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CASE REPORT
Heart failure

Multidisciplinary diagnostic approach for fulminant myocarditis related to coronavirus disease 2019 messenger RNA vaccines: a case report

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Background Recent reports have raised serious concerns regarding acute myocarditis related to coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) vaccines. There are only a few reports of fulminant lymphocytic myocarditis that developed after vaccination. Although the diagnostic approach varied among them, no cases with multidisciplinary diagnostic approaches, including cytokine analysis, have been reported.

Case summary A 59-year-old male with no medical history complained of chest pain a day after receiving the first dose of COVID-19 mRNA (BNT162b2) vaccination. On hospital Day 3, he developed a refractory cardiogenic shock and pulseless ventricular tachycardia, requiring mechanical circulatory support secondary to an exacerbation of myocarditis. Based on the clinical course and examination results, including histologic findings showing a diffuse lymphocytic inflammatory infiltrate with abundant T cells and macrophages in the myocardium, and cardiac magnetic resonance (CMR) findings showing a high-intensity signal on the T2-weighted image and late gadolinium enhancement, he was diagnosed with fulminant myocarditis related to COVID-19 mRNA vaccination. His haemodynamic status gradually improved without immunosuppressive or anti-inflammatory therapy, and he was discharged from hospital on Day 47. To investigate the pathogenesis, we performed cytokine analysis, which showed an increase in serum IP-10, MCP-3, and MIG concentrations, suggesting that Th1-type chemokines preferentially promote cellular immunity.

Discussion In the present case of a patient with fulminant myocarditis following COVID-19 mRNA vaccination diagnosed through histopathological and CMR findings, additional cytokine analysis revealed that elevated levels of cytokines pertaining to Th1 immune response may be involved in disease pathogenesis. A multidisciplinary diagnostic approach is crucial not only to comprehend an individual patient's condition but also to clarify the disease pathogenesis.

Keywords Coronavirus disease 2019 messenger RNA vaccination • Myocarditis • Cytokines • Case report

ESC Curriculum 2.3 Cardiac magnetic resonance • 7.1 Haemodynamic instability • 6.4 Acute heart failure

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Learning points

- Acute myocarditis after coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) vaccination may turn fulminant, requiring mechanical cardiac support devices.
- Elevated levels of cytokines involved in the Th1 immune response may play some roles in the pathogenesis of fulminant myocarditis following COVID-19 mRNA vaccination.
- Multidisciplinary diagnostic approaches, including cytokine analysis, are crucial not only to comprehend an individual patient's condition but to also clarify the underlying pathogenesis.

Introduction

Coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) vaccines significantly reduce the incidence of COVID-19-related hospitalization and death. Recent reports have also shown that mRNA-based COVID-19 vaccines are associated with acute myocarditis, raising serious concerns.[1,2] Although the post-vaccination clinical presentation of myocarditis is usually mild,[3] some patients have been reported to have developed fulminant lymphocytic myocarditis after receiving their dose.[4,5] Among them, the diagnostic approach varies; however, there have been no reports citing diagnostic investigations including cytokine analysis. Herein, we present a case of a patient with fulminant lymphocytic myocarditis related to COVID-19 mRNA vaccination in which a multidisciplinary diagnostic approach with cardiac imaging, histological assessment, and cytokine analysis was used to investigate the pathogenesis.

Timeline

Time	Events
Three days before the admission	First dose of coronavirus disease 2019 messenger RNA (BNT162b2) vaccination (Comirnaty, BioNTech/Pfizer)
Two days before admission	Complaint of chest pain
Day 1	Admission to an affiliated hospital and performing urgent coronary angiography revealing no obstructive coronary arteries
Day 3	Veno-arterial extracorporeal mechanical oxygenation (VA-ECMO), intra-aortic balloon pumping (IABP), and a temporary transvenous pacemaker introduced due to refractory cardiogenic shock and ventricular tachycardia
Day 6	IABP switched to Impella CP; right ventricular endomyocardial biopsy performed
Day 7	Transfer to our hospital
Day 8	Withdrawal of VA-ECMO
Day 13	Withdrawal of Impella CP
Day 22	Transfer to the general ward after discontinuation of vasopressors
Day 43	Contrast-enhanced cardiac magnetic resonance imaging performed (diffuse high T2-weighted signal intensity of the left ventricular myocardium, specifically in the basal inferior wall)
Day 47	Discharge

