

Clinical Manifestations of Influenza A Myocarditis During the Influenza Epidemic of Winter 1998 - 1999

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Abstract

Objectives. The clinical features of myocarditis that developed during the influenza epidemic of winter 1998 - 1999 were investigated to emphasize the need for medical attention to this disease.

Methods. Nine patients were treated under diagnoses of acute myocarditis during the winter of 1998 - 1999. Five (two males and three females, mean age 52 ± 18 years) were examined with myocarditis associated with influenza A. The diagnosis of influenza A myocarditis was based on electrocardiographic and echocardiographic abnormalities, increased creatine kinase levels and at least a four-fold increase in influenza A virus titers using paired sera.

Results. All patients had preceding flu-like symptoms and fever. Cardiac involvement developed between 4 and 7 days after the onset of influenza symptoms. Dyspnea progressively worsened in three patients, one went into shock and one had persistent fever, cough and mild dyspnea without apparent cardiac symptoms. Three patients had ST elevation associated with Q waves and one had complete left bundle branch block. The creatine kinase levels were abnormally increased and global wall motion of the left ventricle on echocardiography was decreased in all patients. Two patients had diagnoses of fulminant myocarditis. One patient died of pneumonia following cerebral infarction, but the left ventricular dysfunction normalized in the remaining four patients.

Conclusions. Cardiac involvement occurred between 4 and 7 days after the onset of influenza symptoms, and worsening dyspnea was the most common symptom. Electrocardiography, echocardiography and creatine kinase levels should be checked to determine the potential for cardiac involvement when

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Manuscript received January 9, 2001; revised March 7, 2001; accepted March 12, 2001

patients present with suspected influenza associated with worsening dyspnea or prolonged weakness. Increasing the awareness of influenza myocarditis may help in the earlier identification and treatment of this disease during influenza epidemics.

J Cardiol 2001; 37(6): 315 - 323

Key Words

Myocarditis(influenza A myocarditis)

Heart failure

Electrocardiography

Echocardiography, transthoracic

Infectious disease

INTRODUCTION

Influenza is defined as an acute respiratory illness that includes the upper and/or lower respiratory tracts and is characterized by the abrupt onset of systemic signs and symptoms such as fever, headache, myalgia, arthralgia, malaise and weakness¹⁾. The presentation of myocarditis ranges from nonspecific systemic syndromes including fatigue, dyspnea and palpitations, to sudden death²⁾. Myocarditis is entirely self limiting and often unrecognized in most patients³⁾, whereas most hospitalized patients have congestive heart failure which may be severe or fatal²⁾. The influenza A virus is believed to be one of several pathogens responsible for viral myocarditis⁴⁾. In fact, cardiac involvement or myocardial damage in patients diagnosed with influenza during outbreaks has repeatedly been described in the clinical literature⁵⁻⁸⁾. Nonetheless, cardiac symptoms tend to be misdiagnosed as respiratory symptoms during an influenza epidemic.

The most extensive and severe influenza outbreaks are caused by influenza A viruses. Influenza A epidemics begin abruptly, reach a peak over a 2- to 3-week period, generally last for 2 to 3 months and often subside almost as rapidly as they emerge¹⁾. From January 1 through March 31, 1999, the Japanese Ministry of Health and Welfare reported 1,287 deaths due to influenza⁹⁻¹¹⁾, which was the highest number since 1976. However, the incidence of myocarditis and cardiac death related to influenza infection during epidemics in Japan has not been reported. We emphasize the need for medical attention to this disease during influenza outbreaks. We retrospectively investigated the clinical features of influenza A myocarditis associated with the influenza epidemic during the winter of 1998 - 1999. Understanding the clinical signs and symptoms of influenza myocarditis may contribute to its earlier identification and treatment and may help to avoid misdiagnosis during influenza outbreaks.

