INTERNAL MEDICINE

□ CASE REPORT □

A Fatal Case of Acute Myocardial Infarction following the Improvement of Influenza A(H1N1)pdm2009-related Acute Myocarditis

Naoki Iwanaga[1,2], Shigeki Nakamura[1], Yuichi Fukuda[2], Takahiro Takazono[1], Yoshifumi Imamura[1], Koichi Izumikawa[1], Katsunori Yanagihara[3], Hiroshi Soda[2], Takayoshi Tashiro[4] and Shigeru Kohno[1]

Abstract

A 52-year-old Indian man was hospitalized due to dyspnea and a high fever caused by influenza A(H1N1) pdm2009. Elevated cardiac enzymes, a chest X-ray showing bilateral infiltrative shadows, cardiomegaly and pleural effusion and echocardiography indicating diffuse hypokinesis of the left ventricle suggested cardiac failure due to acute myocarditis. Owing to the administration of combined modality therapy, including steroids and intravenous γ-globulin, the patient's clinical symptoms of influenza completely resolved. However, he suddenly complained of epigastric pain due to acute myocardial infarction and died. This report is an educational case, the results of which suggest that greater attention should be paid to the potential for myocardial infarction even after an influenza virus infection is found to improve.

Key words: influenza A(H1N1)pdm2009, acute myocarditis, myocardial infarction, excessive inflammatory cytokines, C-reactive protein

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Introduction

In March 2009, a novel H1N1 strain of the influenza A virus was detected, and, at that time, it was estimated that H1N1 may affect 50% of the US population, requiring 1.8 million hospitalizations and potentially resulting in 30,000 to 90,000 deaths (1, 2). The number of hospitalizations and admissions to intensive care units due to this strain are characteristically relatively higher among children and young adults than previous seasonal influenza strains (Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza. 2010). Meanwhile, myocarditis is an inflammatory disease of the myocardium whose etiology is thought to be either idiopathic, infectious or autoimmune. Among viral pathogens, enterovirus and adenovirus are common causes of acute myocarditis; however, influenza virus infection is thought to be rare, as the myocardiogenicity of the influenza virus appears to be rather weak. The frequency of myocarditis in severely ill patients due to previous seasonal influenza virus infections is reported to be 0.4-13% (3), yet the incidence of myocarditis associated with influenza A(H1N1)pdm2009 is assumed to be higher (4). Ukimura et al. report that the conditions of 10 of 15 patients with myocarditis due to influenza A(H1N1) pdm2009 were severe, requiring treatment under mechanical circulatory support [i.e., intra-aortic balloon pumping (IABP) and/or percutaneous cardiopulmonary support (PCPS)]; additionally, 13 of the 15 patients were rescued (5).

Some studies suggest myocardial infarction can be induced by viral or bacterial infections (6, 7). Various causa-

[1]Department of Molecular Microbiology and Immunology, Nagasaki University School of Medicine, Japan, [2]Division of Respiratory Medicine, Sasebo City General Hospital, Japan, [3]Department of Laboratory Medicine, Nagasaki University Hospital, Japan and [4]Department of Health Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki University School of Medicine, Japan
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Correspondence to Dr. Shigeki Nakamura, moju516@nagasaki-u.ac.jp