Case presentation

A 59-year-old male with no medical history complained of chest pain a day after receiving the first dose of COVID-19 mRNA (BNT162b2) vaccination (Comirnaty, BioNTech/Pfizer) and was admitted to an affiliated hospital 3 days after this vaccination. On physical examination, the vital signs were shown as follows: body temperature 37.0°C, pulse 100/min, blood pressure 104/62 mmHg, and respiratory rate 20/min, and his oxygen saturation was 98% on room air. The results of cardiac and pulmonary examinations were normal. Electrocardiography showed sinus tachycardia with ST elevation in Leads V1–V3, aVR, and aVL (*Figure 1A*). An initial laboratory investigation showed a high-sensitivity cardiac troponin I concentration of 25.47 pg/mL (normal range < 0.047 pg/mL) and creatine kinase (CK) concentration of 549 U/L (normal range < 248 U/L). The result of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction test of a nasopharyngeal swab was negative. Serological examination for viruses associated with myocarditis, such as coxsackievirus and influenza virus, revealed no evidence of active viral infections. The test results of autoimmune disease–associated autoantibodies were also negative. Transthoracic echocardiography (TTE) demonstrated a moderately reduced left ventricular ejection fraction (LVEF) of 46% (normal range ≥ 55%) with slight pericardial effusion (see Supplementary material online). Urgent coronary angiography revealed non-obstructive coronary arteries. The clinical course suggested acute myocarditis accompanied by pericarditis, followed by an administration of loxoprofen sodium hydrate. On hospital Day 3, the patient's haemodynamic state became unstable despite a maximum dose of vasopressor infusion. High-sensitivity cardiac troponin I and CK levels were elevated to 8.15 pg/mL and 1229 U/L, respectively. Electrocardiography showed a new-onset intra-ventricular conduction disturbance with a transient complete atrioventricular block (*Figure 1B*). Repeated TTE showed severe left ventricular systolic dysfunction with an ejection fraction of 20% (see Supplementary material online). As pulseless ventricular tachycardia refractory to electrical defibrillation occurred, veno-arterial extracorporeal mechanical oxygenation (VA-ECMO), intra-aortic balloon pumping (IABP), and temporary transvenous pacemaker were introduced. On hospital Day 6, IABP was replaced by a percutaneous left ventricular assist device (Impella CP), and simultaneously, right ventricular endomyocardial biopsy (EMB) was performed. Histological and immunohistological findings showed a diffuse lymphocytic inflammatory infiltrate with mild fibrosis in the interstitium with abundant T cells (CD3, CD4, and CD8) and macrophages (CD68) (*Figure 2*).

On hospital Day 7, the patient was transferred to our hospital because of the possible introduction of an implantable left ventricular assist device, which had not been available at the previous hospital. Electrocardiography demonstrated a low voltage in all leads (*Figure 1C*). Transthoracic echocardiography showed that the severe left ventricular systolic dysfunction decreased to an LVEF of 15% (see Supplementary material online). IgG antibody against SARS-CoV-2 spike protein was detected at a titre of 1:320; immunoglobulin G (IgG) antibody against anti-nucleocapsid was