PATIENTS AND METHODS

Nine patients(six males and three females, mean age 52 ± 23 years)admitted to our four institutions (Miyazaki Medical College Hospital, Miyazaki Medical Association Hospital, Miyazaki Cardiovascular Hospital, Miyazaki Prefectural Hospital)during the winter of 1998 - 1999 had diagnoses of myocarditis. No histological diagnosis was obtained in the present study except for one patient with eosinophilic myocarditis. However, the diagnosis of myocarditis was based on the criteria of the study group of the Japanese Ministry of Health and Welfare, which include electrocardiographic(ECG)abnormalities such as ST elevation and abnormal Q waves, left ventricular wall motion abnormalities on echocardiograms and increased levels of cardiac enzymes such as creatine kinase (CK)¹²⁾. A cardiac catheterization study confirmed the absence of coronary lesions in eight of the nine patients. Influenza A myocarditis was identified in five(two males and three females, mean age 52 ± 18 years)of these patients who developed progressive heart failure, shock, or prolonged respiratory symptoms with mild dyspnea following an influenza-like illness. The diagnosis was confirmed by at least a four-fold increase in influenza A virus titers of paired sera using either the hemagglutination inhibition or the complement-fixation method. The patients were further classified as having fulminant myocarditis according to the criteria of Lieberman *et al.*¹³⁾and McCarthy *et al.*¹⁴⁾. However, we did not perform an endomyocardial biopsy, but based the diagnoses on the following clinical features: severe hemodynamic compromise requiring high doses of vasopressors($\geq 5 \mu\text{g}/\text{kg}/\text{min}$ of dopamine or dobutamine)and/or intraaortic balloon pumping(IABP) and the distinct onset of cardiac involvement. Informed consent was obtained from all patients on admission to our hospitals.

RESULTS

Case reports

1) Patient 1

A 33-year-old man presented with acute onset of flu-like symptoms on December 27, 1998, followed by worsening dyspnea and fever. He was admitted to our hospital on December 31, 1998. On admission, his body temperature was 39.3 °C, blood pressure was 184/114 mmHg and heart rate was 140 beats/min. He had orthopnea, and wheeze and crackles were audible in the bilateral lung fields. Chest radiography on admission showed cardiomegaly [cardiothoracic ratio (CTR): 61%] associated with pulmonary congestion and pleural effusion. Sinus tachycardia and ST segment depression with flat T waves in leads I, II, aF and V₆ were noted, but these did not change over the 4 weeks after admission. Echocardiography demonstrated diffuse hypokinesis of the left ventricular wall motion, ejection fraction of 28% and left ventricular end-diastolic dimension (LVDd) of 66 mm. The CK, CK-MB and C-reactive protein (CRP) levels were 1,918 IU/l, 43 IU/l and 7.3 mg/dl, respectively. Right heart catheterization revealed moderately elevated pulmonary artery pressure (68/26 mmHg). The paired sera test revealed an 8-fold increase (4-fold on admission to 32-fold) in antibody titer against the influenza A virus. He was treated with intravenous dopamine (3 µg/kg/min), dobutamine (4 µg/kg/min) and a diuretic. Echocardiography 4 weeks after admission showed that the ejection fraction value had increased to 59% and LVDd decreased to 56 mm. Coronary angiography revealed no coronary lesions and no ergonovine-provoked coronary spasm, and left ventriculography confirmed normal wall motion 4 weeks after admission. He was discharged on February 2, 1999.

2) Patient 2

An 80-year-old woman developed flu-like symptoms with worsening dyspnea and was transferred to our hospital 5 days later because of congestive heart failure on January 22, 1999. On admission, her body temperature, blood pressure and heart rate were 38.6 °C, 70/50 mmHg and 110 beats/min, respectively. Chest radiography showed mild cardiomegaly (CTR: 55%) associated with mild pulmonary congestion. ECG on admission revealed sinus tachycardia and ST elevation in leads I, aL, and V₁ to V₆ associated with abnormal Q waves in leads I, aL, and V₁ to V₅. Echocardiography

revealed left ventricular global hypokinesis and an ejection fraction of approximately 40%. The CK and CRP levels were 3,067 IU/l and 8.0 mg/dl, respectively. Troponin T was also positive on admission. Hemodynamic study showed mildly elevated pulmonary artery diastolic pressure (28/16 mmHg) and mean pulmonary atrial wedge pressure (14 mmHg). The cardiac index was 2.7 l/min/m² and coronary angiography demonstrated no coronary lesions on admission. The paired sera test revealed elevated influenza A viral titer from 4 to 256-fold. The patient was treated with dopamine (10 µg/kg/min), dobutamine (10 µg/kg/min), diuretics, IABP and artificial ventilation because of progressively worsening pulmonary congestion and hypotension. Her hemodynamic status improved, and echocardiography demonstrated improved left ventricular wall motion and ejection fraction of 62% on the 15th hospital day. ECG 3 months after admission revealed normal sinus rhythm and negative T waves in leads V₂ to V₆, but Q waves were absent in all leads. She remained in hospital for 5 months because she needed physical rehabilitation, but she was discharged on July 1, 1999.

