ESC HEART FAILURE
ESC Heart Failure 2023; **10**: 1435–1439
Published online 23 November 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14252

CASE REPORT

Multisystem inflammatory syndrome and lymphohistiocytic myocarditis after Covid-19 vaccine in a middle-aged woman

Kosuke Kobayashi[1], Yasuhiro Hamatani[1], Koki Moriyoshi[2], Moritake Iguchi[1], Nobutoyo Masunaga[1], Mariko Terashima[3], Mitsuru Abe[1], Nozomu Sasahashi[3] and Masaharu Akao[1]*

[1]*Department of Cardiology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan;* [2]*Department of Diagnostic Pathology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan; and* [3]*Department of Trauma and Critical Care, National Hospital Organization Kyoto Medical Center, Kyoto, Japan*

Abstract

We describe a 51-year-old otherwise healthy woman hospitalized for hypotension, fever, and weakness 4 days after the second-dose Covid-19 mRNA vaccine. Elevated inflammatory markers, natriuretic peptide levels and troponin levels, and slightly reduced left ventricular ejection fraction of 50% were noted. We also found the multiple organ damage, including mucocutaneous, gastrointestinal, and neurologic systems. In addition, we revealed the positive results for anti-nucleocapsid SARS-CoV-2 IgG, albeit negative for SARS-CoV-2 polymerase chain reaction testing, suggesting the prior asymptomatic Covid-19 infection. We finally diagnosed her as multisystem inflammatory syndrome after vaccination. Of note, we obtained myocardial specimen from the patients and demonstrated the lymphohistiocytic myocarditis, which is a rare form of myocarditis.

Keywords Multisystem inflammatory syndrome; Myocarditis; Covid-19; Vaccination

Received: 25 July 2022; Revised: 28 October 2022; Accepted: 14 November 2022
**Correspondence to: Masaharu Akao, Department of Cardiology, National Hospital Organization Kyoto Medical Center, 1-1, Mukaihata-cho, Fukakusa, Fushimi-ku, Kyoto 612-8555, Japan. Email: akao@kuhp.kyoto-u.ac.jp*

Introduction

Coronavirus disease 2019 (Covid-19) has been a growing pandemic, and vaccines are considered the most promising approach for controlling the pandemic. Vaccines are generally safe and well tolerated, but adverse effects such as myocarditis have been rarely reported.[1,2] The multisystem inflammatory syndrome (MIS) was firstly described in patients following the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, typically characterized by systemic inflammation with multi-organ involvement.[3,4] Recently, MIS has been reported after Covid-19 vaccination[5]; however, the pathophysiology of this syndrome remains poorly understood. Thus, we herein described the case of MIS after vaccination, in which myocardial tissue was obtained, revealing a rare type of myocarditis called lymphohistiocytic myocarditis.

Case report

A 51-year-old Japanese woman was admitted to our institution for hypotension, fever, and weakness. Before admission, she had been well without significant past medical history. Three months before admission, Covid-19 was prevalent at her workplace, but she was asymptomatic. A month before admission, she received her first-dose Covid-19 messenger ribonucleic acid (mRNA) vaccine from Moderna (mRNA-1273). On the following day, fever and fatigue appeared. Her fever broke the next day, but fatigue continued for about 2 weeks. She did not undergo SARS-CoV-2 antigen test or real-time polymerase chain reaction (PCR) testing at that time. Four days before admission, she received her second-dose mRNA-1273 vaccine. Again, a high-grade fever and fatigue appeared on the following day. Weakness, diarrhoea, and fainting also appeared on the day of admission, and she was transferred to our hospital.