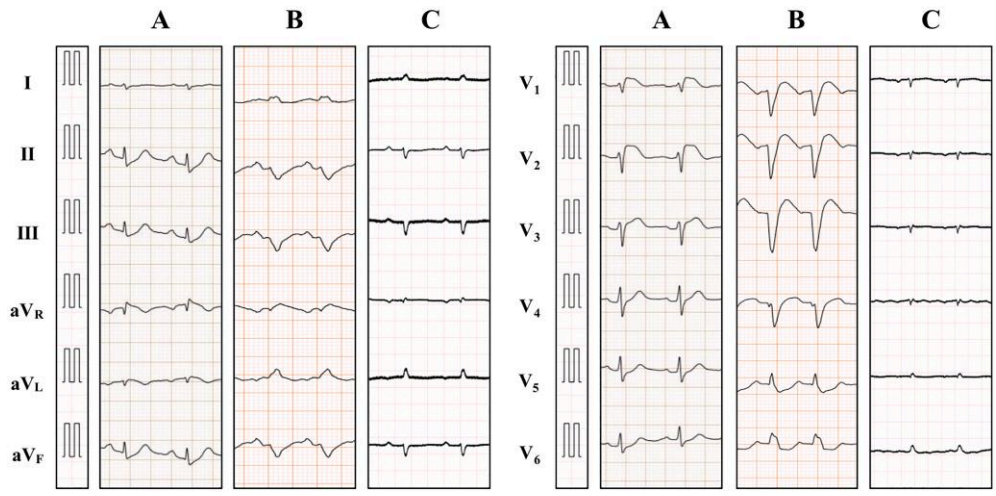


Figure 1 Electrocardiogram findings. Electrocardiogram on admission (*A*), on hospital Day 3 (*B*), and at the time of transfer to our hospital (*C*).

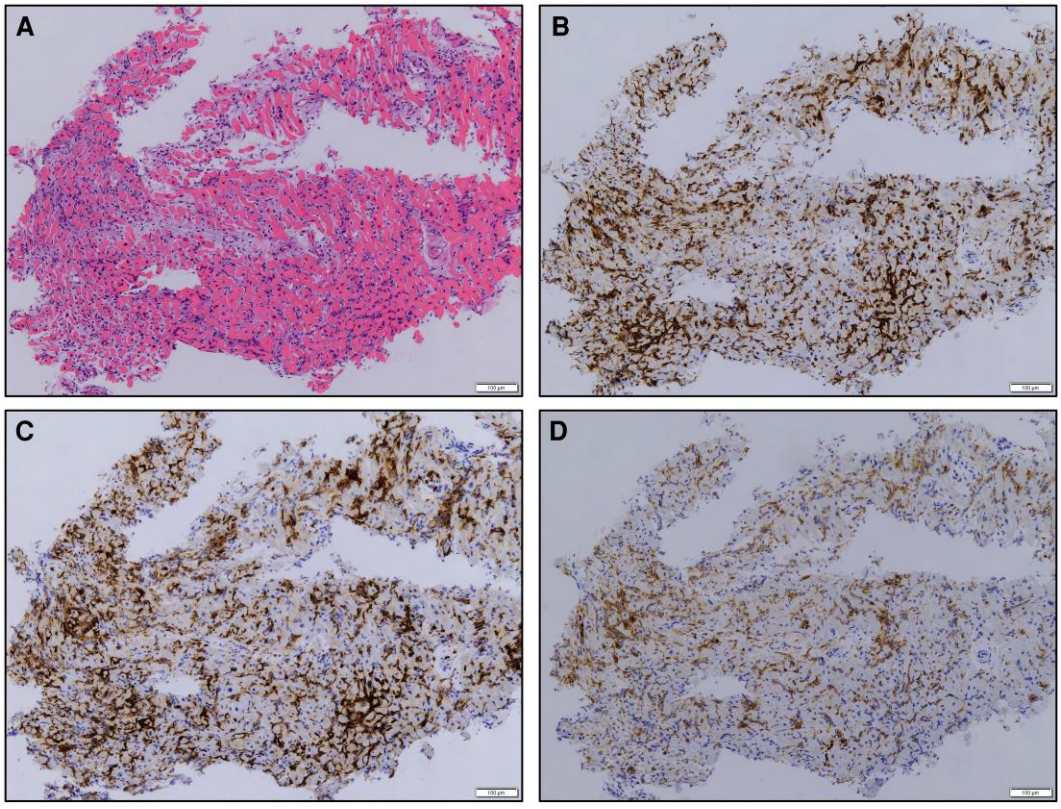


Figure 2 Histological and immunohistological findings from endomyocardial biopsy. Haematoxylin–eosin staining shows a diffuse lymphocytic inflammatory infiltrate with few eosinophils and mild fibrosis in the interstitium (*A*). CD3 staining highlights an abundance of T cells (*B*). CD8 staining highlights abundant amounts of CD8+ cytotoxic T cells (*C*). CD68 staining highlights macrophages (*D*).

