A National Survey on Myocarditis Associated With the 2009 Influenza A (H1N1) Pandemic in Japan

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Background: An influenza pandemic occurred in 2009 and myocarditis associated with the 2009 influenza A (H1N1) pandemic was reported among hospitalized patients from August 2009.

Methods and Results: The Japanese Circulation Society organized the Clinical Research Committee on Myocarditis Associated with Influenza Pandemic A (H1N1) 2009 and called for a case report on myocarditis for a national survey. The diagnosis of myocarditis was performed using the Guidelines for the Diagnosis and Treatment of Myocarditis (JCS 2009). Fifteen patients were reported to the committee. Fulminant myocarditis developed in 10 patients. Mechanical circulatory support (intra-aortic balloon pumping (IABP) and/or percutaneous cardiopulmonary support (PCPS)) was used on all 10 patients, 8 of whom were rescued. Abnormalities on echocardiography and elevated cardiac enzymes were seen in most of the patients. Myocarditis was found by endomyocardial biopsy in 6 patients. Three patients had complications with pneumonia.

Conclusions: In reality, myocarditis associated with pandemic influenza A (H1N1) seemed to be more common in hospitalized patients, compared with previous seasonal influenza virus outbreaks. To avoid misdiagnosis of acute myocarditis associated with influenza pandemic A (H1N1) 2009, it is essential to determine the characteristic symptoms, signs, and laboratory findings of acute myocarditis during influenza pandemics. Mechanical circulatory support (IABP and/or PCPS) was required to rescue patients with fulminant myocarditis. (*Circ J* 2010; **74**: 2193–2199)

Key Words: Influenza; Myocarditis; Pandemic

Influenza pandemics occur every 10 to 50 years, and the 2009 influenza A (H1N1) pandemic has been spreading worldwide since the first cases were identified in the USA and the United Mexican States in April 2009.^{1–6} Most people infected with the 2009 influenza A (H1N1) pandemic recovered without any sequelae, and hospitalizations were quite rare in Japan until June 2009.^{4,5} However, some Japanese cases of myocarditis including fulminant myocarditis caused by the 2009 influenza A (H1N1) pandemic began to be reported in hospitalized patients from August 2009.⁶ Thus, a Japanese National Survey, to investigate what is going on in the real world around myocarditis associated with the 2009 influenza A (H1N1) pandemic, was initiated by the Japanese Circulation Society.

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Acute myocarditis is a potentially lethal disease, and the etiological agents of viral myocarditis are enteroviruses including coxsackieviruses, adenoviruses, parvoviruses, hepatitis C virus, human immunodeficiency virus, influenza, and others.^{7–13} Fulminant myocarditis causes severe hemodynamic dysfunction and requires high-dose catecholamine and mechanical circulatory support. Fulminant myocarditis caused by viral infection is an uncommon type of myocarditis.^{7–9} The frequency of myocardial involvement in influenza infection has varied and fulminant myocarditis associated with influenza infection is exceedingly rare as shown by previous papers, although this probability depends on low affinities

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Table 1. Profile, Baseline Disease, Symptoms and Laboratory Findings of 15 Patients With Myocarditis Associated With Pandemic Influenza A (H1N1) 2009 in Japan

