular septal, and posterolateral walls of the LV (A, short-axis) and late gadolinium enhancement in the posterolateral wall of the LV (B: short-axis view, C: long-axis view, D: four-chamber view; arrows).**

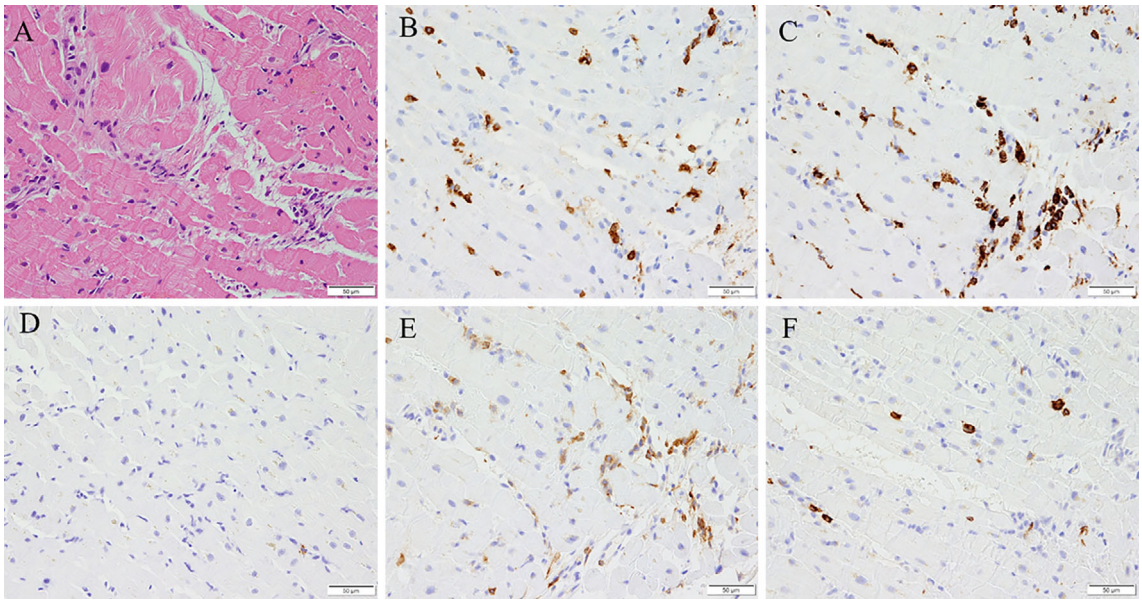

Figure 3. **A histopathological evaluation revealed interstitial mono-nuclear cell infiltration (A, Hematoxylin and Eosin staining). Infiltrating cells were mainly CD3-positive (T-cells) (B) and CD68-positive (macrophages) (C), with few CD20-positive cells (B-cells) (D) and more CD4-positive cells (E) than CD8-positive cells (F).**

vealed a high signal of T2-weighted black blood in the anterior, interventricular septal, and posterolateral walls of the LV (Fig. 2A) as well as late gadolinium enhancement in the lateral wall of the LV (Fig. 2B-D). Although coronary angiography was normal, left ventriculography showed diffuse hypokinesis of the LV with an ejection fraction of 49%. An

endomyocardial biopsy was thus performed.

A histopathological evaluation revealed infiltration of interstitial mononuclear cells (Fig. 3). Infiltrating cells were mainly T-cells and macrophages, with more CD4-positive cells than CD8-positive cells, and few B-cells (Fig. 3). RT-PCR SARS-CoV-2 was negative in the myocardium.

Electron microscopy revealed inflammatory cell infiltration and myocyte damage compatible with myocarditis (Fig. 4). However, viral particles were not detected in the high-power fields.

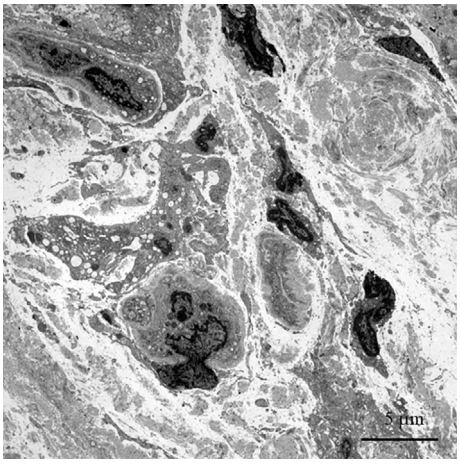

Figure 4. Electron microscopy showed myocardial damage and interstitial cell infiltration.

