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ORIGINAL ARTICLE

A national survey on myocarditis associated with influenza H1N1pdm2009 in the pandemic and postpandemic season in Japan

Akira Ukimura · Yukimasa Ooi · Yumiko Kanzaki · Takayuki Inomata · Tohru Izumi

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Abstract An influenza pandemic occurred in 2009. We performed a retrospective national questionnaire survey about H1N1pdm2009 myocarditis to compare influenza A H1N1pdm2009 myocarditis in the pandemic (2009/2010) and postpandemic seasons (2010/2011) by collecting data from 360 hospitals. The diagnosis of myocarditis was performed using the guidelines for Diagnosis and Treatment of Myocarditis published by the Japanese Circulation Society (JCS 2009). Twenty-nine patients with influenza A H1N1pdm2009 myocarditis were reported, with 25 from the 2009/2010 season and only 4 patients from the 2010/2011 season. Morbidity and mortality was 28 % (8/29) among all the myocarditis patients. Six patients with myocarditis were complicated by pneumonia. Myocarditis was proved by endomyocardial biopsy or autopsy in 9 patients, although histological findings showed mild myocarditis even in clinically defined fulminant myocarditis cases. Seventeen patients were diagnosed with fulminant H1N1pdm2009 myocarditis with fatal arrhythmias or varying degrees of cardiogenic shock. Fifteen fulminant myocarditis patients were seen in the 2009/2010 season and only 2 in the 2010/2011 season. Ventilators were used in 16 patients. Mechanical circulatory support with intraaortic balloon pumping or percutaneous cardiopulmonary support (IABP/PCPS) was emergently inserted in 13 patients. Of these, 9 patients were rescued with mechanical circulatory support, and 4 patients died. Four fulminant myocarditis patients treated without IABP/PCPS died. We described the clinical features of patients with myocarditis associated with influenza H1N1pdm2009 in the pandemic and postpandemic seasons and demonstrated the high prevalence of fulminant myocarditis (17/29, 59 %). The number of patients with myocarditis associated with influenza A virus seemed to increase in the pandemic season.

Keywords Myocarditis · Influenza A · Pandemic

Introduction

Acute myocarditis is a potentially lethal disease: the etiological agents of viral myocarditis include enteroviruses, adenoviruses, parvoviruses, cytomegalovirus, and influenza viruses [1–7]. Fulminant myocarditis causes severe hemodynamic dysfunction that requires high-dose catecholamine and mechanical circulatory support [1, 7]. Although the frequency of myocardial involvement in influenza infection is variable, that of fulminant myocarditis associated with influenza infection is rare, as shown in previous papers [1–4]. An influenza pandemic occurred in 2009 [8–12]. The Ministry of Health, Labor and Welfare of Japan (MHLW) confirmed only 198 deaths among about 20.61 million patients infected with influenza A H1N1pdm2009 in the 2009/2010 season and 150 deaths among about 10.3 million patients in the 2010/2011 season in Japan [10, 11]. Although usually

A. Ukimura and T. Izumi belong to the Clinical Research Committee on Myocarditis Associated with H1N1pdm2009 in Japan Organized by the Japanese Circulation Society.

A. Ukimura (✉) · Y. Ooi
Department of General Internal Medicine, Osaka Medical College, 2-7 Daigaku-machi, Takatsuki 569-8686, Japan
e-mail: in3011@poh.osaka-med.ac.jp

Y. Kanzaki
Third Department of Internal Medicine, Osaka Medical College, Takatsuki, Japan

T. Inomata · T. Izumi
Department of Cardio-Angiology, Kitasato University School of Medicine, Sagamihara, Japan

both the diagnosis and treatment of the pathogen involved in myocarditis are difficult, in the 2009/2010 pandemic, adequate diagnostic methods, such as the rapid influenza tests and reverse transcription-polymerase chain reaction (RT-PCR) for influenza H1N1pdm2009, and treatment with neuraminidase inhibitors were already available [10–13]. By conducting a cross-sectional national survey with assistance from all members of the Japanese Circulation Society (JCS) in the 2009/2010 influenza season, we previously reported 15 H1N1pdm2009 myocarditis patients and demonstrated their clinical features [13]. The Japanese Circulation Society performed a prospective study of patients with myocarditis associated with H1N1pdm2009 in the 2010/2011 season using their website, although no case was reported. Therefore, to compare myocarditis associated with influenza H1N1pdm2009 in the pandemic (2009/2010) and post-pandemic (2010/2011) seasons, we performed a national survey with a fill-in-the-blanks and multiple-choice questionnaire mailed to hospitals in Japan that have cardiology or pediatric departments or both.