Patient No.	Age/sex	Baseline disease	Symptoms of influenza	Cardiac symptom/onset (day post symptoms of influenza)	Type of myocarditis and complication	ECG findings	CAG	Cardiac enzyme (peak)	UCG
1	6/M	Asthma	Cough, dyspnea, fever (37.5°C)	Dyspnea/day 3	Fulminant myocarditis, viral pneumonia	VF, Torsade de pointes	Not done	CPK (25,244 IU/L)	Diffuse hypokinesia EF 33.5%, effusion
2	11/F	None	Cough, dyspnea, fever (39.8°C)	Shock/day 3	Fulminant myocarditis, shock	ST elevated	Not done	CPK (4,793 IU/L)	Diffuse hypokinesia EF 25%, pericardial effusion
3	24/F	None	Fever, vomiting	Dyspnea, hypotension/day 6	Fulminant myocarditis, alveolar hemorrhage	ST elevated	Normal CAG	CPK (2,681 IU/L)	Diffuse hypokinesia EF 11%, pericardial effusion
4	30/M	None	Fever, dyspnea, chest pain	Chest discomfort/day 10	Fulminant myocarditis	T inverted	Normal CAG	CPK (971 IU/L)	Diffuse hypokinesia EF 10%, edema of LV wall
5	31/M	None	Cough, arthralgia, fever (39°C)	Orthopnea, hypotension/day 9	Fulminant myocarditis, shock	ST elevated	Normal CAG	CPK (800 IU/L)	Diffuse hypokinesia, edema of inferior LV wall, pericardial effusion
6	31/F	Hyperthyroid	Dyspnea, fever (39°C)	Dyspnea, hypotension/day 2	Fulminant myocarditis, MOF, DIC	SVT, AF	Normal CAG	CPK elevated	Severe hypokinesia and akinesis
7	34/F	None	Vomiting	Chest discomfort/day 1	Fulminant myocarditis	VF, complete AV block	Normal CAG	CPK (3,808 IU/L)	Diffuse hypokinesia EF 32%, LV wall thinning
8	44/M	Asthma	Fever	Dyspnea/day 21	Congestive heart failure	Multifocal PVCs SVT	Normal CAG	No information	Diffuse hypokinesia EF 16%
9	44/F	Asthma	Fever (38.3°C)	Dyspnea, hypotension/day 3	Fulminant myocarditis, shock	VF, frequent VT	Normal CAG	CPK (2,911 IU/L)	Diffuse hypokinesia EF 24%
10	53/M	None	Fever	Syncopal/day 3	Complete AV block	Complete AV block	Normal CAG	CPK elevated	Diffuse hypokinesia EF 40%
11	61/M	DM	Nausea, dyspnea, fever (38.8°C)	Dyspnea/day 2	Fulminant myocarditis	AF, T inverted	Normal CAG	Troponin I elevated	Diffuse hypokinesia EF 20%
12	61/F	None	Fever, abdominal pain, disorientation	Dyspnea, hypotension/day 2	Renal failure, septic shock, DIC	ST elevated	Not done	CPK (2,811 IU/L)	Diffuse hypokinesia EF 20%
13	66/M	Emphysema	Common cold-like symptoms	CPA/day 7	CPA, pneumonia (Streptococcus pneumoniae)	VF, complete AV block	Normal CAG	CPK (1,842 IU/L)	Almost normal wall motion
14	69/M	Emphysema, cancer, DM	Fever	CPA/day 8	Fulminant myocarditis, cardiac tamponade	Asystole, complete AV block	Normal CAG	CPK elevated	Diffuse hypokinesia EF 29%
15	72/M	IHD (OMI of posterior wall)	Dyspnea, fever	Dyspnea/day 2	Congestive heart failure, viral pneumonia	Giant negative T	No stenosis (s/p PCI)	CPK (827 IU/L)	Diffuse hypokinesia (anterior + posterior wall) EF 38%

Abbreviations see in text.

Table 2. Viral Diagnosis, Treatment and Outcome of 15 Patients With Myocarditis Associated With Pandemic Influenza A (H1N1) 2009 in Japan