3) Patient 3

A 77-year-old woman was referred to our hospital for further examination and treatment on January 27, 1999. She had a prolonged fever of 38 °C, cough and mild dyspnea over a period of 4 days before admission, but did not complain of chest pain or severe dyspnea. On admission, her body temperature, blood pressure and heart rate were 38.2 °C, 148/80 mmHg and 100 beats/min, respectively. Neither physical examination nor chest radiography indicated congestive heart failure (CTR: 52%). ECG revealed a QS pattern in leads V₁ to V₃ and ST elevation in leads I, II, aF and V₂ to V₆ with terminal negative T waves in leads I, II, aF and V₂ to V₆ on admission. Echocardiography demonstrated hypokinesis on the apex and anterior wall of the left ventricle and ejection fraction of approximately 40%. Laboratory data showed the following values: CK; 507 IU/l, GOT; 134 IU/l, GPT; 37 IU/l and LDH; 700 IU/l. A cardiac catheterization study was not performed. The paired sera test revealed a 32-fold increase in the influenza A virus titer (4-fold to 128-fold). The patient was hemodynamically stable and catecholamine therapy was not required. She improved over the first 10 days after admission, but she suffered sudden onset of disturbed consciousness on

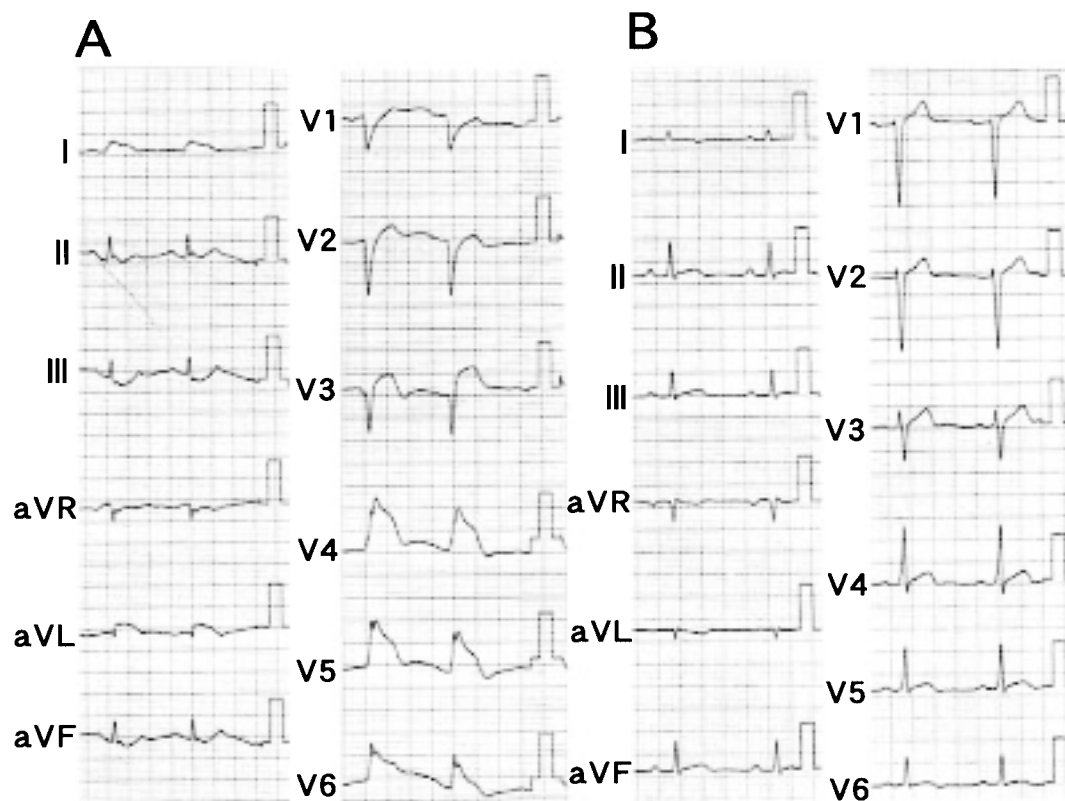


Fig. 1 Twelve-lead electrocardiograms on admission (**A**) and 14 days after admission (**B**) of Patient 4. Abnormal Q waves in leads V_1 to V_3 , ST elevation in leads I , aVL and V_3 to V_6 , and ST depression in leads II and aVF on admission (**A**). Electrocardiogram changes had improved, but not normalized 14 days later (**B**).