Tests for viral antibodies (using 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) were all negative. The final diagnosis was delayed acute perimyocarditis with COVID-19.

Aspirin (3,000 mg/day) and colchicine (1 mg/day) were started, and his condition gradually improved (Fig. 5). Ten days after admission, the patient also had bilateral peripheral facial nerve palsy; he could not close his mouth completely and had a drooping corner of the mouth that was more severe on the left side than on the right. He was also unable to wrinkle his forehead, and brain magnetic resonance imaging showed no abnormal findings. He was negative for anti-GQ1b IgG and anti-GM-1 IgG antibodies, and prednisolone (30 mg/day) was started. After treatment with prednisolone, the perimyocarditis completely improved (LVEF, 59%; LVDD, 49 mm; LVDS, 35 mm; IVS, 10 mm; LVPW, 10 mm; no pericardial effusion) (Fig. 5, 6), and the facial nerve palsy gradually improved and ultimately disappeared (Fig. 6).

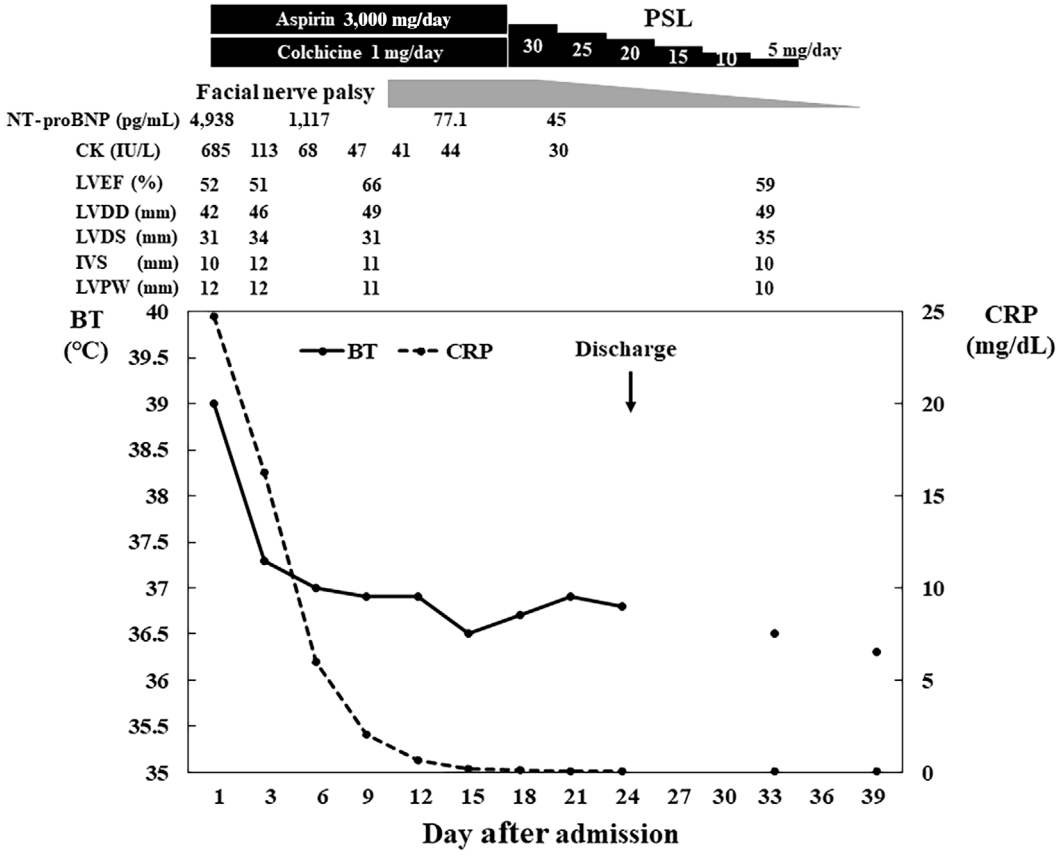

Figure 5. Time course of the data, temperature, facial nerve palsy, and treatments. CK: creatinine kinase, LVEF: left ventricular ejection fraction, LVDD: left ventricular end-diastolic dimension, LVDS: left ventricular end-systolic dimension, IVS: interventricular septum, LVPW: left ventricular posterior wall, PSL: prednisolone