Patient No.	Age/sex	Rapid influenza diagnostic testing	RT-PCR	Ventilator/days	Mechanical support/days	Other treatment	Biopsy or autopsy	Outcome
1	6/M	Negative (day2,3)	2009A (H1N1) (day 3)	Used/14 days	PCPS/11days	Steroid 2 mg/kg, large amount of γ -globulin	Not done	Improved (EF 63%)
2	11/F	Negative (day1) →positive (day3)	Not done	Used/22 days	PCPS/3days IABP/4days	Steroid pulse, large amount of γ -globulin	Not done	Improved (EF 70%)
3	24/F	Positive (day1)	Not done	Used	PCPS/7days IABP	Usual dose γ -globulin	Not done	Improved (EF 71%)
4	30/M	Negative (day1) →positive (day2)	Negative (day 20)	Not used	IABP/3days	Not used	Active myocarditis	Improved
5	31/M	Negative (day1)	2009A (H1N1) (day 9)	Not used	IABP/3days	Not used	Myocarditis (mild)	Improved
6	31/F	Positive (day1)	2009A (H1N1) (day 1)	Used/15days	PCPS/7days IABP/12days	CHDF, plasmapheresis	Myocarditis	Improved
7	34/F	Negative (day1)	2009A (H1N1) (day1)	Used/5 days	PCPS/4days IABP/5days	Plasmapheresis	Not done	Death on day 5
8	44/M	Positive (day2)	Not done (A/CF32X day45)*	Not used	Not used	Not used	Healing myocarditis (day 67)	Incompletely improved (EF 25%)
9	44/F	Negative (day2)	2009A (H1N1) (day 3)	Used	PCPS/6days IABP/12days	Usual dose γ -globulin	Myocarditis (day 3 and 24)	Improved (EF 60%)
10	53/M	Positive (day 1)	2009A (H1N1)	Not used	Not used	Pacemaker	Done	Improved
11	61/M	Positive	2009A (H1N1)	Used	IABP	Not used	Myocarditis (day 4 and 10) negative RT-PCR	Improved
12	61/F	Positive (day1)	Not done	Not used	Not used	Usual dose-globulin	Not done	Improved (EF 50%)
13	66/M	Not done	2009A (H1N1) (day7)	Used/4 days	Not used	Not used	Interstitial fibrosis (day 31)	Improved
14	69/M	Positive (day1)	2009A (H1N1) (day1)	Used/2 days	PCPS/2days	Not used	Interstitial fibrosis (Autopsy)	Death on day 9
15	72/M	Positive (day2)	2009A (H1N1) (day4)	BiPAP	Not used	Usual dose γ -globulin	Interstitial fibrosis (day 8)	Incompletely improved (EF 44%)

*CF titer to Influenza virus A was 1:32 on day 45.
Abbreviations see in text.

to cardiac involvement of the influenza virus and/or the methods used to diagnose myocardial involvement and influenza infection.⁷⁻⁹ Although usually both the diagnosis and treatment of the pathogen involved in myocarditis are difficult, good diagnostic methods, such as influenza tests, which were quickly checked and reverse transcription polymerase chain reaction (RT-PCR) for the 2009 influenza A (H1N1) pandemic, and treatment with neuraminidase inhibitors were already available in this 2009 pandemic.¹⁻⁶

Methods

To investigate what is going on in the real world around myocarditis associated with the 2009 influenza A (H1N1) pandemic, the task forces directed by the Japanese Circulation Society organized a Clinical Research Committee for Myocarditis associated with the pandemic. The Japanese Circulation Society called for a case report on myocarditis associated with the 2009 influenza A (H1N1) pandemic to all members (24,203 persons in total) from all regions of Japan through direct e-mail in November 2009. Fifteen cases were immediately reported to the task forces within 4 months, and all cases were analyzed. The diagnosis of myocarditis was performed using the Guidelines for the Diagnosis and Treatment of Myocarditis (JCS 2009).¹⁰ Compatible clinical symptoms,

echocardiographic abnormalities in the absence of cardiac ischemia, leakage of cardiac enzymes and/or other evidence of myocardial damage provided the highly probable diagnosis for myocarditis. Myocardial biopsy or autopsy provided the histological diagnosis for myocarditis. Laboratory diagnosis of influenza pandemic A (H1N1) 2009 was made by quick influenza diagnostic testing and/or probe-based RT-PCR using a nasopharyngeal swab or sputum.