the 12th hospital day. Emergency computed tomography scanning indicated suspected cerebral infarction and she was placed on an artificial ventilator followed by tracheotomy. However, the patient died of pneumonia 44 days after admission.

4) Patient 4

A 55-year-old man with a past history of bronchial asthma was admitted to a local clinic after an attack of bronchial asthma on January 23, 1999. He complained of sore throat accompanied by high fever on January 28, 1999 and was treated with antipyretics because his temperature reached 39.8°C on February 2, 1999. However, he immediately developed hypotension and disturbed consciousness and was transferred to our hospital on the same day. On admission, he was drowsy, with body temperature, systolic blood pressure and heart rate of 36.0°C , 60 mmHg and 70 beats/min, respectively. No pathological heart murmurs or crackling respiratory sounds were present. Chest radiography confirmed the absence of cardiomegaly (CTR :

52%) and pulmonary congestion. ECG revealed abnormal Q waves in V_1 to V_3 , ST elevation in I , aVL and V_3 to V_6 , and ST depression in II and aVF (**Fig. 1 - A**). Echocardiography revealed global hypokinesis, ejection fraction of 10% and LVDD of 54 mm (**Fig. 2 - A**). The CK level on admission was 870 IU/l and CK-MB was 121 IU/l. Emergency coronary angiography revealed intact right and left coronary arteries. The paired sera test revealed an 8-fold increase in antibody titer against the influenza A virus (16-fold on transfer to 128-fold). He was treated with IABP, intravenous dopamine (15 $\mu\text{g}/\text{kg}/\text{min}$) and dobutamine (15 $\mu\text{g}/\text{kg}/\text{min}$). ECG showed improvement, but not normal findings (**Fig. 1 - B**) by day 14, ejection fraction had increased to 76% and LVDD had decreased to 38 mm by day 28 (**Fig. 2 - B**). The patient was discharged on March 4, 1999.

5) Patient 5

A 67-year-old woman was admitted to our hospital on February 3, 1999 with acute onset of dysp-