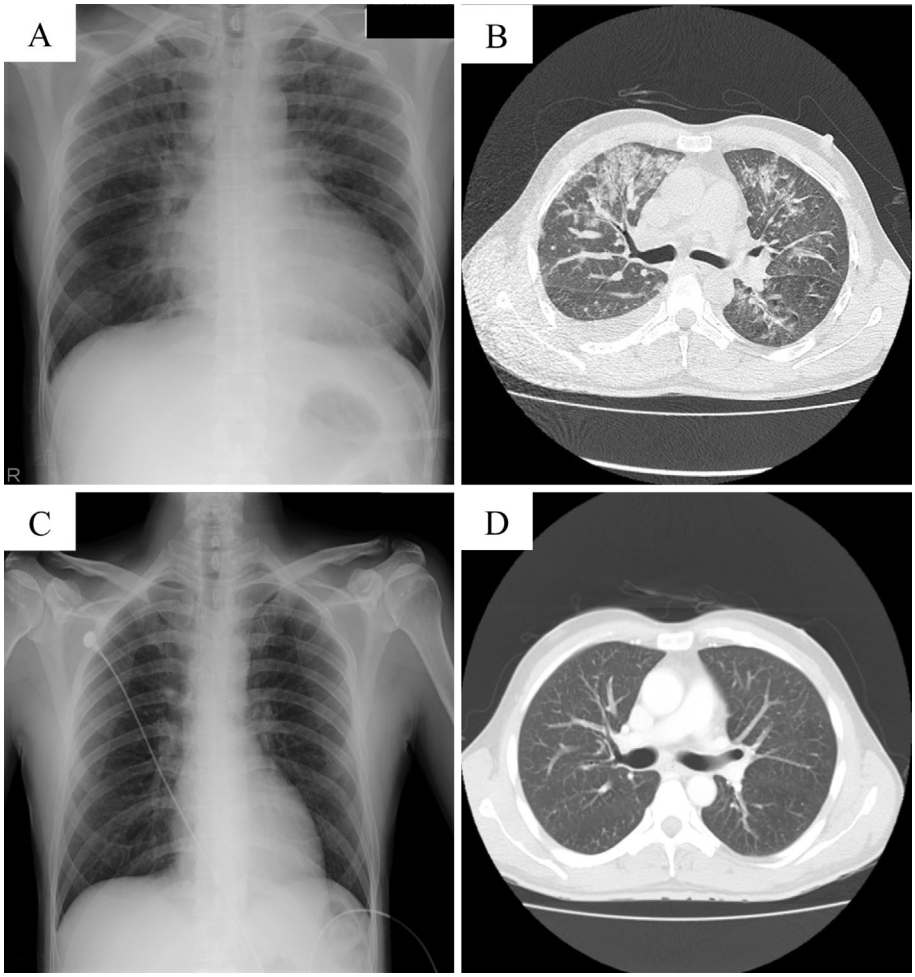


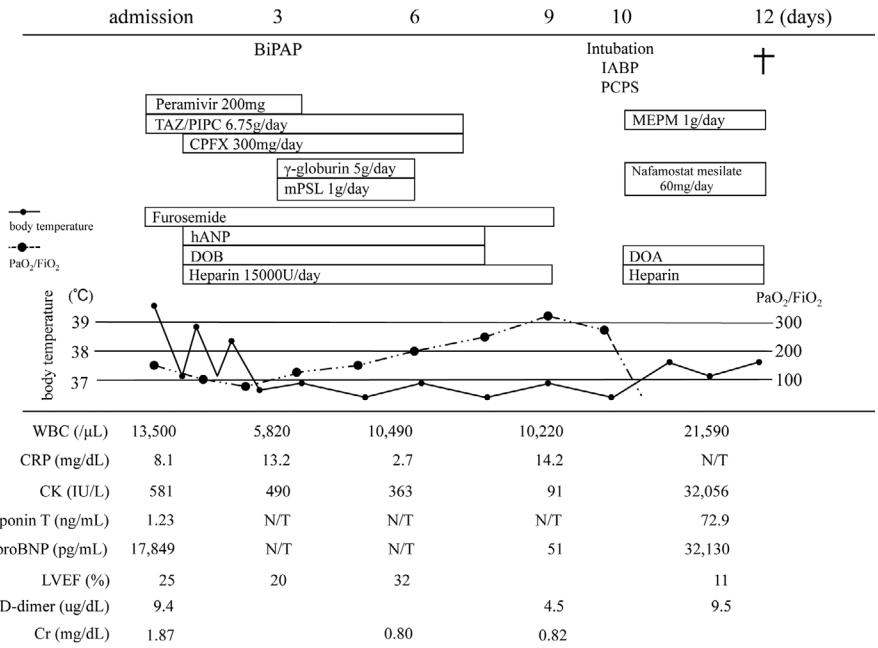
Figure 1. **(A) Chest radiograph obtained on admission showing bilateral infiltration and cardiomegaly. (B) Chest computed tomography (CT) scan performed on admission showing bilateral consolidation with bronchovascular bundles, thickened interlobular septa, interlobar pleura, cardiomegaly and right pleural effusion. (C) Chest radiograph obtained on the eighth clinical day showing diminished infiltration. (D) Chest CT scan obtained on the eighth clinical day shows no abnormal shadows.**