Results

Fifteen patients (9 men and 6 women, mean age 42.4±20.8 years) were reported to the task force of the Clinical Research for Myocarditis associated with the 2009 influenza A (H1N1) pandemic. They were admitted to hospitals from August 2009 to February 2010. The profiles, baseline disease, symptoms and laboratory findings of these 15 patients are shown in Table 1, and the results of diagnostic tests for influenza infection, treatment, histological findings and outcome in Table 2. Myocarditis was proven by endomyocardial biopsy in 6 patients, and myocarditis was clinically diagnosed based on clinical figures, leakage of cardiac enzymes, abnormalities on echocardiography, and other findings in the other 9 patients.¹⁰ History was useful in obtaining the correct diagnosis. Thirteen patients complained of typical symptoms of

Figure. Endomyocardial biopsy (HE staining) from a 31-year-old woman who developed multi-organ failure (case 6) is shown. She was rescued with mechanical circulatory support (IABP and PCPS). Myocyte degeneration with lymphocyte infiltration and interstitial edema can be seen. IABP, intra-aortic balloon pumping; PCPS, percutaneous cardiopulmonary support.

influenza, such as high fever, cough, headache, and arthralgia. Three patients (20%) complained of abdominal symptoms (abdominal pain, nausea, and vomiting), and one patient complained of common cold-like symptoms. Cardiac symptoms such as dyspnea, chest discomfort, hypotension and syncope developed on the 2nd–21st day of sickness. The most frequent baseline disease was a respiratory disorder in 5 (33%) patients (bronchial asthma in 3 patients and emphysema in 2 patients), and others were diabetes in 1 patient and ischemic heart disease in 1 patient. Three patients with myocarditis were complicated by pneumonia: viral pneumonia in 2 patients and bacterial pneumonia in 1 patient.

Most patients exhibited electrocardiogram (ECG) abnormalities, including ventricular fibrillation in 3 patients, complete AV block in 4 patients, ST elevation in 4 patients, giant negative T-waves in 1 patient, and atrial fibrillation in 1 patient. Two patients were emergently admitted because of cardiopulmonary arrest due to ventricular fibrillation or complete AV block. Echocardiography revealed abnormalities of left ventricular wall motion in 14 patients and pericardial effusion in 2 patients. Cardiac dysfunction almost completely recovered in 11 patients but only incompletely in 2 patients. Coronary angiography was performed on 12 patients, which yielded normal results in all. Cardiac enzymes were elevated in 14 patients, with a peak serum creatine kinase concentration of 800 to 25,244 (IU/L). Quantitative troponin testing was measured in 4 patients and was found to be elevated in all patients. Qualitative quick troponin testing was measured in 3 patients, and was positive in 1 patient.

The clinical manifestations of myocarditis caused by influenza pandemic A (H1N1) varied greatly, and 10 patients were diagnosed with fulminant myocarditis with fatal arrhythmias, and/or varying degrees of cardiogenic shock. Cardiopulmonary arrest was the first cardiac symptom in 2 patients. Syncope due to complete AV block was the first cardiac symptom in 1 patient, who was rescued with temporary pacemaker implantation. The clinical course of patients also varied. Cardiac dysfunction progressed rapidly in 12 patients;

10 of these (83%) recovered to their previous condition and 2 died. Cardiac dysfunction developed after recovery from flu-like symptoms in 2 patients, and myocarditis appeared to have persisted for 1.5 months in 1 patient.

Quick diagnostic testing for influenza, performed on the first visit to the clinic, was negative in 5 patients and positive in 8 patients.^{4–6} Quick diagnostic testing, when performed a second time was positive in 2 patients who initially had negative results. RT-PCR testing for the 2009 influenza A (H1N1) pandemic yielded positive results in 10 patients. RT-PCR or quick diagnostic testing yielded positive results in all patients.

Endomyocardial biopsy was performed in 8 patients and an autopsy was performed in 1 patient. Endomyocardial biopsies demonstrated histological myocarditis in 6 patients. Histological findings of an endomyocardial biopsy from case 6, who developed multi-organ failure, are shown in [Figure](#). She was rescued with mechanical circulatory support. Lymphocyte infiltration and interstitial edema could be seen. RT-PCR testing for pandemic influenza A (H1N1) from a biopsy specimen was performed only in 1 case, but it was negative.