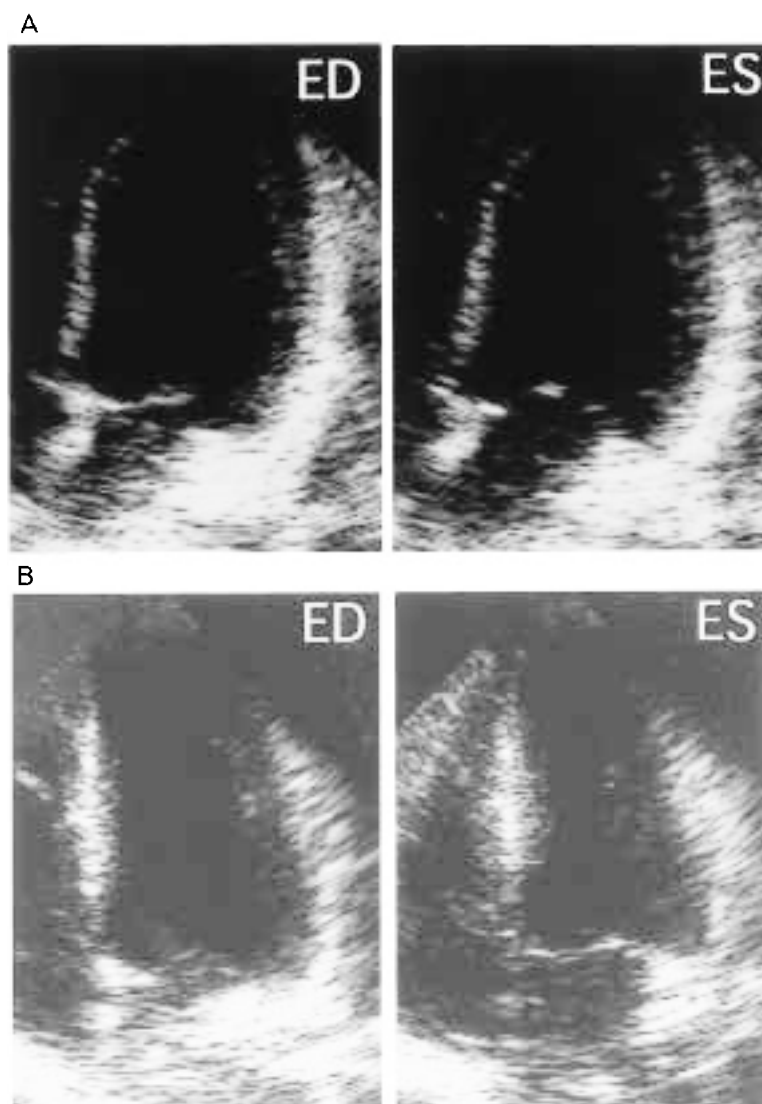


Fig. 2 Apical four-chamber view echocardiograms on admission (A) and 28 days after admission (B) of Patient 4

Global hypokinesis, left ventricular end-diastolic dimension of 54 mm, and ejection fraction of 10% were present on admission (A), but abnormal wall motion resolved, left ventricular end-diastolic dimension decreased to 38 mm and ejection fraction increased to 76% by 28 days after admission (B).

ED = end-diastole; ES = end-systole.

nea. She had a fever of 38 °C and flu-like symptoms 7 days before admission. On admission, her body temperature was 36.8 °C, blood pressure was 160/90 mmHg and heart rate was 90 beats/min. She had orthopnea. Chest radiography showed mild cardiomegaly (CTR: 54%) and severe pulmonary congestion. Complete left bundle branch block (CLBBB) was noted and did not change over the next 2 weeks. Echocardiogram revealed left ventricular global hypokinesis and ejection fraction of 30% on admission. Her CK level was 556 IU/l and

CRP was 4.0 mg/dl. The paired sera test showed the viral titer of influenza A was elevated from 8-fold on admission to 32-fold 10 days after admission. She was initially treated with intravenous dopamine (3 µg/kg/min) and dobutamine (3 µg/kg/min) followed by oral digoxin, diuretics and angiotensin converting enzyme inhibitor. Over the next 2 weeks her symptoms improved and left ventricular ejection fraction increased to 55%. Coronary angiography revealed no organic coronary stenosis and normal wall motion on left ven-

Table 1 Clinical features of five patients with influenza A myocarditis

Pat. No.	Age(yr) /sex	Time after presentation (day)	Fever	Symptom	On admission				Changes in influenza A virus titer		Catechol-amine doses (µg/kg/min)	IABP	Outcome
					ECG changes	Pulmonary congestion	CK (IU/l)	EF (%)	×	×			
1	33/M	4	(+)	CHF	No	(+)	1,918	28	×4	×32	DOA: 3 DOB: 4	(-)	Alive
2	80/F	5	(+)	CHF	ST() Q	(+)	3,067	40	×4	×256	DOA: 10 DOB: 10	(+)	Alive
3	77/F	4	(+)	Persistent fever, cough and mild dyspnea	ST() Q	(-)	507	40	×4	×128	(-)	(-)	Died
4	55/M	5	(+)	Shock	ST() Q	(-)	870	10	×16	×128	DOA: 15 DOB: 15	(+)	Alive
5	67/F	7	(+)	CHF	CLBBB	(+)	556	30	×8	×32	DOA: 3 DOB: 3	(-)	Alive

Pat. No. = patient number; ECG = electrocardiogram; CK = creatine kinase; EF = ejection fraction; IABP = intraaortic balloon pumping; CHF = congestive heart failure; Q = Q wave; CLBBB = complete left bundle branch block; DOA = dopamine; DOB = dobutamine.

tricolography 14 days after admission. She was discharged 21 days after admission.

