【 CASE REPORT 】

# Acute Lymphocyte Myocarditis Associated with Influenza Vaccination

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**Abstract:**

An elderly patient was admitted to our hospital for acute heart failure soon after receiving influenza vaccination. On admission, chest radiography revealed pulmonary edema. An electrocardiogram showed poor R progression, and echocardiography showed diffuse hypokinesis and myocardial edema. The serum troponin level was elevated. A histopathological evaluation indicated active myocarditis with lymphocyte-predominant infiltrates. A drug-induced lymphocyte stimulation test (DLST) was positive. The patient rapidly recovered from heart failure after treatment with conventional heart failure drugs, such as intravenous diuretics and vasodilators. These experimental data and the clinical course suggest that influenza vaccination was responsible for heart failure due to acute lymphocyte myocarditis.

**Key words:** influenza vaccination, acute lymphocyte myocarditis, heart failure

## Introduction

Seasonal influenza epidemics cause serious illness and death worldwide. In particular, elderly patients with multiple comorbidities are at a high risk for complications of influenza, including severe pneumonia, toxic shock syndrome, and central nervous system complications (1). Influenza vaccination not only reduces the risk of influenza infection but also reduces the severity of illness in infected individuals and thus has been shown to confer considerable protection against influenza pandemics. The United States Advisory Committee on Immunization Practices recommends annual influenza vaccination for all individuals ≥6 months old (2, 3). Although inactivated influenza vaccines are generally well tolerated, rare serious adverse events have been reported (4).

We herein report a rare case of acute heart failure due to lymphocyte myocarditis after influenza vaccination.

## Case Report

A 74-year-old man presented with the sudden onset of or-
thopnea at our hospital's emergency department. Two days earlier, he had received a standard dose of a four-component vaccine against seasonal influenza. He had received influenza vaccination in previous years, but this vaccination was the first in this season. He had a history of well-controlled rheumatoid arthritis (RA) since 71 years old and hypertension since 60 years old. His outpatient medications included immunosuppressive and antihypertensive agents such as tacrolimus hydrate, angiotensin II type 1 receptor blockers, and beta-blockers.

On presentation, his consciousness status was unclear because of severe hypoxemia. His oxygen saturation did not improve beyond 90% despite oxygen being delivered through a non-rebreather mask at 10 L/min, so he was intubated for pressure-controlled mechanical ventilation and transferred to the intensive-care unit. The results of physical examination were as follows: temperature, 37.4℃; heart rate, 124 beats per minute; blood pressure, 140/90 mmHg in the right arm; respiratory rate, 20 breaths per minute; and widespread coarse crackle and rhonchi on auscultation of the lung fields. Additional heart sounds (i.e. S3 and S4 gallops) were audible, and the carotid vein was distended. There was no peripheral edema.

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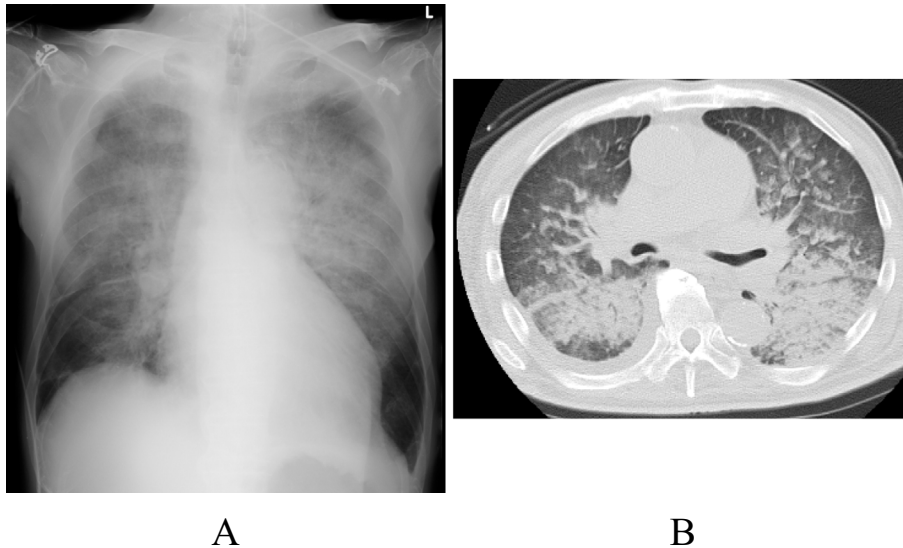
**Figure 1.** Chest radiography (A) and computed tomography (CT) (B) on admission. Anteroposterior chest radiography and chest CT show bilateral pulmonary edema, which is most prominent in the upper and middle lobes.