On arrival, she was drowsy and had a body temperature of 37.9°C, blood pressure of 67/30 mmHg, and heart rate of 123 beats/minute. Laboratory testing identified increased inflammatory markers (C-reactive protein and procalcitonin), abnormal renal function and electrolytes, elevated natriuretic peptide and troponin levels, but normal creatinine phosphokinase levels (*Table 1*). Chest radiography showed no specific abnormalities (*Figure 1A*). A 12-lead electrocardiography demonstrated no obvious ST-segment abnormality (*Figure 1B*). Transthoracic echocardiography demonstrated a slightly reduced left ventricular ejection fraction (50%) without myocardial oedema, pericardial effusion, and vegetations (*Figure 1C,D*). SARS-CoV-2 PCR testing on admission was negative. She was admitted to our hospital with a provisional diagnosis of septic shock considering hypotension, fever, and elevated inflammatory markers. She was treated empirically with broad-spectrum antibiotics and intravenous fluid boluses. Despite these treatments, she remained hypotensive and was given noradrenaline (0.26 γ), pitressin (2 units per hour), and dobutamine (2 γ). For the treatment of septic shock, we added intravenous steroid (hydrocortisone; 200 mg on Days 1 and 2, 100 mg on Day 3, and 50 mg on Day 4). Her symptoms and vital signs gradually improved, and laboratory parameters also started to improve. Vasopressors and inotropes were tapered and stopped on 4 days after admission.

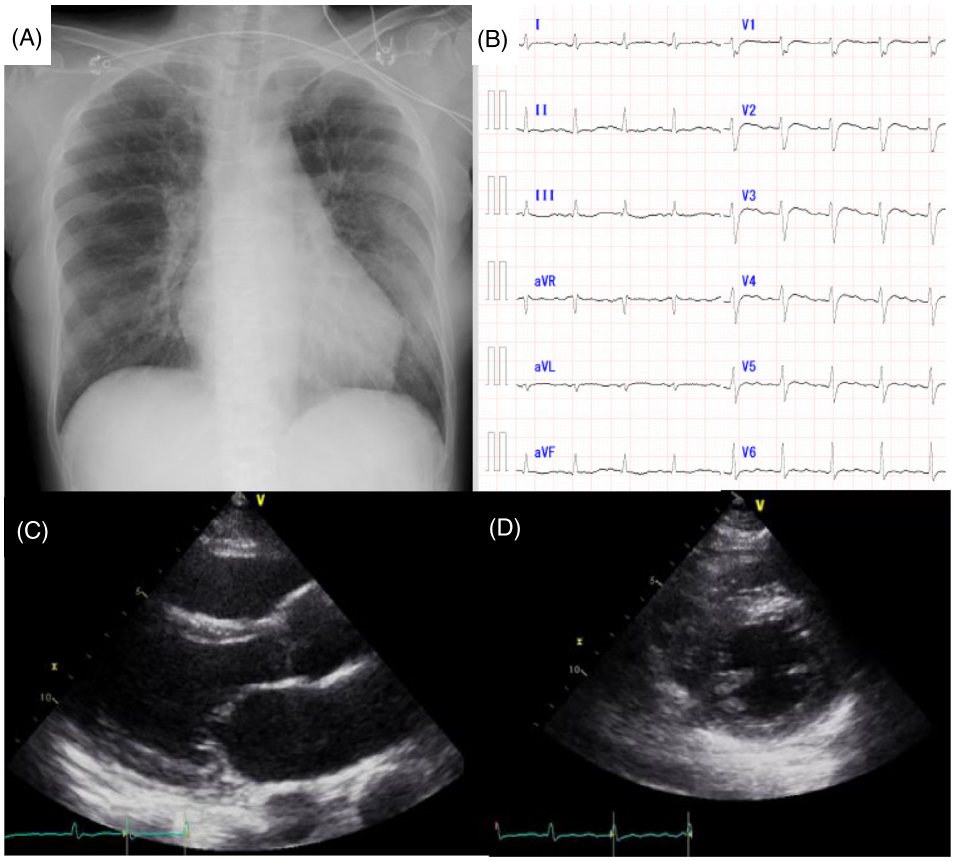
Table 1 Transition of laboratory marker levels

	On admission	2 months after admission	Reference range
WBC (/μL)	31 900	6200	3300–8600
Neutrophil (%)	93.5	51.9	-
Lymphocyte (%)	3.0	38.0	-
CRP (mg/L)	367.5	1.1	<1.4
Procalcitonin (ng/mL)	18.1	0.02	<0.49
Albumin (g/dL)	2.0	4.3	4.1–5.1
Creatinine (mg/dL)	1.57	0.63	0.46–0.79
Sodium (mEq/L)	122	141	138–145
Potassium (mEq/L)	3.1	3.8	3.6–4.8
CPK (U/L)	30	22	41–153
Troponin I (pg/mL)	335	<10.0	<40.0
NT-proBNP (pg/mL)	52,643	79	<125

CPK, creatinine phosphokinase; CRP, C-reactive protein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; WBC, white blood cell.