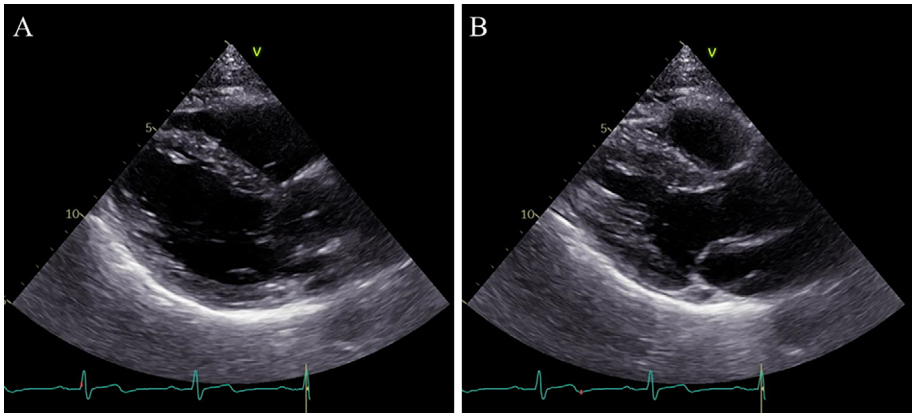

Figure 6. Transthoracic echocardiography after steroid treatment (parasternal long-axis view; A: end-diastolic phase, B: end-systolic phase)

Discussion

In COVID-19, cardiac injury can be induced by direct (viral infiltration into the myocardium) and indirect (cardiac stress related to respiratory failure, systemic hyperinflammation, etc.) mechanisms. However, the pathophysiology of myocarditis caused by COVID-19 is not completely understood. Furthermore, myocardial involvement may occur even in the absence of symptoms of respiratory infection (2).

Only one group reported the case of a 40-year-old man with delayed acute myocarditis confirmed by an endomyocardial biopsy with a nearly 1-month delay between symptoms of COVID-19, including a fever, intense fatigue, myalgia, and anosmia, and acute heart failure (3). The authors mentioned that almost all previously reported cases had heart failure and suspected acute myocarditis within one week from the onset of COVID-19 symptoms, hypothesizing that prolonged systemic inflammation (cytokine storm) led to both tonsillitis and myocardial inflammation in their case (3).

Our patient developed acute myocarditis four weeks after contracting COVID-19 without symptoms of respiratory tract infection and was diagnosed based on a histopathological examination of an endomyocardial biopsy specimen and negative RT-PCR findings for SARS-CoV-2 in the serum and myocardium. These results suggest that acute myocarditis is not directly induced by viral infiltration or cardiac stress due to respiratory failure and systemic hyperinflammation.

In addition, the patient had bilateral facial nerve palsy without any other neurological findings 10 days after admission, and steroid therapy seemed to be effective for both the perimyocarditis and facial nerve palsy. Previous studies have reported that facial nerve palsy is related to COVID-19 (4-6). They suggested that immune-mediated mechanisms may account for this because there was a delay between the onset of facial nerve palsy and COVID-19 in addition to a negative RT-PCR test for SARS-CoV-2 in the cerebrospinal fluid (5). Furthermore, only one patient with unilateral facial nerve palsy 18 days after acute COVID-19 myocarditis has been reported (7). Although there have been no reports of patients with COVID-19 with delayed acute myocarditis and facial nerve palsy, the present findings suggest that both perimyocarditis and facial nerve palsy in the present patient may have been induced by immune-mediated mechanisms.

COVID-19 can induce delayed manifestation in extrapulmonary organs, and myocarditis and facial nerve palsy should be considered as manifestations of post-acute COVID-19 syndrome (PACS), which is defined by persistent symptoms three to four weeks after the onset of COVID-19 (8). Steroid therapy may be effective for in these patients with PACS for treating myocarditis itself and preventing occurrence of facial nerve palsy or other organ diseases later. Only one paper mentioned PACS with the COVID-19 gamma variant (9), and precise data concerning the difference in PACS among COVID-19 variant infections are limited. Further studies are therefore needed to evaluate PACS in different variant infections of COVID-19.

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

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