(A) On admission

(B) Third hospital day
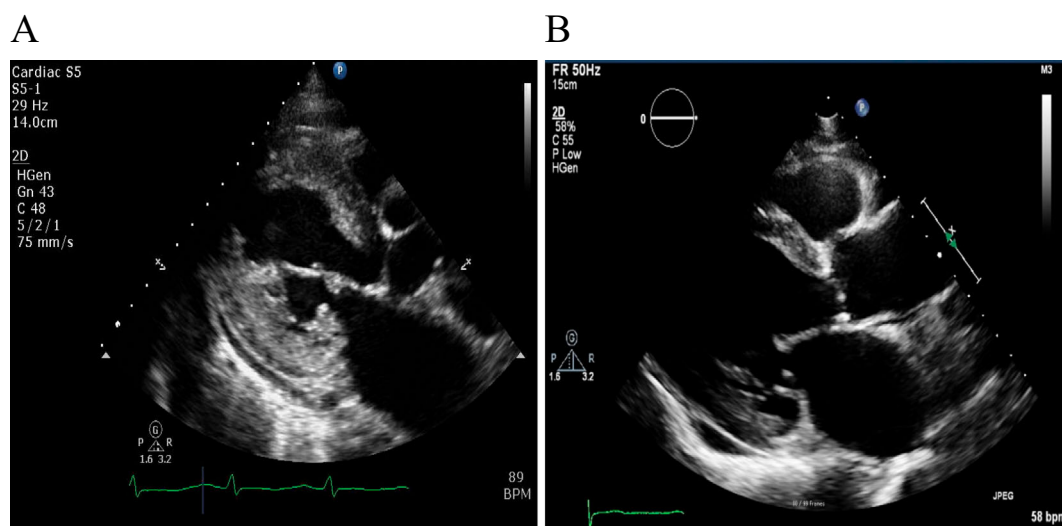
(C) Four month after discharge
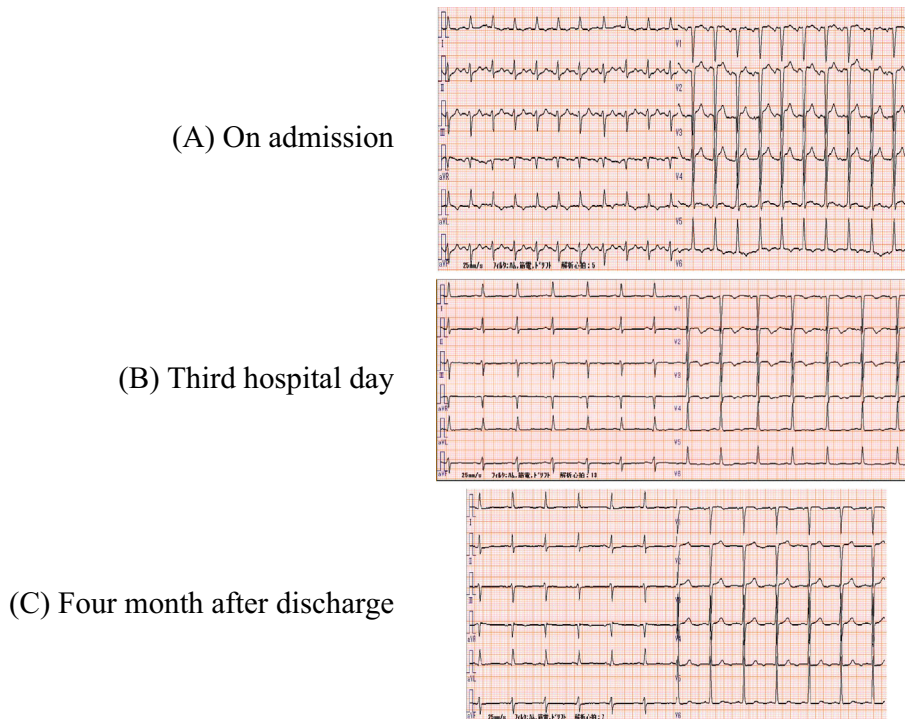
**Figure 2.** Serial electrocardiogram findings. Poor R progression and ST elevation in the precordial leads were seen on admission (A). T-wave inversion was observed at the third hospital day, which resolved with time (B, C).