Patients and methods

We mailed questionnaires to 978 hospitals in Japan that have cardiology and pediatric departments to compare myocarditis associated with influenza H1N1pdm2009 in the pandemic (2009/2010) and postpandemic (2010/2011) seasons. A fill-in-the-blanks and multiple-choice questionnaire was designed to obtain information on patient profiles (sex, age, and baseline disease), symptoms of influenza, symptoms of myocarditis, laboratory findings (e.g., cardiac enzymes, ECG, echocardiogram), treatment (e.g., neuraminidase inhibitors, steroid, mechanical circulatory support, ventilator), outcomes, and other. The questionnaire also included information about the number of hospitalizations associated with H1N1pdm2009 influenza during the two seasons. Myocarditis was diagnosed using the Guidelines for Diagnosis and Treatment of Myocarditis (JCS 2009) [1]. Compatible clinical symptoms, echocardiographic abnormalities in the absence of cardiac ischemia, and leakage of cardiac enzymes or other evidence of myocardial damage aided the diagnosis of myocarditis. Laboratory diagnosis of influenza A H1N1pdm2009 was made by quick influenza diagnostic testing or probe-based RT-PCR using a nasopharyngeal swab or sputum. The study protocol was approved by the Institutional Review Board of Osaka Medical College.

Results

We received completed questionnaires from 360 hospitals. Although 25 patients with myocarditis associated with influenza H1N1pdm2009 (17 men and 8 women; mean age, 39 ± 21 years) were reported to the task force of the Clinical Research for Myocarditis in the pandemic season (2009/2010), only 4 patients (3 men and 1 woman; mean age, 45 ± 15 years) were reported in the postpandemic season (2010/2011). Total mortality rate among all the myocarditis patients in both seasons was 28 % (8/29). Patient profiles, laboratory findings, treatments, and outcomes of patients with myocarditis associated with H1N1pdm2009 are shown in Table 1.

Myocarditis was proved by endomyocardial biopsy or autopsy in 9 patients (31 %); it was clinically diagnosed based on clinical features, leakage of cardiac constitutional proteins, such as troponin T/I, abnormalities on echocardiography, and other findings in the other 20 patients. Cardiac symptoms such as dyspnea, chest discomfort, hypotension, and syncope developed within 3 days of sickness in 16 patients (64 %). The most frequent baseline disease was a respiratory disorder in 7 (24 %) patients, including bronchial asthma in 5 patients (17 %) and emphysema in 2 patients (8 %). Six patients (21 %) with myocarditis were complicated by pneumonia. RT-PCR or quick diagnostic testing yielded positive results in all patients (100 %). Most patients exhibited ECG abnormalities, such as ST-T abnormalities (64 %). Echocardiography revealed abnormalities of left ventricular wall motion in 24 patients (83 %). Seven of the 9 patients of histologically proven myocarditis were fulminant myocarditis patients; 2 had acute myocarditis. Histological findings of these 9 patients showed myocarditis with lymphocyte infiltration. Quantitative assessment of troponin T/I was performed in 5 patients, in all of whom (100 %) it was elevated. On the other hand, qualitative quick troponin testing, which was conducted in 6 patients, was positive in only 3 patients (50 %). Cardiovascular magnetic resonance imaging (MRI) was performed in 2 patients. T_2-weighted cardiovascular MRI showed high-density signals in the region of the left ventricle in a 28-year-old man with fulminant myocarditis; his serial biopsies showed mild inflammation and degeneration of myocytes. RT-PCR testing for H1N1pdm2009 from heart specimens was performed in 2 cases (8 %), in both of whom it was negative. Cardiac dysfunction almost completely resolved in 19 patients (66 %) but remained partly unresolved in 2 patients (8 %). Coronary studies, which were performed in 20 patients (69 %), yielded normal results in all. Twenty-eight patients (96 %) were treated with neuraminidase inhibitors.