A ventilator was used in 6 patients and a biphasic positive airway pressure support system (BIPAP) was used in 1 patient. Mechanical circulatory support with intra-aortic balloon pumping (IABP) and/or percutaneous cardiopulmonary support (PCPS) was emergently inserted in 9 patients. Seven patients were rescued with mechanical circulatory support, and 2 patients died. A temporary pacemaker was implanted into the patient with complete AV block. All patients were treated with neuraminidase inhibitors, and high-dose immunoglobulin was used in 2 patients. Corticosteroid was used only in 2 children, but not in any adult patients.

Discussion

The influenza pandemic began in Kobe and Osaka, the middle region of Japan, in May 2009, and all patients recovered until July 2009 without any sequelae.^{4,5} It was reported that, in Canada, critical illness due to the 2009 influenza A (H1N1) pandemic occurred rapidly after hospital admission, often in young adults, and was associated with severe hypoxemia, multisystem organ failure, which necessitated prolonged mechanical ventilation, and the frequent use of rescue therapy.^{1–3} Hospitalization and death caused by the 2009 influenza A (H1N1) pandemic increased from August 2009, but this was rare in Japan. The Ministry of Health, Labor and Welfare (MHLW) of Japan confirmed only 85 deaths by 1st December 1, 2009, although the estimated number of cases was about 12.6 million by the end of November.⁶ Japanese data obtained from the MHLW website showed that the proportion of influenza-like illness cases in those aged 0–4 years and in adults was lower in Japan, compared with other countries. More than 75% of cases were those aged 5–19 years with a low rate of fatalities in Japan. The mortality rates, both per reported rates and per hospitalizations, increased significantly with age. The mean age of the 15 myocarditis cases associated with the 2009 influenza A (H1N1) pandemic was 42 years, which was higher than the mean of estimated cases and similar to other fatal cases during the pandemic in Japan.⁶

Acute myocarditis is a potentially lethal disease, and the etiological agents of viral myocarditis are enteroviruses including coxsackieviruses, adenoviruses, parvoviruses, hepatitis C virus, human immunodeficiency virus, influenza, and others.^{7–10} Coxsackievirus B has been described as the most common pathogen of viral myocarditis, and hepatitis C virus is associated with many different forms of heart disease world-

wide, however, influenza myocarditis is relatively rare.^{11–16} Bratinssak et al reported four fulminant myocarditis cases in patients aged from 3 to 9 associated with the 2009 influenza A (H1N1) pandemic within a 30-day period, and this suggested that the 2009 influenza A (H1N1) pandemic was more commonly associated with myocarditis than seasonal influenza.¹⁴ Martin et al identified 6 patients with reversible cardiac dysfunction associated with pandemic influenza A (H1N1) out of 123 hospitalized pandemic influenza A (H1N1) patients.¹⁵ There was only 1 case report of fulminant myocarditis with the 2009 influenza A (H1N1) pandemic in Europe.¹⁶ We report herein 15 myocarditis patients varying in age from a child to an old man over 70-year-old as a result of cross-sectional national survey by assist from all members of the Japanese Circulation Society using direct e-mailing system. We suggest that myocarditis is, along with pneumonia and encephalopathy, an important cause of clinical deterioration in influenza patients in Japan. Myocarditis associated with the 2009 influenza A (H1N1) pandemic seemed to be more common in hospitalized patients, compared with previous seasonal influenza virus.⁶