Chest radiography and computed tomography revealed a marked butterfly shadow, indicating acute bilateral pulmonary edema (Fig. 1A, B). An electrocardiogram showed sinus tachycardia with left axis deviation. Poor R progression and ST elevation in precordial leads were also observed on admission, and T-wave inversion appeared on the third hospital day (Fig. 2A, B). Echocardiography showed not only diffuse hypokinesis of the left ventricle wall but also myocardial tissue edema and slight pericardial effusion (Fig. 3A). The cardiac troponin T level was elevated, and the blood level of N-terminal pro-B-type natriuretic peptide was over 2,000 pg/mL (reference range, 0-450 pg/mL) (Table 1). A drug-induced lymphocyte stimulation test (DLST) for the vaccine was performed, with a stimulation index (SI) of 180% considered to indicate a positive response. The influenza vaccine administered to this patient gave a positive response with an SI of 199%.

We treated the patient with conventional heart failure ther-

**Figure 3.** M-mode echocardiogram on admission (panel A) and four months after discharge (panel B). LV hypertrophy and pericardial effusion were present on admission but had completely resolved after four months.

**Table 1.** Laboratory Data.

| Variable | Reference range | On admission | Hospital day 3 | Hospital day 40 |
|---|---|---|---|---|
| Hemoglobin (g/dL) | 13.7-16.8 | 12.8 | 10.4 | 9.4 |
| White-cell count (×10³/μL) | 3.3-8.6 | 9.4 | 7.6 | 3.8 |
| Platelet count (×10⁴/μL) | 15.8-34.8 | 23.5 | 16.2 | 15.3 |
| Sodium (mmol/L) | 138-145 | 140 | 133 | 126 |
| Potassium (mmol/L) | 3.6-4.8 | 5.1 | 3.7 | 4.1 |
| Chloride (mmol/L) | 101-108 | 100 | 98 | 92 |
| Uria nitrogen (mg/dL) | 8.0-20.0 | 16.6 | 37 | 20.2 |
| Creatinine (mg/dL) | 0.65-1.07 | 1.06 | 0.75 | 0.53 |
| Glucose (mg/dL) | 70-110 | 224 | 81 | 90 |
| C-reactive protein (mg/dL) | 0.00-0.14 | 0.35 | 2.19 | 0.36 |
| Troponin T (ng/mL) | 0.00-0.10 | 0.193 | 0.163 | 0.126 |
| Creatine kinase (U/L) | 59-248 | 168 | 71 | 62 |
| Creatine kinase MB isoenzyme (U/L) | 0-13.0 | 9 | 5 | 3 |

apy, including intravenous diuretics and continuous infusion of isosorbide dinitrate. On the second hospital day, the pulmonary edema and dyspnea had almost resolved, and the trachea was extubated. The next day, an endomyocardial tissue biopsy was performed for the right ventricular septum. A histopathological examination revealed the focal accumulation of mononuclear cells in the edematous stroma. No overt interstitial fibrosis or proximity effects or myocardial tissue necrosis was observed (Fig. 4).
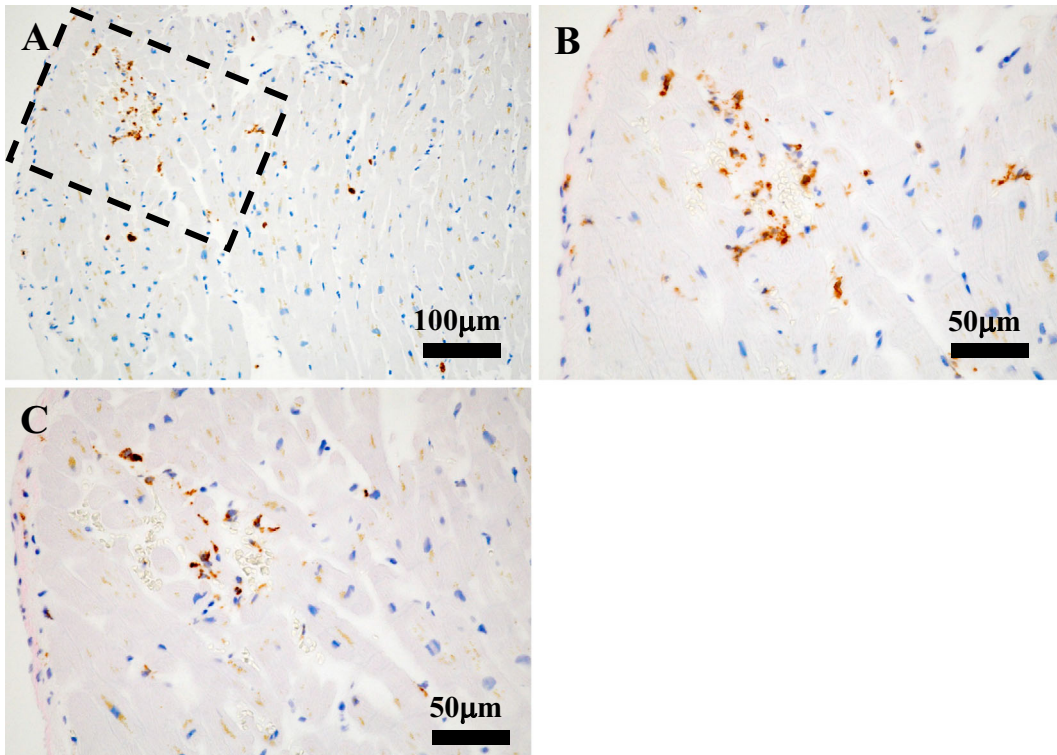
Immunohistochemical staining showed that inflammatory infiltrates were predominantly leukocyte common antigen (LCA/CD45)-positive lymphocytes and CD68-positive macrophages (Fig. 5). Few eosinophils were noted in this case. We performed stress perfusion imaging using adenosine Thallium-201(Tl) myocardial perfusion single photon emission computed tomography (SPECT) on the sixth hospital day. It did not indicate a myocardial perfusion defect, so we were able to rule out the possibility of ischemic heart disease, such as acute coronary syndrome. Taken together, the laboratory findings and the patient's clinical course suggested that influenza vaccination had induced acute myocarditis, resulting in acute heart failure and pulmonary edema.