tive pathogens are assumed to be responsible for myocardial infarction, including *Chlamydophila pneumoniae*, cytomegalovirus, herpes simplex virus type 1 and 2, enteroviruses, hepatitis A virus and influenza virus (7). Furthermore, a meta-analysis recently indicated that influenza can trigger acute myocardial infarction (8). The extensive effects of the influenza virus on inflammatory and coagulation pathways are assumed to be the underlying causes of these diseases, which may lead to occlusion of the coronary arteries. However, the precise underlying mechanism remains unknown.

We herein report a rare case of influenza A(H1N1)pdm 2009-induced myocarditis complicated with fatal myocardial infarction.

Case Report

A 52-year-old Indian man was admitted to our hospital with flu-like symptoms and dyspnea on the day of symptom onset. He had a history of smoking (30 cigarettes a day for 30 years) and untreated diabetes mellitus (HbA1c: 8.1%). He had not received the influenza vaccination or had a history of hypertension, dyslipidemia or coronary artery disease. His physical characteristics on admission were as follows: height, 188 cm; weight, 85 kg; body temperature, 40.0 ℃; blood pressure, 122/81 mmHg; heart rate, 120 beats/min and regular; and respiratory rate, 32/min. The patient had no peripheral lymphadenopathy or skin lesions, although his jugular vein was dilated. Auscultation revealed bilateral inspiratory coarse crackles and end-expiratory wheezing. A laboratory examination revealed elevated markers of inflammation, including the white blood cell count (13.75×10^3/mm^3), serum C-reactive protein (CRP) level (8.1 mg/dL) and procalcitonin level (3.3 ng/mL). Similarly, cardiogenic markers, such as the levels of aspartate aminotransferase (94 IU/L), lactate dehydrogenase (414 IU/L), creatine kinase (581 IU/L), N-terminal pro-B-type natriuretic peptide (17,849 pg/mL) and troponin T (1.23 ng/mL), were elevated. A chest radiograph showed bilateral infiltrative shadows and cardiomegaly (Fig. 1A). Chest computed tomography (CT) also indicated bilateral consolidation with thickened interlobular



WBC (/μL)	13,500	5,820	10,490	10,220	21,590
CRP (mg/dL)	8.1	13.2	2.7	14.2	N/T
CK (IU/L)	581	490	363	91	32,056
Troponin T (ng/mL)	1.23	N/T	N/T	N/T	72.9
NTproBNP (pg/mL)	17,849	N/T	N/T	51	32,130
LVEF (%)	25	20	32		11
D-dimer (ug/dL)	9.4			4.5	9.5
Cr (mg/dL)	1.87		0.80	0.82	

Figure 2. Clinical course after admission. TAZ/PIPC: tazobactam/piperacillin, CPFX: ciprofloxacin, mPSL: methylprednisolone, hANP: carperitide, DOB: dobutamine, MEPM: meropenem, DOA: dopamine, N/T: not tested, LVEF: Left Ventricular Ejection Fraction

septa and bronchovascular bundles, cardiomegaly and right pleural effusion (Fig. 1B). An analysis of arterial blood gases drawn under 5 L/min O_2 administered nasally revealed the following findings: pH, 7.48; PaO_2, 48.8 Torr; $PaCO_2$, 31.8 Torr; HCO_3, 24.1 mmol/L; and base excess, 1.3 mmol/L. ECG demonstrated only sinus tachycardia. Transthoracic echocardiography showed global left ventricular systolic dysfunction (ejection fraction, 24%). A rapid test (ESPLINE® INFLUENZA A&B-N Kit, FUJIREBIO, Tokyo, Japan) for influenza virus infection was positive, and influenza A(H1N1)pdm2009 was detected on real-time reverse transcription-polymerase chain reaction (RT-PCR). Sputum and blood cultures were negative for causative pathogens. Urinary antigen tests for Streptococcus pneumoniae and Legionella pneumophila were negative. The patient was diagnosed with acute cardiac failure due to acute myocarditis induced by influenza A(H1N1)pdm2009.