not detected, indicating that the patient acquired immunity through COVID-19 mRNA vaccination without a history of infection. We diagnosed fulminant myocarditis and pericarditis that developed after COVID-19 mRNA (BNT162b2) vaccination. His haemodynamic status gradually improved, without immunosuppressive or anti-inflammatory therapy. On hospital Days 8 and 13, the VA-ECMO and the Impella CP were withdrawn, respectively. After the patient was weaned off the vasopressors, he was transferred to the general ward on hospital Day 22: thereafter, bisoprolol, losartan potassium, and spironolactone were introduced sequentially and titrated. Follow-up TTE performed on hospital

Day 29 showed that LVEF improved to 35% (see Supplementary material online). Contrast-enhanced cardiac magnetic resonance (CMR) imaging was performed on hospital Day 43 (*Figure 3*). T2-weighted image showed diffuse high signal intensity of the LV myocardium, specifically in the basal inferior wall (*Figure 3*). A serial serum sample analysis showed a marked increase in the serum concentrations of IP-10 (CXCL10), MCP-3 (CCL7), and MIG (CXCL9) at 3 days after vaccination and a non-significant increase in those of IL-4 and IL-13 (*Figure 4*) and other cytokines (data not provided). On hospital Day 47, the patient was discharged on a course of bisoprolol (2.5 mg/day), losartan potassium (25 mg/day), and spironolactone (25 mg/day). He had no recurrence at 1-year follow-up from the day of discharge.

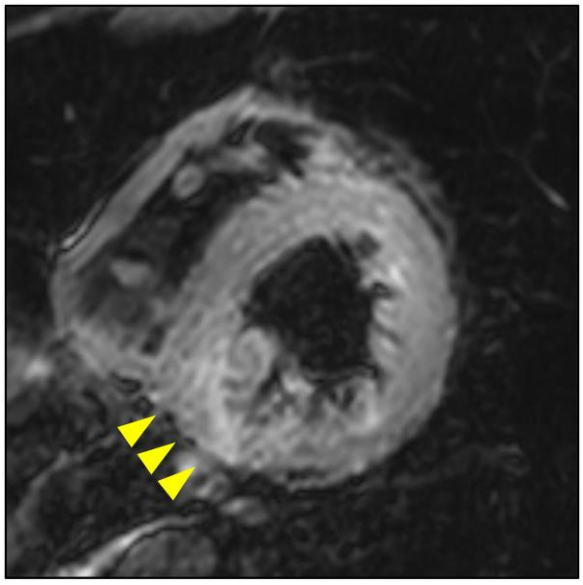


Figure 3 Contrast-enhanced cardiac magnetic resonance imaging. Short-axis images at the papillary muscle level in T2-weighted show diffuse high signal intensity in the left ventricular myocardium, specifically in the basal inferior wall (arrowheads). Late gadolinium enhancement image is omitted due to low image quality.

Discussion

Coronavirus disease 2019 mRNA vaccination–related myocarditis usually has a benign clinical course. Contrary to most patients who responded well to conservative therapy, the patient in this case had a malignant clinical course requiring mechanical cardiac support devices. Moreover, myocarditis after mRNA COVID-19 vaccination commonly occurs in males aged <30 years within several days of the second dose[6] and rarely in middle-aged individuals after the first dose. According to a previous report, the crude rate of myocarditis or pericarditis cases after mRNA COVID-19 vaccination is <1.0 case per million doses in men aged >50 years.[2] The current case suggests that, even in middle-aged individuals after the first dose, watchful observation is needed.