The diagnosis of myocarditis was performed using the Guidelines for the Diagnosis and Treatment of Myocarditis (JCS 2009) with a hybrid of compatible clinical symptoms, evidence of cardiac dysfunction, abnormality of cardiac enzymes in the absence of active coronary ischemia or other evidence of myocardial damage.¹⁰ Clinical symptoms of these patients were not specific; however, most patients complained of not only upper respiratory symptoms but also systemic symptoms. ST elevation was seen in 4 patients and giant negative T-wave was seen in 1 patient, so ECG findings were not specific. Echocardiography revealed reversible abnormalities of left ventricular wall motion, and cardiac enzymes were elevated in most patients. Quantitative troponin was measured in 4 patients and elevated in all; however, qualitative quick troponin testing was measured in 3 patients, but was positive in only 1 patient in this study. Reichlin et al reported that sensitive cardiac troponin assays improve the early diagnosis of myocardial infarction, so we recommend that these assays might be useful for the diagnosis and management of myocarditis.¹⁷ Cardiac scintigram is also useful.^{10,18,19} A new approach to diagnose myocarditis is cardiovascular magnetic resonance (CMR) imaging.¹⁰ Liu and Yan observed that CMR imaging is helpful for the detection of myocarditis, because CMR can visualize the entire myocardium.¹⁸ CMR probably has good sensitivity in detecting patchy processes and changes in tissue composition associated with inflammation. To avoid misdiagnosis of acute myocarditis as a complication of influenza infection, it is essential to determine the characteristic symptoms, signs, and laboratory findings of acute myocarditis during influenza infection. Myocarditis is probably underdiagnosed, so we have to strongly suspect myocarditis in hospitalized patients during an influenza pandemic.

Influenza is an acute respiratory illness caused by infection with influenza viruses. The most frequent baseline disease in the present study was lung disease, in 5 (33%) patients (asthma in 3 patients and emphysema in 2 patients). RT-PCR assays or quick diagnostic testing yielded positive results in 15 patients, and viral pneumonia were complicated in 2 patients in this study. Nasopharyngeal smears or sputum were positive for influenza pandemic A (H1N1) 2009 virus on RT-PCR assay in 10 patients. RT-PCR assay was not performed or was negative, and further characterization of the virus was not performed in the other 5 patients. However,

pandemic influenza A (H1N1) infection was strongly suspected, because it was previously revealed that over 99% of influenza A positive samples were identified with pandemic influenza A (H1N1) during this period by RT-PCR analysis. Although quick diagnostic testing for influenza is usually performed in Japan, the sensitivity of this type of testing is not high enough.^{4–6} Quick diagnostic testing for influenza, which was performed at the first visit to the clinic, was negative in 5 patients. One child who was hospitalized in the Osaka Medical College Hospital under the diagnosis of viral pneumonia caused by pandemic influenza A (H1N1) was found to be positive for viral pneumonia based on the chest X-ray, accumulated white blood cell counts in the absence of bacterial infection, high serum C-reactive protein concentrations and negative quick diagnostic testing for influenza on the 2nd day of sickness. Itoh et al reported that the 2009 influenza A (H1N1) pandemic caused more severe pathological lesions in the lungs of infected mice, ferrets, and non-human primates than the seasonal human H1N1 virus.²⁰ Nakajima et al reported that the concentrations of various cytokines/chemokines in the serum and autopsied lung tissue were elevated in both of the first autopsy cases in Japan.²¹ Muneuchi et al reported that myocarditis associated with influenza B virus appeared to be caused by endothelial impairment and disturbance of microcirculation rather than direct injury to cardiac myocytes.²² These findings suggest that a negative quick diagnostic test of patients with systemic symptoms might lead to hospitalization due to symptomatic viral pneumonia, or myocarditis, and the pathogenesis of systemic complications of influenza might be related to the induction of inflammatory cytokines produced by infected alveolar cells.