Antimicrobial therapy, including a neuraminidase inhibitor and broad-spectrum antibiotics, was administered, and non-invasive positive-pressure ventilation was introduced due to the exacerbation of hypoxia despite treatment with diuretics, dobutamine and carperitide for cardiac support. On the third day after admission, we administered steroid pulse therapy (methylprednisolone, 1 g/day for three days) and intravenous γ-globulin (5 g/day for three days) for suspected myocarditis, as the patient's cardiac function showed gradual deterioration. Subsequently, his low cardiac function was promptly restored and he required no oxygen supply on the eighth clinical day. He had recovered completely in view of the findings of a chest radiograph (Fig. 1C) and CT scan (Fig. 1D).

The CRP level then began to increase gradually, although with no complaints. On the 10th clinical day, however, the patient suddenly complained of epigastric pain and experienced hemodynamic collapse. An ECG suggested ventricular tachycardia with V2-6 ST segment elevation. The patient was assisted with IABP and PCPS to maintain his blood pressure. Despite this intensive therapy, he died after two days. Fig. 2 summarizes his clinical course.

An autopsy revealed hemorrhagic infarction of the left ventricular anterior wall with neutrophil infiltration and stenosis of the left anterior descending coronary artery (Fig. 3), suggesting acute myocardial infarction as the leading cause of death. Myocarditis itself was unlikely to be the cause of death because the hemorrhaging was confined to the nearby area of necrosis and no interstitial edema or prevalent monolymphocytic infiltrates were detected. Posterolateral fibrosis of the left ventricular wall was also observed, which implied a previous episode of myocardial infarction. Both lungs exhibited congestion, based on which it was speculated that the lung damage was due to cardiac failure. In addition, Kimmelstiel-Wilson nodules were detected in both kidneys, suggesting the existence of diabetic nephropathy. Attempts to isolate the influenza virus from the myocardium and lung tissue using immunostaining and quantitative RT-PCR was unsuccessful, similar to that observed in previous reports (9). As to the present case, however, it cannot be denied that the influenza virus was eliminated due to the administration of antiviral drugs.

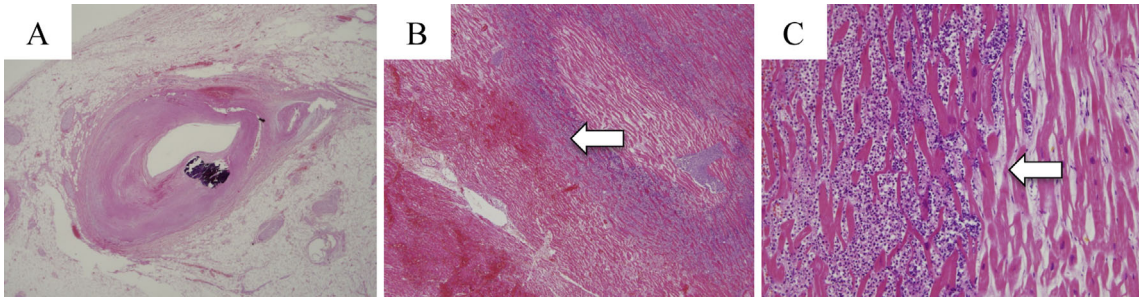


Figure 3. **Histopathological findings of the heart obtained at autopsy showing stenosis of the left anterior descending coronary artery (A), hemorrhagic infarction of the left ventricular anterior wall (B) (arrow, b) and neutrophil infiltration in the left ventricular anterior wall (C) (arrow, c).**

Discussion

The patient in the present case was diagnosed with acute myocarditis based on his clinical manifestations, including the acute onset of heart failure, elevated cardiac enzymes and transient cardiac global dysfunction with reversibility on echocardiography, as isolating the virus from the myocardium is generally difficult (9, 10). The patient's clinical course coupled with the detection of influenza A(H1N1) pdm2009 on real-time RT-PCR is highly suggestive of influenza virus infection as the primary cause of the myocarditis. Meanwhile, there were no clinical findings suggestive of acute myocardial infarction, such as chest pain or electrocardiogram abnormalities with ST-T irregularities on admission.