Cardiac magnetic resonance and EMB are useful for establishing the diagnosis of acute myocarditis and for monitoring disease progression. However, they are not easily accessible due to their limited capacity and are thus performed only in specific hospitals. If the recognition of myocarditis is to be improved, this disease should be clinically suspected based on the clinical presentation and the results of non-invasive tests other than EMB and CMR. Meanwhile, it is also crucial to reach a definitive diagnosis to implement appropriate treatments such as providing

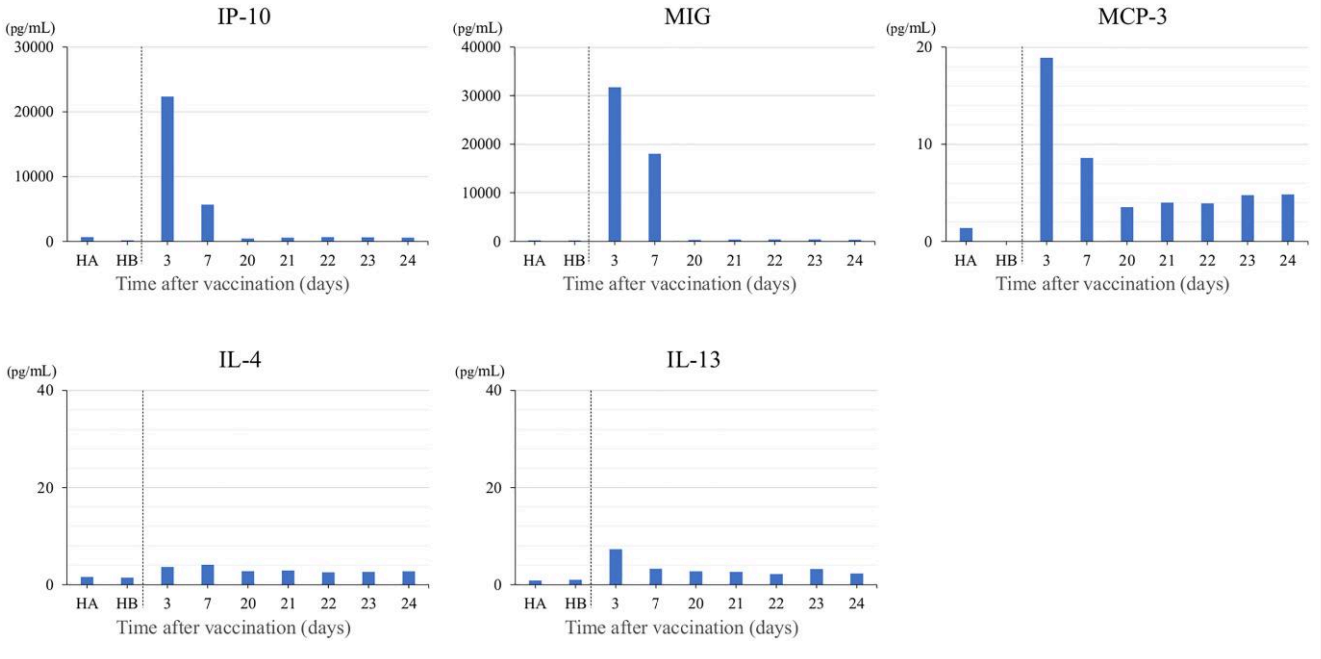


Figure 4 Cytokine profiles in the case patient relative to unvaccinated naive and coronavirus disease 2019 patient samples. The results for healthy controls are represented by healthy individual A (HA) and healthy individual B (HB), respectively. Cytokines and chemokines were analysed in serum samples from patients 3, 7, and 20–24 days after vaccination. IL-4, interleukin-4; IL-13, interleukin-13; IP-10, interferon gamma-induced protein 10; MIG, monokine induced by interferon gamma; MCP-3, monocyte chemotactic protein 3.