Two sets of blood cultures and urinary culture were all negative, and no focal signs of infection were found on whole-body computed tomography. As septic shock was unlikely the cause of her conditions, myocarditis after

Figure 1 Imaging data on admission. (A) Chest radiography, (B) electrocardiography, and (C,D) transthoracic echocardiography.



Covid-19 vaccination was suspected considering the elevated cardiac biomarkers and slightly reduced left ventricular ejection fraction. Cardiac magnetic resonance (CMR) performed 1 week after admission revealed a high-intensity lesion on T2 weighted image (*Figure 2A*) and a diffusely increased native T1 value of 1600–1800 msec on T1 mapping (*Figure 2B*), indicating the presence of myocarditis.

In addition to myocarditis, she had a history of diarrhoea and fainting and was noted after admission to have lymphadenopathy, bilateral conjunctivitis (*Figure 3A*), swelling and cracking of her lip (*Figure 3B*), and chilblain-like lesions on her toes and fingers (*Figure 3C*), all of which could not be explained solely by myocarditis. The rheumatology, haematology, and infectious disease workups were all unremarkable. Therefore, MIS was suspected, considering the multi-organ involvement including cardiac, renal, gastrointestinal, neurologic, and dermatologic systems in addition to the raised inflammatory markers. Overall, the patient's clinical features were consistent with the Brighton Collaboration definition of MIS. As there was no alternative diagnosis that explained the patient's status, she was diagnosed as MIS. She also had a positive result for anti-nucleocapsid SARS-CoV-2 IgG and high levels of anti-SARS-CoV-2 spike IgG, indicating previous SARS-CoV-2 infection and vaccine-induced antibody responses.

During hospitalization, cardiac catheterization was performed. Coronary angiography showed no evidence of stenosis or aneurysmal changes. Myocardial specimens obtained from right ventricular septum showed interstitial oedema and inflammatory cell infiltration. In particular, CD3 positive T cells (CD8 dominant) and CD68-positive macrophages were found, demonstrating lymphohistiocytic myocarditis (*Figure 4*).

Two weeks after admission, she was discharged without any medication. Two months after admission, she had no symptoms or physical abnormalities. All laboratory test abnormalities resolved (*Table 1*), and her left ventricular function normalized. Follow-up CMR evaluation showed no high-intensity lesions on T2-weighted image and a normal native T1 value (*Figure 2C,D*). She was followed up on an outpatient basis where she remained clinically well.

Figure 2 Cardiac magnetic resonance imaging performed 1 week after admission (A,B) and 2 months after admission (C,D). (A) T2-weighted image. White arrows indicate the high-intensity lesion. (B) T1 mapping. Yellowish myocardium indicates the prolongation of native T1 value. (C) T2-weighted image. There was no high-intensity lesion. (D) T1 mapping. Reddish myocardium indicates normal T1 value.