Seventeen of the 29 patients (59 %) were diagnosed with fulminant myocarditis with fatal arrhythmias and/or varying degrees of cardiogenic shock. Fifteen fulminant myocarditis patients (15/25, 60 %) were seen in the 2009/2010 season and only 2 (2/4, 50 %) in the 2010/2011 season. The clinical data of these 17 fulminant myocarditis patients are shown in Table 2. Nine (53 %) of the 17 fulminant myocarditis

Table 1 Patient profiles, laboratory findings, results of endomyocardial biopsies and/or autopsies, treatments, and outcomes of patients with myocarditis associated with H1N1pdm2009 in the 2009/2010 and 2010/2011 influenza seasons in Japan

	2009/2010 season	2010/2011 season
Number of H1N1pdm myocarditis cases	25	4
Sex (male/female)	17 (68 %)/8 (32 %)	1 (25 %)/3 (75 %)
Age (mean ± SD)	39 ± 21	45 ± 15
Survival	19 (76 %)	2 (50 %)
Adult/children	20 (80 %)/5 (20 %)	4 (100 %)/0 (0 %)
Fulminant myocarditis (adult/child)	15 (60 %) (11/4)	2 (50 %) (2/0)
Biopsy/autopsy	10 (40 %)/3 (12 %)	0/1 (25 %)
Baseline disease	Asthma, emphysema 6 (24 %)	Asthma 1 (25 %)
	DM 2 (8 %)	Hypertension 1 (25 %)
	None 14 (56 %)	None 1 (25 %)
Pneumonia	Viral 2 (8 %)/bacterial 2 (8 %)	Viral 1 (25 %)/bacterial 1 (25 %)
Cardiac symptoms	Dyspnea 13 (52 %)	Dyspnea 3 (75 %)
	Chest pain 4 (16 %)	Shock 1 (25 %)
	Syncope 3 (12 %)	Cyanosis 1 (25 %)
Onset of cardiac symptoms	1st–3rd day of sickness 16 (64 %)	1st–3rd day of sickness 0 (0 %)
	4th–10th day of sickness 6 (24 %)	4th–10th day of sickness 4 (100 %)
	Over 11th day of sickness 3 (12 %)	Over 11th day of sickness 0 (0 %)
ECG abnormalities	ST-T abnormalities 16 (64 %)	PSVT 2 (50 %)
	VT, VF 5 (20 %)	WNL 1 (25 %)
	Complete AV block 3 (12 %)	
	No information 2 (8 %)	No information 1 (25 %)
Echocardiogram	Wall motion abnormalities 21 (84 %)	Wall motion abnormalities 3 (75 %)
	Pericardial effusion 3 (12 %)	Pericardial effusion 1 (25 %)
	No information 2 (8 %)	No information 1 (25 %)
Peak CPK values	13,639 ± 42,495 IU/l	14,604 ± 18,770 IU/l
Coronary artery (CAG/CT)	No stenosis 15 (60 %)	No stenosis 3 (75 %)
	Not examined 10 (40 %)	Not examined 1 (25 %)
Other diagnostic tool (positive/examined)	Qualitative troponin 3/6 (50 %)	Qualitative troponin 0/0
	Quantitative troponin T/I 5/5 (100 %)	Quantitative troponin T/I 0/0
	MRI 1/2 (50 %)	MRI 0/0
Antiviral drug	24 (96 %)	4 (100 %)
Other treatment	Steroid 5 (20 %)	Steroid 0 (0 %)
	γ-Globulin 6 (24 %)	γ-Globulin 0 (0 %)

patients had no baseline disease. Three fulminant myocarditis patients (17 %) were complicated by pneumonia. Myocarditis was proved by endomyocardial biopsy or autopsy in 7 (41 %) of the 17 fulminant myocarditis patients. Histological findings were classified by the Dallas Criteria [14]. The first biopsy, obtained from a 44-year-old woman on day 1 showed myocarditis with lymphocytic infiltration, degeneration of myocytes, and interstitial edema; the second biopsy on day 23 showed resolving myocarditis. Histological findings in the other 8 patients showed myocarditis with infiltration of lymphocytes (ranging from mild to moderate, but not severe). Autopsy of the patient with fulminant myocarditis (on day 9) showed only interstitial fibrosis without lymphocytic infiltration. Ventilators were used in 16 patients (94 %). Mechanical circulatory support with intraaortic balloon pumping (IABP) and/or percutaneous cardiopulmonary support (PCPS) was emergently inserted in 13 patients. Nine of