Summary of the clinical features of five patients

Nine patients were treated under diagnoses of acute myocarditis during the winter of 1998 - 1999 influenza epidemic, and five cases (56%) were associated with influenza A infection. The clinical features of the five patients with influenza A myocarditis are summarized in **Table 1**. The development of myocarditis was preceded in all patients by flu-like symptoms and fever. The cardiac involvement developed between 4 and 7 days after the onset of flu-like symptoms. Dyspnea progressively worsened in three patients, one went into shock (Patient 4), and one had persistent fever, cough and mild dyspnea without apparent cardiac symptoms (Patient 3). None of the patients had chest pain. ECG showed ST elevation and Q waves in the precordial leads in three patients and CLBBB in one. The CK levels were abnormally increased and global wall motion of the left ventricle on echocardiography was decreased in all patients. Although histological diagnosis was not obtained in the study, the symptoms of two patients (Patients 2 and 4) were compatible with a diagnosis of fulminant myocarditis according to the classification of Lieberman *et al.*¹³ and McCarthy *et al.*¹⁴. One elderly patient (Patient 3) died of pneumonia following cerebral infarction. However, left ventricular dysfunction eventually normalized after treat-

ment in the remaining four patients.

DISCUSSION

A high incidence of myocarditis has been linked with influenza epidemics⁵⁻⁸. Karjalainen *et al.*⁸ reported that the incidence of influenza A myocarditis diagnosis based on serial ECG changes and echocardiography was 9 % among 67 verified and suspected cases of influenza. Most of the patients had markedly mild myocarditis. In fact, the ECG anomalies completely normalized within 1 - 2 weeks in five of six patients, and normalized in two within 24 hr. Kitaura *et al.*¹⁵ also found that quite few of patients who develop myocarditis due to influenza become severely ill in contrast to those infected with Coxsackie virus. In contrast, five fatal myocardial involvements were reported during the A2 England influenza epidemic of the winter of 1972 - 1973⁷. Autopsies of two patients who died within 24 hr of the onset of influenza symptoms also showed early necrosis of myofibrils, suggesting that death was directly due to cardiac involvement. Two of our patients (Patients 2 and 4) with fulminant myocarditis required IABP and catecholamine to improve hemodynamic instability. Although some patients with influenza myocarditis are completely asymptomatic and not hospitalized^{2,3}, others become severely ill. An animal study revealed that viral infection results in death within 4 days even in the absence of histologically apparent myocarditis¹⁶. In some strains of mice, the ini-

tial noninflammatory phase is not immediately lethal and is followed by marked myocarditis between 4 and 14 days after infection¹⁷). Considering that the incubation period of influenza ranges from 18 to 72 hr¹), the time courses of the two patients who died within 24 hr in the A2 England influenza epidemic⁷) and the five patients who showed cardiac involvement between 4 and 7 days after the presentation of influenza symptoms in our study are very compatible with those of animal models of viral myocarditis^{18,19}). We could not determine the incidence of influenza myocarditis during the influenza epidemic in this study, because the exact number of patients with influenza was not available. Although our experience with influenza A myocarditis was limited, influenza A viral infection as the pathogenesis was found in 56% of patients with myocarditis during the influenza epidemic of winter 1998 - 1999.

ECG abnormalities such as ST elevation and Q waves are helpful in the diagnosis of myocarditis. Repolarization abnormalities and arrhythmias suggesting myocardial involvement can be identified during either the acute phase of an infectious disease including viral illness, or the convalescence period^{20,21}). Complete atrioventricular block occasionally causes sudden death in patients with myocarditis²²), but most patients do not have other clinical manifestations³). These ECG changes may reflect subclinical myocardial involvement, conversely suggesting that a diagnosis of subclinical viral myocarditis is essentially dependent on whether or not an ECG is recorded at the initial stage of the disease. The development of Q waves is rare²). However, the present study found ST elevation and Q waves in three of five patients (60%) and CLBBB in one (20%). Morgera *et al.*²²) reported ECG changes in 45 patients with a histological or postmortem diagnosis of active myocarditis. They found Q waves, CLBBB, ST elevation, and complete atrioventricular block in 16 - 18% of their patients, a difference from our report that may be ascribed to the study population.

