CASE REPORT

Repetitive Fulminant Influenza Myocarditis Requiring the Use of Circulatory Assist Devices

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Abstract

A 52-year-old man was admitted to our hospital due to shortness of breath that developed one week after the diagnosis of influenza infection. He had a past history of myocarditis associated with influenza B infection 16 years before the current admission. The patient’s left ventricular function showed diffuse hypokinesis with a left ventricular ejection fraction of 28%. Due to the progression of heart failure, the infusion of catecholamines and insertion of an intra-aortic balloon pump were required. The patient was discharged uneventfully on the 23rd hospital day. A significant increase in the serum antibody titer against influenza A virus subtype H3N2 led to a diagnosis of recurrent fulminant influenza myocarditis.

Key words: influenza virus, viral myocarditis, fulminant myocarditis, cardiac support therapy

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Introduction

Many viruses are thought to cause myocarditis (1), with adenoviruses and enteroviruses having been identified as the most common pathogens (2). With advances in molecular techniques, the spectrum of the most frequently detected viruses has shifted toward parvovirus B19 and human herpesvirus 6 (3, 4). Influenza myocarditis is considered to be a rare condition owing to the low affinity of the virus to the human heart (5), although diagnosing viral myocarditis is challenging in part due to the limited performance of endomyocardial biopsies and/or autopsies. On the other hand, together with the development of sensitive assays for measuring myocardial damage, such as tests for the levels of creatinine kinase (CK), CK-MB, troponin I and T and the presence of myosin light chains, advancements in rapid influenza diagnostic testing are changing our understanding of the involvement of the influenza virus in the myocardium (6, 7). Several studies have shown that myocardial involvement occurs in approximately 10% of cases of influenza infection (8, 9). Nevertheless, clinically apparent influenza myocarditis is not common.

On the other hand, influenza myocarditis leading to a fatal outcome (fulminant form) does exist (6, 10), with a reported mortality rate of 28% among myocarditis patients in pandemic and post-pandemic seasons in Japan (11). In response to this situation, national surveys of influenza myocarditis have been implemented in Japan to clarify the clinical features of patients suffering from influenza myocarditis (11, 12).

Fulminant viral myocarditis can occur recurrently over a short period of time; however, few reports exist regarding recurrent fulminant influenza myocarditis (13). We herein report a patient who experienced repetitive fulminant myocarditis associated with serologically confirmed influenza B and A infections, two episodes of which were spaced more than 10 years apart.

Case Report

A 36-year-old man experienced dyspnea and cold-like symptoms and was admitted to the hospital due to hypotension and disturbed consciousness in February 1997. The
next day, epigastric pain developed and ST-segment elevation with low voltage was observed. Under a diagnosis of myocarditis, the patient was referred to a cardiovascular center. Soon after arriving at the center, his cardiac rhythm changed to ventricular fibrillation. As a result, he underwent tracheal intubation, insertion of percutaneous cardiopulmonary support (PCPS) and intra-aortic balloon pumping (IABP) devices with catecholamine infusion. Following PCPS insertion, the patient’s cardiac rhythm was converted to a sinus rhythm. Cardiac catheterization was then performed, which showed normal coronary arteries without significant valvular disease. Echocardiography showed a severely reduced left and right ventricular function. Weaning from the PCPS and IABP was performed seven and nine days, respectively, after the insertion of these mechanical support devices. The patient was discharged from the hospital approximately one month after his admission. Together with a significant elevation in the serum titer of influenza B virus from ×32 to ×256, the patient’s symptoms and clinical findings led to a diagnosis of fulminant myocarditis associated with influenza virus B infection.

In March 2001, four years after the first episode, the patient felt cold-like symptoms, including a fever, cough and nasal discharge. One week later, he felt epigastric pain and malaise and was thus admitted as an emergency patient to the cardiovascular center. On admission, his initial vital signs included a blood pressure of 110/70 mmHg and a heart rate of 95 beats/min. Electrocardiography showed low-voltage and sinus tachycardia. On echocardiography, a left ventricular ejection fraction (LVEF) of 25% and moderate pericardial effusion were observed. Laboratory studies showed a WBC count of 8,390/μL, a hemoglobin level of 16.7 g/dL, a C-reactive protein concentration of 5.76 mg/dL and a CRP level of 0.12 mg/dL. The total and MB fractions of CK were 753 U/L and 76 U/L, respectively, and the level of cardiac troponin was 0.815 ng/mL (normal range, ≤0.014 ng/mL), indicating the presence of myocardial damage. The serum level of brain natriuretic peptide (BNP) was elevated to 1,485 pg/mL. A cardiac troponin test was positive. On admission, the following titers of antibodies against suspected viruses were measured: influenza A (H1N1), ×20; influenza A (H3N2), ×80; parainfluenza 2, ×10; and parainfluenza 3, ×320. The titers of antibodies against the following species were negative: influenza B, adenovirus, echovirus 3, echovirus 11, coxsackie virus A9, coxsackie virus B3 and parainfluenza 1.