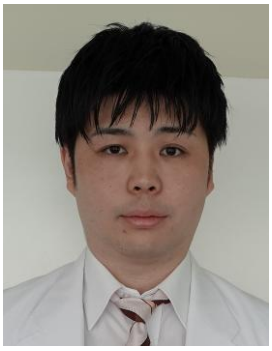
immunosuppressive agents. In this regard, according to the centers for disease control and prevention (CDC) working case definition for acute myocarditis, either CMR or EMB is essential.[6] Specifically in most reported cases of suspected post-COVID-19 vaccination myocarditis, the diagnosis of myocardial inflammation was based on CMR findings due to its lower invasiveness compared with that of EMB.[7] However, the drawback of CMR is its low diagnostic accuracy and low specificity.[8] Therefore, EMB is necessary to obtain an accurate diagnosis of acute myocarditis, specifically fulminant myocarditis. In fact, expert consensus highly recommends EMB as the gold standard for the diagnosis of fulminant myocarditis.[9] The cases of a few patients in whom EMB was performed for suspected post-COVID-19 vaccination myocarditis have been reported previously;[4,10] in these studies, the histopathological and immunohistological findings were similar to those of lymphocytic myocarditis demonstrating primary T-cell and macrophage infiltration, which are in line with the current patient case.

Cytokine analysis is widely used to understand the functional alterations of the host immune system. Recent assays are designed to quantify multiple cytokines in various matrices, including serum samples and tissue culture supernatants, and obtain more accessibility. We consider that this analysis can provide us with crucial clues to unveil the pathogenesis of inflammatory heart disease including myocarditis. Generally, lymphocytic myocarditis is attributed to immune-mediated myocardial damage, including virus infections, in systemic inflammatory diseases.[11] In the current patient case, cytokine analysis showed notable increases in IP-10 (CXCL10), MCP-3 (CCL7), and MIG (CXCL9) levels compared with those in the reference groups, which are categorized as Th1-type chemokines that preferentially promote cellular immunity by activating the chemotaxis of CXCR3+ cells including activated T lymphocytes (CD8), B lymphocytes, and monocytes. Meanwhile, compared with those in the reference group, we observed only a subtle increase in the IL-4 and IL-13 levels, which are categorized as Th2-type chemokines, and comparable levels of the other cytokines measured (Bio-Plex Pro Human Cytokine Screening Panel, 48-Plex). Recently, COVID-19 mRNA (BNT162b2) vaccination has been reported to induce cytokine signatures featuring IP-10 (CXCL10) in addition to IL-15 and interferon (IFN)-γ.[12] Similarly, IP-10 has been reported to be induced in heart tissue infected with coxsackievirus B3 (CVB3) and to cause myocardial injury.[13] Furthermore, MCP-3 (CCL7) and MIG (CXL9) have been reported to induce histiocyte chemotaxis, followed by the development of CVB3 myocarditis via the Th1 immune response.[7,14] In the current patient case, negative antibody tests against coxsackievirus confirmed that fulminant myocarditis was caused by COVID-19 mRNA vaccination. We believe that elevated levels of these cytokines in the Th1 immune response are involved in the pathogenesis of myocarditis related to COVID-19 mRNA vaccination. Interestingly, similar to this form of myocarditis, CVB3 myocarditis also shows sex differences, with increased severity in males.[15] The potential underlying mechanism is the inhibition of anti-inflammatory cells by testosterone, followed by its involvement in a Th1-type immune response.[2,16] A similar mechanism may explain sex differences in myocarditis related to COVID-19 mRNA vaccination.

Conclusions

Here, we have reported a rare case of a patient with fulminant myocarditis following COVID-19 mRNA vaccination by using a multidisciplinary diagnostic approach, suggesting that elevated levels of cytokines involved in the Th1 immune response may be responsible for its pathogenesis. A multidisciplinary diagnostic approach, including cytokine analysis, is crucial in terms of not only understanding the individual patient's condition but also clarifying the pathogenesis of post-COVID-19 mRNA vaccination myocarditis.

Lead author biography



Masayoshi Fujii graduated from Hyogo College of Medicine in 2016. He completed his residency programme at the Steel Memorial Hirohata Hospital and worked as a fellow in cardiology at the Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Hyogo, Japan. Currently, he continues his fellowship at the Division of Cardiovascular Medicine, Hyogo Brain and Heart Center, Himeji, Japan.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports*.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and related text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

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