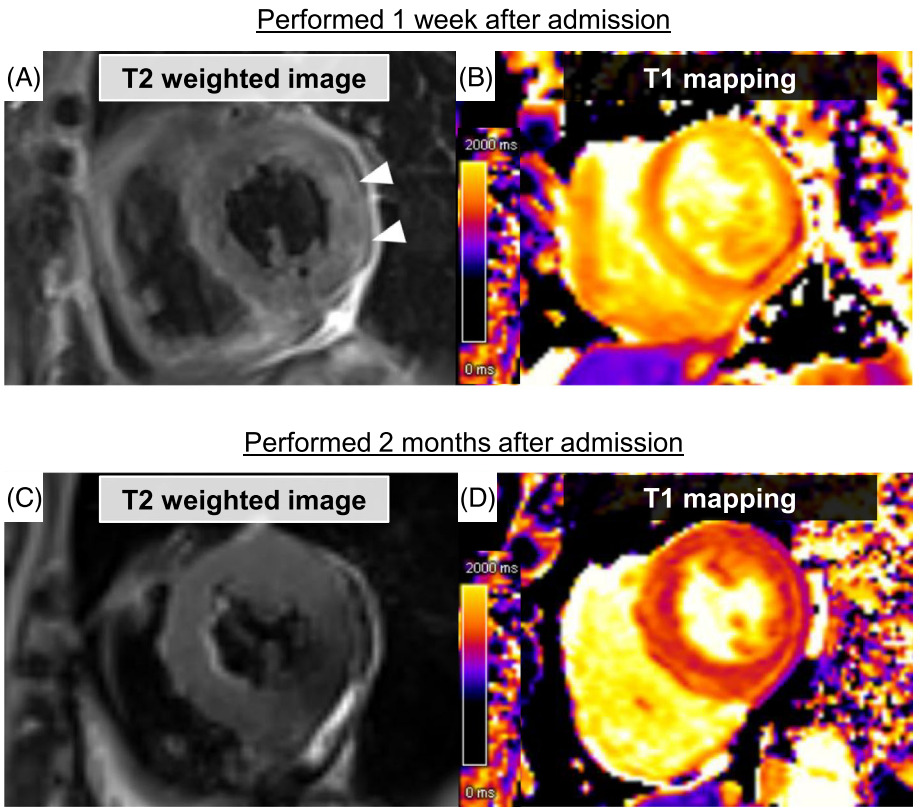


Figure 3 Physical findings. (A) conjunctivitis, (B) lip swelling and cracking, and (C) chilblain-like lesions on the fingers.

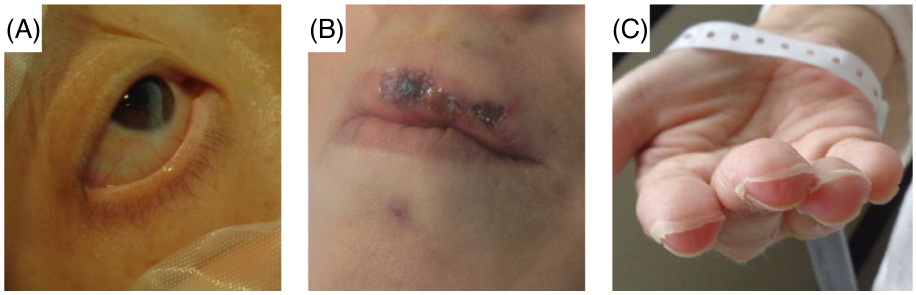
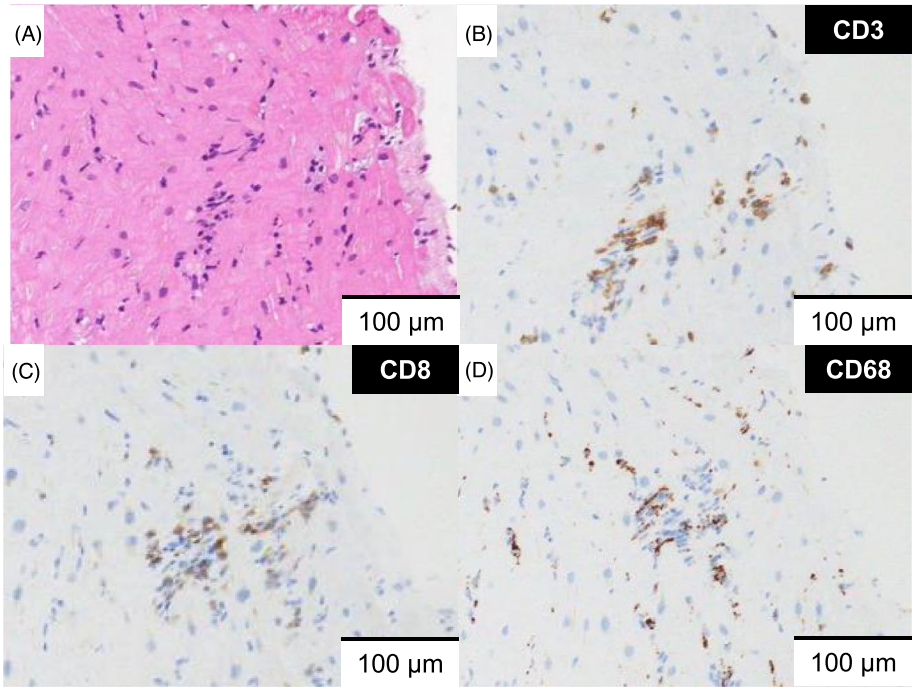