Table 2 Patient profiles, laboratory findings, reports of endomyocardial biopsies and/or autopsies, treatments, and outcomes of patients with fulminant myocarditis associated with influenza A H1N1pdm2009 in Japan

	Fulminant myocarditis
Number of cases (adult/children)	17 (13/4)
Sex (male/female)	10 (58 %)/7(42 %)
Age (mean ± SD)	32 ± 19
Survival	9/17 (53 %)
Baseline disease	Asthma, emphysema 4 (24 %)
	DM 2 (12 %)
	None 9 (53 %)
Complicated pneumonia	3 (18 %)
Histological findings of heart tissue by Dallas criteria (1987) [14]	Resolving myocarditis (1st biopsy on day 1: myocarditis, LI, IE, MD; 2nd biopsy on day 23: LI)
	Myocarditis on day 1 (moderate LI, IE, MD)
	Myocarditis on day 1 (moderate LI, IE, MD)
	Myocarditis on day 4 (mild LI, IE, MD)
	Myocarditis on day 32 (mild LI, IE, MD)
	Borderline myocarditis (LI)
	Borderline myocarditis on day 7 (LI)
	No myocarditis on day 9 (IF)
	No myocarditis on day 16 (IF)
RT-PCR from heart tissue	0/2 (0 %) (on days 8 and 9)
Peak CPK values	23,640 ± 52,471 IU/l
Other diagnostic tool (positive/examined)	Qualitative troponin 2/3 (67 %)
	Quantitative troponin T/I 5/5 (100 %)
	MRI 1/2 (50 %)
Ventilator	15 (88 %)
IABP/PCPS	13 (76 %)
Survival with IABP/PCPS	9/13 (69 %)
Antiviral drug	16 (96 %)

Histological findings were classified by the Dallas Criteria [14]. First biopsy: myocarditis, borderline myocarditis, no myocarditis. Subsequent biopsies: ongoing myocarditis, resolving myocarditis, resolved myocarditis

LI lymph node infiltration, *IE* interstitial edema, *DM* diabetes mellitus, *MD* degeneration of myocyte, *IF* interstitial fibrosis

these 13 patients (69 %) were successfully rescued with mechanical circulatory support; the remaining 4 patients died (31 %). Four fulminant myocarditis patients treated without IABP/PCPS also died (100 %).

Discussion

The MHLW of Japan confirmed only 198 deaths (9.6×10^{-4} %) among about 20.61 million patients infected with influenza A H1N1pdm2009 in the 2009/2010 season, and 150 deaths (15×10^{-4} %) among about 10.3 million patients in the 2010/2011 season in Japan [10, 11]. The low case-fatality rate in Japan may be a result of early diagnosis and aggressive early intervention with antiviral drugs [9–11]. Twenty-five influenza H1N1pdm2009 myocarditis patients ($\geq 0.20 \times 10^{-4}$ %) were reported in the 2009/2010 season, although only 4 patients ($\geq 0.031 \times 10^{-4}$ %) were documented in the 2010/2011 season in the present study. The number of patients with clinically defined myocarditis associated with the influenza A virus seemed to increase in the pandemic season and obviously decrease in the postpandemic season compared to the pandemic season [2–4, 12, 13, 15–17]. The mean age (39 years) of myocarditis patients associated with H1N1pdm2009 influenza seemed to be lower than the age of patients with serious illness associated with seasonal influenza in the present study, probably indicating an age shift to a younger population in myocarditis patients with high fatality.

The frequency of myocardial involvement in influenza infection is variable, with fulminant myocarditis associated with seasonal influenza infection being rare, as shown in previous papers, probably because of the low affinity of the influenza virus for the myocardium [1–6]. Small autopsy-based studies demonstrated the complication rate of focal to diffuse myocarditis in fatal cases as 39 % with the 1957 Asian influenza pandemic and 48 % with the Spanish influenza pandemic [2]. Myocarditis caused by influenza is likely to be a terminal event in patients during influenza pandemics. In our survey, a total of 17 fulminant myocarditis patients were reported, 8 of whom died (47 %), although fulminant myocarditis caused by influenza infection is an uncommon type of myocarditis. We demonstrated a high prevalence of fulminant myocarditis