We carefully monitored his respiratory and hemodynamic states after the acute clinical phase. He had no recurrence of heart failure and was discharged on the 40th hospital day. At the four-month follow-up visit, the echocardiographic findings of diffuse wall motion abnormality, myocardial tissue edema, and pericardial effusion and electrocardiogram findings of ST elevation and T-wave inversion had completely resolved (Figs. 2C and 3B, Table 2). No clinical signs of heart failure indicating recurrence of myocarditis were observed.
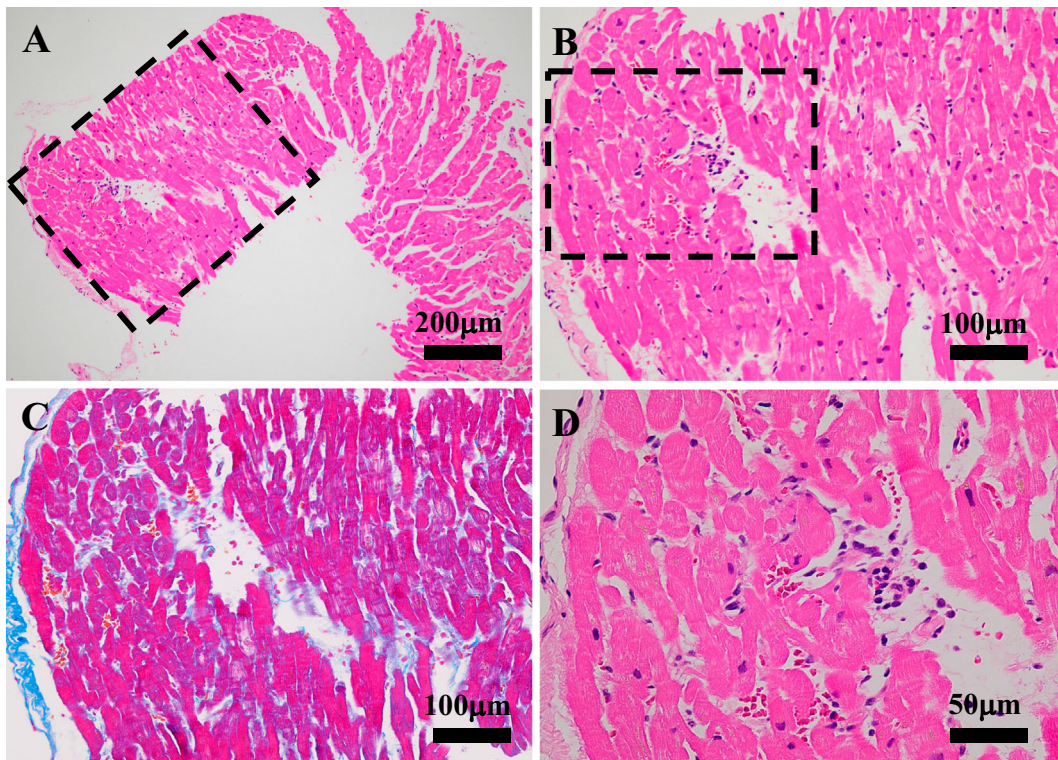
**Figure 4.** Hematoxylin and Eosin staining of the endomyocardial biopsy specimen shows mononuclear cell infiltrates in the edematous stroma (representative area is indicated with dotted square in panels A and B, and high-power view in panel D). Masson's trichrome staining showed no overt interstitial fibrosis (C). The actual scale bar length is illustrated in each panel.