Figure 4 Pathological findings of the myocardium. (A) Haematoxylin and eosin staining and (B–D) immunohistochemical staining. CD3-positive, CD8-positive, and CD68-positive cells were infiltrated on myocardium.



Discussion

In this case, myocarditis after Covid-19 vaccination was initially suspected. Myocarditis has been recognized as a rare complication, especially in adolescent males, usually occurring 2–3 days after the second-dose mRNA vaccine.[2] Patients with myocarditis following Covid-19 vaccination typically have chest symptoms with mildly elevated creatine phosphokinase levels and rarely require inotrope and/or vasopressor supports.[2] Although this patient, based on the CMR and pathological findings, had myocarditis, she was middle-aged, without chest symptoms or elevated creatine phosphokinase levels, but required inotrope and vasopressor supports. These features were atypical for myocarditis after Covid-19 vaccination. In addition, the various abnormalities in multiple organs and remarkable increase in inflammatory response could not be explained solely by myocarditis. Therefore, we further examined other underlying causes and considered MIS as a differential diagnosis, consistent with this case.

MIS is characterized by an intense inflammatory activation that involves multisystem presentation with organ dysfunction in the absence of associative infective or alternative diagnoses.[6] Typically, MIS develops 2–6 weeks after recovery from Covid-19 infection in children (called MIS-C),[3] as well as in adults (called MIS-A).[4] There are increasing reports of MIS following Covid-19 vaccination (called MIS-V),[7] and a case definition of MIS has been proposed by the Brighton Collaboration Project.[6] Our patient's clinical features and

DOI: 10.1002/ehf2.14252

biochemical markers were consistent with the definitive case of MIS, including fever for 3 consecutive days, all four clinical features (mucocutaneous, gastrointestinal, shock/hypotension, and neurologic abnormalities), laboratory evidence of inflammation, and measures of disease activity (elevated natriuretic peptide levels, neutrophilia and lymphopenia, evidence of cardiac involvement by echocardiography, and findings consistent with myocarditis). Additionally, the patient received her second-dose Covid-19 mRNA vaccine 4 days before admission. Interestingly, recent case series reported that a number of MIS-V cases had a history of Covid-19 infection before vaccination,[7] and potent immune response can lead to hyperinflammation, which can paradoxically cause harm to the host. Indeed, our patient also had a positive SARS-CoV-2 nucleocapsid antibody result, indicating the possibility of MIS-V.

To date, there is a paucity of literature regarding the histopathology of MIS-V. Of particular note, a myocardial specimen was obtained from the patient complicated with MIS-V. Our case demonstrated lymphohistiocytic myocarditis, considered to be a rare form of myocarditis. A previous case report found this type of myocarditis in MIS following Covid-19 natural infection.[8] Lymphohistiocytic myocarditis has also been reported in immune checkpoint inhibitor-associated myocarditis.[9] One case series study concluded that the diffuse lymphohistiocytic myocarditis associated with immune checkpoint inhibitor is relatively distinctive.[10] Taken together with our case and previous reports, myocarditis in MIS and immune checkpoint inhibitor associated myocarditis seem to have similar histopathological findings, suggesting that a dysregulated immune system is involved in the mechanism of MIS. In this regard, although speculative, intravenous steroids may be effective for improving the patient's condition. However, as the efficacy of immunosuppressive treatment for MIS-V has not been confirmed to date, treatment strategies must be determined case by case.