The clinical manifestations of myocarditis quite varied. Cardiac dysfunction progressed rapidly in 12 patients, and cardiac dysfunction developed after recovery from flu-like symptoms in 2 patients, and probably persisted for 1–1.5 months in 1 patient. Cases including slow progressive myocarditis and repetitive myocarditis are very rare. Takehana et al reported that a 75-year-old man who recovered from myocarditis associated with influenza A developed cardiogenic shock and died of fulminant myocarditis.²³ Most patients who survived recovered without any cardiac sequelae in this study, quite similar to previous reports. The degree of myocarditis associated with the 2009 influenza A (H1N1) pandemic was in the present study relatively mild even in patients with fulminant myocarditis.²⁴ Kotaka et al reported that murine influenza myocarditis was histologically mild and brief in duration compared to coxsackievirus B3 myocarditis.²⁵ We suggest that the pathogenesis and pathomechanism of pandemic influenza myocarditis differ depending on the pathogen,²⁵ and moreover, that significant mechanisms of cardiac injury, such as cytokine storm, endothelial dysfunction, oxidative stress and other factors, might play significant roles in the pathogenesis of pandemic influenza myocarditis.^{21–27} RT-PCR testing for pandemic influenza A (H1N1) from biopsy specimens was performed in only 1 case, and was negative. To evaluate influenza viral persistence in the myocardium in cases with myocarditis, further evaluation of viral replication in the myocardium using RT-PCR or in situ hybridization methods for pandemic influenza A (H1N1) from myocardial specimens is inevitable.

The first therapy for myocarditis patients with heart failure is supportive intervention. The recent application of PCPS and/or IABP to serious cases of viral myocarditis has yielded good outcomes.^{5,29} The severity and grade of cardiac and renal

dysfunction are important factors in connection with the prognosis. In this study, 8 patients were rescued using mechanical circulatory support and 2 patients died. It is important to recognize that patients with influenza infection might have acute myocarditis with heart failure, and that early diagnosis is required for adequate treatment.

Neuraminidase inhibitors work by blocking the function of the viral neuraminidase protein and thus prevent the virus from reproducing by budding from the host cell, and are useful for treating and preventing influenza virus infections.^{1-6,20} Itoh et al reported that the 2009 influenza A (H1N1) pandemic is sensitive to neuraminidase inhibitors, suggesting that these drugs could function as a first line of defense against the 2009 influenza A (H1N1) pandemic.^{1-6,20} Treatment with neuraminidase is also recommended by the Japanese Association of Infection. The low rate of case fatality in Japan could be a result of aggressive early intervention using with antiviral drugs such as oseltamivir and zanamivir. All of the present patients were treated with oseltamivir. In Japan, 3 types of neuraminidase inhibitors are available: oseltamivir, zanamivir, and peramivir. Adamantine, a M2 protein blocker, is resistant to the 2009 influenza A (H1N1) pandemic, while oseltamivir and zanamivir exhibit lower frequencies of antiviral resistance.²⁹ Oseltamivir is orally available, while zanamivir is inhaled.²⁵ Halvala et al identified 10 patients who developed the H275Y oseltamivir-resistance mutation out of 1,802 samples in Scotland.³⁰ The new neuraminidase inhibitor, peramivir, is formulated for intravenous administration and it has resulted in a good IC₅₀ response for pandemic influenza virus. Peramivir is recommended for patients requiring ventilation with difficulty in absorption of oseltamivir.²⁹ Treatment with high-dose immunoglobulin was used in 2 patients, which is still controversial.³¹ Corticosteroid was used only in 2 children, but not in adult patients. We know that inflammatory cytokines are important in the infection course of influenza; however, immunosuppression therapy with corticosteroids is not recommended, and this is supported by previous evidence.^{2,10} Moderate- to high-dose steroids are not recommended by the World Health Organization, because they are of unproven benefit and potentially harmful.

Conclusion

As a result of the present national survey in Japan, myocarditis associated with the 2009 influenza A (H1N1) pandemic seemed to be more common, compared with previous seasonal influenza viruses. To avoid misdiagnosis of acute myocarditis caused by influenza pandemic A (H1N1) 2009, the characteristic symptoms, signs, and laboratory findings of acute myocarditis during influenza pandemics must be determined. Mechanical circulatory support (IABP and/or PCPS) was required to rescue myocarditis patients by all means. Appropriate treatment using neuraminidase inhibitors must be recommended for patients with myocarditis associated with the influenza A (H1N1) pandemic.

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