**Figure 5.** Immunohistochemical staining showed that inflammatory infiltrates were predominantly LCA/CD45-positive lymphocytes (A, B: high-power view of the area of dotted squire in the panel A) and CD68-positive macrophages (C). The actual scale bar length is illustrated in each panel.

**Table 2. Echocardiographic Findings.**

| Variable | Reference range | On admission | 4-month follow-up |
|---|---|---|---|
| LV dimension | | | |
|     LV diastolic diameter (mm) | 42-59 | 57 | 53 |
| Septal wall thickness (mm) | 6-10 | 12 | 9 |
| Posterior wall thickness (mm) | 6-10 | 13 | 10 |
| LV volume | | | |
|     LV diastolic volume (mL) | 67-155 | 132 | 124 |
|     LV systolic volume (mL) | 22-58 | 72 | 57 |
| LV ejection fraction (%) | >55 | 46 | 54 |

LV: left ventricular

LV dimension and each wall thickness were obtained by M-mode measurement with two-dimensional echocardiographic guidance. LV volume and LV ejection fraction were obtained by biplane Simpson method with two-dimensional echocardiographic guidance.

## Discussion

Acute myocarditis is an inflammatory cardiac disease primarily caused by viral infections. In addition, myocarditis can be caused by a direct toxic or immune-mediated reaction to drugs, including immune checkpoint inhibitors, and by systemic autoimmune disease (5). Vaccine-associated acute myocarditis, especially from the smallpox vaccine, is known to cause myocarditis. The U.S. Department of Defense Smallpox Vaccination Clinical Evaluation Team identified a significantly increased incidence of myocarditis after widespread smallpox vaccination in late 2002 (6). In addition, vaccines for many other diseases, including diphtheria-tetanus-polio, tetanus, cholera, and typhoid-cholera vaccines, are also associated with myocarditis (7-11).

The incidence of new-onset cardiac symptoms, such as chest pain, dyspnea, and/or palpitations, reportedly occurs in 2.6% of cases after influenza vaccination (12). To our knowledge, however, there have been only a few reports of critical myocarditis after influenza vaccination. Recently, there were two case reports of cardiogenic shock due to fulminant myocarditis following influenza vaccination, which were treated with advanced circulatory support. Both patients had been previously healthy and were under 30 years old. Kim et al. proved acute myocardial inflammatory changes using non-invasive imaging modalities, such as cardiac magnetic resonance imaging (MRI) (13). Nagano et al. observed massive CD-3- and CD68-positive cells infiltration in myocardial biopsy specimens (14). In contrast to these reports, the inflammatory infiltration was relatively mild and limited in the focal area in our case. The proximity effects of inflammatory cells and myocardial necrosis were also not evident. These findings are thought to be characteristic of self-limiting acute myocarditis rather than of fulminant myocarditis, consistent with previous reports (15-17). Thus, our case seems to differ from these recent reports in terms of the severity of myocarditis (fulminant vs. acute non-fulminant). Furthermore, these two recent reports involved previously healthy young patients, in contrast to our elderly patient with comorbidities.

Immunohistochemical staining showed that inflammatory infiltrates were predominantly leukocyte common antigen (LCA/CD45)-positive lymphocytes and CD68-positive macrophages. Because of the limited amount of endomyocardial biopsy specimen available, we were unable to perform additional immunostaining for CD3, CD4, CD8, and CD20 as well as viral polymerase chain reaction. Consequently, we cannot confirm the pathophysiological mechanism underlying the inflammatory changes induced by influenza vaccination.