In conclusion, we experienced a middle-aged woman complicated with MIS-V and lymphohistiocytic myocarditis after second-dose Covid-19 mRNA vaccine. We have to consider MIS-V as a differential diagnosis when we see a patient with multi-organ involvements after vaccination.

Conflict of interest

The authors have reported that they have no conflicts of interest to disclose.

Funding

None.

References

1. Mevorach D, Anis E, Cedar N, Bromberg M, Haas EJ, Nadir E, Olsha-Castell S, Arad D, Hasin T, Levi N, Asleh R, Amir O, Meir K, Cohen D, Dichtiar R, Novick D, Hershkovitz Y, Dagan R, Leitersdorf I, Ben-Ami R, Miskin I, Saliba W, Muhsen K, Levi Y, Green MS, Keinan-Boker L, Alroy-Preis S. Myocarditis after BNT162b2 mRNA vaccine against Covid-19 in Israel. *N Engl J Med* 2021; **385**: 2140–2149.
2. Witberg G, Barda N, Hoss S, Richter I, Wiessman M, Aviv Y, Grinberg T, Auster O, Dagan N, Balicer RD, Kornowski R. Myocarditis after Covid-19 vaccination in a large health care organization. *N Engl J Med* 2021; **385**: 2132–2139.
3. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, Barranco MA, Maxted AM, Rosenberg ES, Easton D, Udo T, Kumar J, Pulver W, Smith L, Hutton B, Blog D, Zucker H. Multisystem inflammatory syndrome in children in New York state. *N Engl J Med* 2020; **383**: 347–358.
4. Patel P, DeCuir J, Abrams J, Campbell AP, Godfred-Cato S, Belay ED. Clinical characteristics of multisystem inflammatory syndrome in adults: a systematic review. *JAMA Netw Open* 2021; **4**: e2126456.
5. Nune A, Iyengar KP, Goddard C, Ahmed AE. Multisystem inflammatory syndrome in an adult following the SARS-CoV-2 vaccine (MIS-V). *BMJ Case Rep* 2021; **14**: e243888.
6. Vogel TP, Top KA, Karatzios C, Hilmers DC, Tapia LI, Moceri P, Giovannini-Chami L, Wood N, Chandler RE, Klein NP, Schlaudecker EP, Poli MC, Muscal E, Munoz FM. Multisystem inflammatory syndrome in children and adults (MIS-C/A): case definition & guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2021; **39**: 3037–3049.
7. Belay ED, Godfred Cato S, Rao AK, Abrams J, Wilson WW, Lim S, Newton-Cheh C, Melgar M, DeCuir J, Webb B, Marquez P, Su JR, Meng L, Grome HN, Schlaudecker E, Talaat K, Edwards K, Barnett E, Campbell AP, Broder KR, Bamrah MS. Multisystem inflammatory syndrome in adults after SARS-CoV-2 infection and COVID-19 vaccination. *Clin Infect Dis* 2022; **75**: e741–e748.
8. Bemtgen X, Klingel K, Hufnagel M, Janda A, Bode C, Staudacher DL, Supady A, Jandova I. Case report: Lymphohistiocytic myocarditis with severe cardiogenic shock requiring mechanical cardiocirculatory support in multisystem inflammatory syndrome following SARS-CoV-2 infection. *Front Cardiovasc Med* 2021; **8**: 716198.
9. Champion SN, Stone JR. Immune checkpoint inhibitor associated myocarditis occurs in both high-grade and low-grade forms. *Mod Pathol* 2020; **33**: 99–108.
10. Sobol I, Chen CL, Mahmood SS, Borczuk AC. Histopathologic characterization of myocarditis associated with immune checkpoint inhibitor therapy. *Arch Pathol Lab Med* 2020; **144**: 1392–1396.