The pathogenesis of influenza myocarditis remains unclear. The clinical course of influenza myocarditis varies from asymptomatic infection to early fulminant myocarditis, cardiogenic shock and death. The development of influenza myocarditis may depend on the virus-host interaction, suggesting that the host immune response plays an important role in addition to direct cytolysis by the viral pathogen (3). Some reports have indicated that the excessive inflammatory cytokines produced during influenza virus infection can harm various organs, including the heart (11).

Sequential episodes of myocardial infarction caused the present patient's death despite his favorable recovery from myocarditis. Previous studies have reported the possibility of viral or bacterial infection as a predisposing cause of myocardial infarction, especially during the endemic period of influenza virus infection (6, 12). An epidemiological association between influenza epidemics and cardiovascular mortality has also been demonstrated. Moreover, the influenza vaccine can protect against cardiovascular complications in people with pre-existing coronary artery disease (11). Although the precise mechanism underlying the increase in cardiovascular deaths remains unknown, the influenza virus is assumed to extensively affect inflammatory and coagulation pathways. This theory is consistent with the findings in the present case considering the persistence of inflammation, that is, the re-elevation of the CRP level following the cessation of corticosteroids and the onset of hemostatic abnormalities (Fig. 2), which may destabilize atherosclerotic plaques, leading to coronary artery occlusion (13). There are some reports to support the concept that systemic inflammation itself alters the probability of a cardiovascular event (6, 7, 14). On the other hand, the present patient exhibited components of cardio-renal syndrome (CRS) types 4 and 5 as the cause of multiple organ failure, as he had both chronic kidney disease due to diabetic nephropathy and systemic disorder-induced severe heart failure and diabetes mellitus (15). We therefore speculate that the influenza A(H1N1)pdm2009 infection was potentially related to the patient's cardiovascular disease in addition to his basic illnesses, including diabetes mellitus, and smoking history.

No studies have investigated whether neuraminidase inhibitors are able to reduce the duration of influenza myocarditis in order to decrease mortality. Peramivir can be administered intravenously, allowing the drug concentrations at infectious sites to reach sufficient levels more rapidly (16). The improvement observed in the present case may be attributable to the effects of this antiviral drug. Furthermore, such an effect is also likely to be the case in reports in which most hospitalized patients with severe influenza infection survived, with the benefits of peramivir, after they had deteriorated, despite receiving other antiviral treatments (17, 18).

The use of corticosteroids and immunoglobulin as adjunctive therapy for myocarditis remains controversial. Although corticosteroid administration is tolerated in severe cases according to the guidelines for myocarditis (19), some authors do not recommend its use (20). Meanwhile, some case reports have demonstrated the effectiveness of high-dose intravenous immunoglobulin for acute myocarditis, promoting an antiviral effect and suppressing the inflammatory cytokine expression (21). Considering the present case, in which the patient's condition deteriorated despite the administration of supportive therapies but began to improve promptly after the initiation of the aforementioned treatment, these immunomodulatory agents may be candidates for the treatment of influenza myocarditis.

In conclusion, we herein reported a case of fulminant myocarditis complicated with acute myocardial infarction induced by influenza A(H1N1)pdm2009 infection. This case is

an educational case that highlights the need to pay attention to pulmonary as well as cardiovascular complications, especially in patients with non-seasonal influenza infection, since virulence and host susceptibility differ in each case. During influenza epidemics, when treating patients with pre-existing coronary artery disease and/or risk factors for coronary disease, adequate observation is required, even after the influenza virus infection improves, considering the potential for acute myocardial infarction.

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

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