Given the heterogeneous nature of myocarditis, neither symptoms nor clinical course of myocarditis has been shown to correlate with histopathological features, such as the extent of lymphocytic infiltrate or fibrosis (16). The echocardiographic findings of acute phase in our case showed diffuse hypokinesis of the left ventricle wall and a mildly reduced systolic function (LVEF: 46%). Felker et al. reported various histopathological and echocardiographic findings of two different types of myocarditis: fulminant and acute. In their report, 81% of acute myocarditis cases showed mild focal inflammation despite the reduced LV systolic function (18). Overall, the diagnosis of acute myocarditis in our case was confirmed by the patient's clinical course, serologic changes (positive cardiac troponin), and serial electrocardiogram and echocardiography findings. The histopathological findings were consistent with the features of a relatively favorable clinical course for acute myocarditis. These findings almost completely resolved with conventional heart failure treatment. Consequently, we did not attempt complementary treatment, such as steroids and immunoglobulins (19). We did not actively suspect viral infection because our patient presented with the sudden onset of orthopnea and did not have typical clinical signs of viral infection, such as cough and general malaise, on admission. We ruled out the possibility of bacterial infection by serial negative blood cultures.

The causal relationship between influenza vaccination and acute myocarditis relies heavily on the temporal relationship between the timing of vaccination and the onset of acute

heart failure (two days after vaccination in our case). This temporal relationship has been reported in many other cases of vaccine-associated acute myocarditis (6). In our case, causality was further suggested by the positive DLST findings. The DLST has been well-established in recent years, and its usefulness has been demonstrated in various diseases and with many different drugs. As it is an *in vitro* test, it is not harmful to patients, and it has a general sensitivity of 60-70% and overall specificity of ≥85% (20).

The precise mechanism underlying vaccine-associated myocarditis remains unknown. Whether the underlying myocardial dysfunction in vaccine-associated myocarditis is a result of infectious, toxic, or immunologically mediated myocardial damage is unclear. Immune suppressant therapy with steroids may be uniquely beneficial in myocarditis related to smallpox vaccination compared with other types of myocarditis, suggesting that the hypersensitivity reaction to this vaccine may be responsible for myocardial damage (21, 22). Adjuvants increase the antigen-specific immune response, which improve vaccine immunogenicity. Regarding influenza vaccination, the immune response to adjuvant compounds is suggested as a possible mechanism underlying the unfavorable inflammatory response. Influenza vaccination in patients with type II diabetes induced a significant increase in monocyte-platelet aggregates and monocyte-platelet membrane receptors expression according to flow cytometry, suggesting vaccine-related monocyte activation. Together with the onset of inflammatory reaction, the index of cardiac sympathetic activity became augmented, including the heart rate variability as measured by a Holter electrocardiogram monitor (23). We speculate that these mechanisms are at least partially responsible for influenza vaccine-associated myocarditis and cardiac dysfunction.

It is important to consider the underlying patient risk of cardiac complications due to influenza vaccination. Whether or not comorbidities (RA in this case) and medications (immunosuppressive agents) increase the risk of vaccine-induced myocarditis is unclear. In our case, the patient has been treated with immunosuppressive agents, such as tacrolimus hydrate for RA, and the disease activity was well controlled. As with this case, elderly patients with RA are at a potentially greater risk for complications of influenza infection than younger ones. In terms of safety, previous reports have demonstrated that the influenza vaccine is safe in patients with RA. Current guidelines recommend that patients with RA on immunomodulatory medications be considered for annual influenza vaccination during the stable disease phase (24).

The reasons for the lack of overt cardiac complications due to previous influenza vaccinations in our patient remain unknown. Because the constituents of the seasonal influenza vaccine change every year, we cannot exclude the possibility that different component of adjuvants caused the myocardial complication in this case. Furthermore, we were unable to exclude the possibility of subclinical myocardial complication following previous influenza vaccinations. The recurrence of pericarditis after repeated influenza vaccinations has been reported. As a result, we do not recommend future influenza vaccinations in this case to avoid any recurrence of myocardial complications (25). Given the advent of the global coronavirus pandemic in recent years, there are several reports indicating a temporal association between myocarditis and vaccination against SARS-CoV-2 in younger generations (26, 27). In conclusion, inactivated influenza vaccines are generally safe and well-tolerated in all generations. Vaccine-associated myocarditis is rare, especially in older people, and expected to be self-limited.

Primary care physicians should carefully inquire about the history of cardiac symptoms not only during the immediate post-vaccination period but also following previous vaccinations. Complications, such as acute heart failure and arrhythmia, should be closely monitored and treated quickly and appropriately to save the patient's life.

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

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