Four patients were treated with catecholamine with or without IABP. No steroids were administered to any of the patients in this study. Corticosteroids cause increased viral replication and tissue necrosis when administered early to animals with acute myocarditis, but may be safer late in the course of the disease^{23,24}). Non-steroidal anti-inflammatory drugs are contraindicated in the early

stages of viral myocarditis because they also increase myocardial necrosis, probably as a result of altering the host response to infection²⁵). Indeed, Patient 4 developed shock followed by fulminant myocarditis after the administration of non-steroidal antipyretics. Since shock developed so suddenly, the above mechanism could not be considered as the direct cause. However, this drug might have been partially responsible for this patient developing fulminant myocarditis. Matsumori *et al.*²⁶) reported that digoxin increases both the expression of proinflammatory cytokines and mortality in a murine model of viral myocarditis and that digoxin should be used with caution and only at low doses. Patient 5 was treated with intravenous dopamine followed by the oral administration of digoxin (0.125 mg), diuretics and angiotensin converting enzyme inhibitor. Left ventricular dysfunction was improved 2 weeks after initiating these therapeutic strategies. Patients 2 and 4 with fulminant myocarditis completely recovered after intensive treatment. Aggressive hemodynamic support elicited favorable results against fulminant myocarditis, a finding that was compatible with those of McCarthy *et al.*¹⁴). The outcome after viral myocarditis is quite variable²) and may be related to individual genetic susceptibility.

CONCLUSIONS

Identifying the signs and symptoms of myocarditis is paramount for successful management and early treatment. Cardiac involvement appeared between 4 and 7 days after the onset of influenza symptoms, and worsening dyspnea was the most common symptom. However, clinical signs and symptoms in some patients may not be helpful to differentiate myocarditis from respiratory symptoms. Increasing the awareness of influenza myocarditis may help in the earlier identification and treatment of this disease during influenza outbreaks. Echocardiography, ECG and CK level measurement should all be performed when patients present with suspected influenza associated with worsening dyspnea or prolonged weakness to detect potential influenza myocarditis.

Acknowledgements

We thank Drs. Shigeru Fukuda, Kazuo Nakamura, and Saburo Takeuchi (Takeuchi Hospital) for referring a patient to us and Ms. Norma Foster for critical reading of the manuscript.

要 約

1998 - 1999年冬のインフルエンザ流行期に発症した
インフルエンザA心筋炎の臨床像

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目 的: 1998 - 1999年冬のインフルエンザ流行期に我々が経験したインフルエンザA心筋炎の臨床像を検討し, インフルエンザ流行期における本疾患認識の重要性を唱えることを目的とした.

方 法: 1998 - 1999年にかけての冬期に我々の4施設で経験した急性心筋炎患者9例のうち, インフルエンザA心筋炎と診断した5例(男性2例, 女性3例, 平均年齢 52 ± 18 歳)の患者を対象とした. インフルエンザA心筋炎の診断は心電図変化, 心臓超音波による壁運動異常, 血清クレアチンキナーゼ値の上昇およびペア血清による4倍以上のインフルエンザAウイルス抗体価の上昇に基づいて行った.

結 果: 全例に心筋炎発症前に発熱を伴う感冒様症状の出現が認められた. インフルエンザ発症後4 - 7日の間に心筋炎が発症した. 心筋炎の主症状としては増悪する呼吸困難が3例, ショックが1例で, 残りの1例は持続する発熱, 咳と軽度の呼吸困難で, 明らかな心症状を欠いていた. 心電図ではQ波を伴うST上昇が3例, 完全左脚ブロックが1例に認められた. 血清クレアチンキナーゼ値の上昇と心臓超音波上のび慢性左室壁運動異常が全例に認められた. このうち2例は劇症型心筋炎の臨床像を呈した. 脳梗塞発症後の肺炎で死亡した1例を除き, 残りの4例はすべて心機能は正常化した.

結 論: インフルエンザA心筋炎は感冒症状出現から4 - 7日後に発症し, 心不全症状が最も多い心筋炎に伴う症状であった. インフルエンザ流行期にその感染が疑われる患者で増悪する呼吸困難や感冒症状の長期化を伴う場合には, 心筋炎合併の可能性を考慮して心電図, 心臓超音波, 血清クレアチンキナーゼ値の検査を施行すべきである. インフルエンザ心筋炎の周知はインフルエンザ流行期における本疾患の早期診断, 早期治療に重要な役割を担うものと思われる.

J Cardiol 2001; 37(6): 315 - 323

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