among all the myocarditis patients (17/29, 59 %). We found that, along with pneumonia and encephalopathy, myocarditis was an important cause of clinical deterioration in patients infected with H1N1pdm2009 in Japan [9, 10, 13, 15]. The influenza A virus might be more commonly associated with severe forms of myocarditis in the pandemic season than other seasons [2–4, 13, 15–17]. Because there was no significant difference in the H1N1pdm2009 virus in the 2009/2010 and 2010/2011 seasons [10, 12], we speculate that the pathological mechanism of influenza myocarditis differs depending on the pathogen, and may depend on host immunity, as indicated by anti-H1N1pdm2009 titers.

In our study, quantitative values of troponin I/T were elevated in all five patients in whom it was measured (100 %). Conversely, the qualitative quick troponin test was positive in only three of the six patients (50 %) in whom it was measured. Hence, we recommend that quantitative troponin I/T assays may be useful for the diagnosis and management of myocarditis.

Many kinds of viruses have been implicated as causes of myocarditis, with different viruses having different potentials to cause myocarditis [2–7, 12, 13, 15–17]. In their study, Bowles et al. reported that endomyocardial biopsy samples from 624 patients with clinically defined myocarditis were analyzed by PCR to detect various viral genes, of which 239 samples were positive [4]. Adenovirus was detected from 142 samples, enteroviruses from 85 samples, cytomegalovirus from 18 samples, and influenza A from 5 samples (0.8 %) [4]. In the present study, RT-PCR testing for H1N1pdm2009 from heart specimens were negative in both patients in which it was performed. Although it is well known that coxsackie viruses present a high affinity for cardiac myocytes, the pathological effects of influenza virus myocarditis in humans and mice are reportedly milder than coxsackie virus myocarditis and are more localized [4–6, 18]. The affinity of the influenza virus for cardiac myocytes is also reportedly low [3, 4, 6, 18]. Pan et al. reported the molecular mechanism of myocarditis associated with the influenza virus and revealed the importance of trypsin induction and increased production of pro-inflammatory cytokines in the pathogenesis of acute myocarditis [17–20]. Besides the direct effect of influenza virus infection, pro-inflammatory cytokines are thought to contribute to the pathogenesis of severe clinical features, including severe cardiac dysfunction, in influenza patients [13, 15, 18–21].

Myocarditis was proved by endomyocardial biopsy or autopsy in nine patients in this study, although the pathological findings were mild even in clinically defined fulminant myocarditis patients. A new approach to diagnosing myocarditis is cardiovascular magnetic resonance imaging (MRI) [1, 15]. MRI was indicative of myocarditis in one of two (50 %) patients in this study in whom it was performed. Hence, MRI might be more useful than invasive cardiac biopsy for diagnosing H1N1pdm2009 myocarditis and for estimating the activity and severity of inflammation, although further evaluation of its diagnostic efficacy is recommended.

There are some limitations to this study. We planned a statistical analysis between the number of myocarditis patients and the number of hospitalizations associated with H1N1pdm2009 influenza. However, this was not possible because of the low response rate to the question about the number of hospitalizations (responses were obtained from only 40 hospitals); further, many hospitalizations in the 2009/2010 season were for social reasons rather than serious illness.

Our study suggests that because cardiac symptoms developed within 3 days of sickness in 17 patients and cardiac dysfunction rapidly progressed in H1N1pdm2009 myocarditis, early diagnosis and prompt treatment of acute myocarditis with heart failure is required in patients with influenza infection during the pandemic season. Appropriate intervention in patients with fulminant influenza myocarditis consists of treatment with neuraminidase inhibitors to eliminate the causative virus, and mechanical circulatory support [intraaortic balloon pumping (IABP)/percutaneous cardiopulmonary support (PCPS)] to treat the depressed myocardial function [1, 7, 12, 13, 15].

In conclusion, we confirmed the clinical features of patients with clinically defined myocarditis associated with influenza H1N1pdm2009 and demonstrated the high prevalence of fulminant disease (17/29, 59 %) in patients with influenza myocarditis. The number of patients with myocarditis associated with influenza A virus seemed to increase in the pandemic season but not in the nonpandemic season.

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Conflict of interest None declared.

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