A chest X-ray obtained on the second hospital day revealed mild cardiomegaly with a cardiothoracic ratio of 53% and moderate pericardial effusion were observed. Laboratory studies showed a white blood cell (WBC) count of 8,390/μL, a hemoglobin level of 16.7 g/dL, a platelet count of 11.6×10^4/μL and a C-reactive protein (CRP) level of 0.5 mg/dL. A cardiac troponin test was positive. The level of serum CK was within the normal limits at the time of admission (226 U/L); however, it rose to 1,103 U/L on the fourth hospital day. After receiving support therapy, the patient’s cardiac function improved to an LVEF of 59%, and he was discharged on the 16th hospital day. Neither measurement of the antiviral antibody titers nor rapid influenza tests were performed during this admission.

In 2009, echocardiography performed at a nearby clinic showed an LVEF of 58% and LV end-diastolic dimension of 46 mm. In January 2013, the patient, then 52 years of age, was febrile. He was diagnosed with influenza A infection at a nearby clinic and started on oral oseltamivir. Although his fever was alleviated, his chest symptoms occurred intermittently and his hemodynamic condition gradually deteriorated. As a result, he was admitted as an emergency patient to our hospital seven days after the onset of fever.

Laboratory studies showed a WBC count of 1,020/μL, a hemoglobin level of 15.7 g/dL, a platelet count of 14.8×10^4/μL, a C-reactive protein concentration of 5.76 mg/dL and a CRP level of 0.12 mg/dL. The total and MB fractions of CK were 753 U/L and 76 U/L, respectively, and the level of cardiac troponin was 0.815 ng/mL (normal range, ≤0.014 ng/mL), indicating the presence of myocardial damage. The serum level of brain natriuretic peptide (BNP) was elevated to 1,485 pg/mL. A cardiac troponin test was positive. On admission, the following titers of antibodies against suspected viruses were measured: influenza A (H1N1), ×20; influenza A (H3N2), ×80; parainfluenza 2, ×10; and parainfluenza 3, ×320. The titers of antibodies against the following species were negative: influenza B, adenovirus, echovirus 3, echovirus 11, coxsackie virus A9, coxsackie virus B3 and parainfluenza 1.
Fusion was observed. Emergency coronary angiography again showed normal coronary arteries. An endomyocardial biopsy was not performed due to the instability of the patient’s condition. His blood pressure had decreased and his hemodynamic condition was decompensating. As a result, the insertion of an IABP and infusion of catecholamines were ultimately required to maintain the patient’s peripheral circulation (Fig. 4).

Together with treatment with this cardiac function support, a neuraminidase inhibitor, peramivir hydrate, was administered intravenously. Neither corticosteroids nor immunosuppressants were administered. During the therapy, electrocardiography showed various changes, including a reduction of the R voltage wave in V1-3, recovery of the voltage and limb leads, T wave inversion and ST-segment depression in the left precordial leads (Fig. 2), consistent with the clinical course of myocarditis. The patient’s cardiac function gradually improved to an LVEF of 38% on the third hospital day (Fig. 3), with thickening of the LV wall. Echocardiography performed on the fourth hospital day continued to show thickening of the LV wall; however, the LVEF had slightly improved to 48% (Fig. 3, 4). Cardiac MRI obtained on the 22nd hospital day demonstrated delayed enhancement in the anterior wall of the left ventricle (Fig. 4F). On the seventh hospital day, the patient’s left ventricular function was substantially improved; however, prominent postsystolic ventricular shortening was observed (Fig. 5). The patient was discharged on the 23rd hospital day.

The serum titer of influenza A virus (H3N2) was significantly elevated from ×80 to ×1,280, consistent with a diagnosis of fulminant myocarditis associated with influenza A virus infection. The viral titers against influenza A (H1N1), influenza B, echoviruses, coxsackie viruses and parainfluenza viruses were not significantly elevated (data not shown). No ST-segment elevation was apparent on an electrocardiogram obtained on the 22nd hospital day (Fig. 2C); however, T wave inversion was observed in II, III, aVF and V4-6. The BNP level remained within the normal range.

**Figure 2.** Electrocardiograms (ECGs) of the patient. A: An ECG recorded six months before the latest admission. No apparent abnormal findings were observed. B: An ECG recorded on the latest admission showing ST-segment elevation in the II, III, aVF and precordial leads. C: An ECG recorded on the 22nd hospital day of the latest admission. T wave inversion was observed in II, III, aVF and V4-6.

**Figure 3.** Clinical course of the patient. Following the administration of cardiac support therapy, the patient’s left ventricular ejection fraction (LVEF) and cardiac index (CI) returned to (near) normal levels. IABP: intra-aortic balloon pumping.

(49.2 pg/mL), and the postsystolic ventricular shortening observed on echocardiography improved two weeks after discharge.

Discussion

We herein reported the case of a patient who experienced myocarditis and pericarditis with influenza A infection. Dur-
ing the patient’s latest admission, owing to the ongoing instability of his hemodynamic status, circulatory support using IABP was needed. Following the administration of cardiac support therapy and antiviral treatment, the patient was discharged with mild LV dysfunction. The reported frequency of myocardial involvement in patients with influenza infection varies and depends on the levels of markers indicating myocardial damage or the results of physiological tests used for diagnosis (6). Although the exact frequency remains unclear, the development of myocarditis with infection with influenza virus, either type A or type B, has been reported (11, 14), and either type may manifest as “fulminant” myocarditis. What is remarkable about the present case is that the patient had experienced fulminant myocarditis with influenza B infection 16 years previously. In recent studies, Pan et al. demonstrated that, in a case of myocarditis associated with influenza infection, the induction of myocardial trypsin and upregulation of proinflammatory cytokines and metalloproteinases play a crucial role in the pathogenesis of the condition (15, 16). Whether these findings are more prominent in those who experience fulminant form of influenza myocarditis should be examined in future studies.

In general, repetitive or recurrent viral myocarditis is considered to be extremely rare (13, 17). Recurrent myocarditis can cause symptoms of angina (18). As a result, coronary angiography and other diagnostic modalities, such as cardiac MRI, may be required to discriminate it from ischemic coronary artery disease; thus, its prevalence may be underestimated. Karavadis et al. reported a case of recurrent coxsackie B viral myocarditis that resulted in progressive LV dysfunction over an 8-year period (19). Such observations suggest that repetitive viral infection may underlie the development of progressive heart failure in some patients with dilated cardiomyopathy. Reports of the repetitive fulminant form of myocarditis are the most rare. Hebert et al. reported a patient with repetitive viral myocarditis in whom the latest infection was fatal. The involvement of two or more different viral species was suspected to underlie the multiple episodes of myocarditis observed in that patient (17). Takehana et al. described a patient who experienced recurrent viral, presumably influenza, myocarditis within two weeks of the recovery of a prior myocarditis episode (13). In our patient, influenza virus infection -- one case of type B and one case of type A -- was confirmed serologically in two episodes that occurred 16 years apart.

No endomyocardial samples were obtained from the patient due to the instability of his condition. Although histologic findings are valuable for making a diagnosis of viral myocarditis, endomyocardial biopsies are associated with certain risks, including cardiac tamponade (20). In addition, only mild inflammation may be observed in urgent situations or cases involving localization of the region with severe inflammation (21). Although real-time polymerase chain reaction (RT-PCR) of viral genomes present in cardiac samples may aid in diagnosing viral myocarditis, this technique is hampered by sampling errors in cases of focal disease with uncertain sensitivity. According to the American Heart Association/the American College of Cardiology Foundation/the European Society of Cardiology Scientific Statement, endomyocardial biopsies are indicated in situations of unexplained heart failure, unexplained arrhythmias, suspected cardiac tumors, arrhythmogenic right ventricular dysplasia/cardiomyopathy and anthracycline-induced cardiomyopathy (22). In addition, the results of RT-PCR of the influenza virus can be negative in patients who have been diagnosed serologically (23, 24). In our case, the patient had a past history of viral myocarditis, a positive rapid test for influenza A virus and abnormal cardiac MRI findings; thus, conducting a histologic assessment may not be essential for diagnosing and managing this patient.

In summary, we herein presented a rare case of recurrent fulminant myocarditis with two episodes of influenza infection that occurred 16 years apart. The administration of circulatory support therapy successfully helped the patient to survive two episodes of severe impairment of the cardiac function. To the best our knowledge, this is the first report to describe the repetitive fulminant form of myocarditis occurring in association with infection with two types of influenza virus: type B and type A. Although influenza myocarditis is considered to be a rare condition, physicians should be aware of the possibility for circulatory decompensation in influenza infection patients with a prior episode of heart failure associated with influenza infection.

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

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