

Case Report

Influenza-associated septic shock accompanied by septic cardiomyopathy that developed in summer and mimicked fulminant myocarditis

Masaki Fujioka,^{1,2,†} Kei Suzuki,^{1,3,4,†} Yoshiaki Iwashita,¹ Kyoko Imanaka-Yoshida,⁵ Masaaki Ito,² Naoyuki Katayama,⁴ and Hiroshi Imai¹

¹The Emergency and Critical Care Center, Mie University Hospital, ²Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, ³Department of Infectious Diseases, Mie University Hospital, ⁴Department of Hematology and Oncology, and ⁵Department of Pathology and Matrix Biology, Mie University Graduate School of Medicine, Tsu, Mie, Japan

Case: Fulminant myocarditis (FM) and septic cardiomyopathy (SC) are two different disease entities, and distinction between them is important. A 34-year-old man had refractory shock, multiple organ failure, and elevation of cardiogenic markers. Echocardiogram showed tachycardia with extended ST elevation, and a rapid test for influenza A virus was positive. He was admitted with suspected FM induced by influenza.

Outcome: Echocardiography showed severe left ventricular dysfunction and dilatation, but no myocardial edema. Inconsistent with FM, a right heart catheter examination showed preserved cardiac output. Therefore, SC was considered and standard therapy for septic shock was initiated. He was stabilized in the first 72 h without mechanical circulatory support.

Conclusion: Influenza A infection can cause septic shock accompanied by SC. This condition is confusing in the clinical appearance of FM. However, SC shows critically different features of FM, and it might not occur in the epidemic period.

Key words: Fulminant myocarditis, influenza, sepsis-induced cardiomyopathy, septic cardiomyopathy, septic shock

BACKGROUND

ALTHOUGH CLINICALLY APPARENT influenza-associated cardiac complications are rare, their mortality rate in patients with fulminant myocarditis (FM) is high.¹ Septic cardiomyopathy (SC), which is induced by septic shock, is characterized by left ventricular (LV) dilatation and a depressed ejection fraction (EF) that typically normalize within 7–10 days.² For these reasons, FM and SC are two different disease entities and distinction between them is important. We report a patient who developed SC that mimicked FM; however, the case showed different features from FM and was induced by influenza A infection, even in summer.

†These authors contributed equally to this work.

Corresponding: Kei Suzuki, MD, PhD, The Emergency and Critical Care Center, Mie University Hospital, 2-174, Edobashi, Tsu, Mie, 514-8507, Japan. E-mail: keis@clin.medic.mie-u.ac.jp.

Received 12 Sep, 2018; accepted 12 Jan, 2019; online publication 10 Feb, 2019

Funding information

No funding information provided.

CASE

A 34-YEAR-OLD JAPANESE man without a remarkable medical history was transferred to our hospital because of catecholamine-resistant hypotension with multiple organ failure, despite vigorous fluid loading, in early September 2017. He was admitted to another hospital complaining of fever 2 days previously. He attended a crowded fireworks event just before developing a fever. At presentation, he was in severe cardiovascular instability with severe hypotension. His initial blood temperature, pulse rate, blood pressure, and respiratory rate were 39.7°C, 157 b.p.m., 49/30 mmHg (he received noradrenaline at 0.1 µg/kg/min), and 40 breaths/min, respectively, along with oliguria and an altered mental status (Glasgow Coma Scale score, 13; E3V4M6). A laboratory examination showed multiple organ dysfunction in the liver, kidney, and lungs, and coagulation was confirmed in addition to cardiogenic dysfunction (Table 1). A chest X-ray taken at a previous hospital did not show overt pulmonary involvement (Fig. 1A). However, this finding dramatically changed and showed pulmonary edema with cardiomegaly during a short period (Fig. 1B).

An electrocardiogram showed tachycardia with extended ST elevation (Fig. 1C). He was admitted with suspected FM induced by influenza A infection because no obvious site infection could be identified and a rapid test for influenza A virus was positive.

The patient was intubated and transported to the intensive care unit because of refractory shock. High-dose vasopressor therapy (noradrenaline up to 0.4 µg/kg/min and vasopressin up to 2 units/h) was initiated, and renal replacement therapy (CRRT) was begun. Hydrocortisone (300 mg/day) was induced as adjunctive therapy. Antimicrobial therapy, including a neuraminidase inhibitor (peramivir 300 mg/day for 2 days) and empiric broad-spectrum antibiotics (meropenem 2 g/day with linezolid 1,200 mg/day), was given after appropriate cultures were obtained.

Transthoracic echocardiography (TTE), which was carried out after admission, showed severe global LV systolic dysfunction (EF, 20%) and LV dilatation (LV end-systolic diameter, 66 mm). However, TTE did not show myocardial edema, unlike in typical cases of FM (Fig. 1D). Moreover, cardiac catheterization showed normal coronary arteries. However, a right heart catheter examination showed a

cardiac output of 12.0 L/min (confidence interval, 6.16 L/min/m²) and pulmonary capillary wedge pressure of 17 mmHg, which was inconsistent with FM. Additionally, myocardial biopsy findings did not indicate FM (Fig. 1E).

The patient was considered to suffer from SC, which is characterized by LV dilatation and a depressed EF² with preserved cardiac output.^{3,4} He was treated with fluid resuscitation (crystalloids and colloids), high-dose vasopressors, and CRRT according to global sepsis guidelines. The patient responded after 12 h and became increasingly stabilized. Vasopressors were tapered, and noradrenaline and vasopressin were discontinued in 72 and 60 h, respectively. Daily TTE was used to estimate the patient's cardiac function, and his EF gradually improved up to 38% in the first 5 days. Laboratory values showed marked improvement of inflammatory and cardiogenic markers. The clinical course during the first week is shown in Figure 2.

Blood, urine, sputum culture aspirated by bronchoscopy, and radiological studies failed to show any bacterial infection. Therefore, antibiotics were discontinued on the 10th hospitalized day. He was extubated, and CRRT was discontinued on the 12th hospitalized day. His low LV function

Table 1. Laboratory findings at admission of a 34-year-old man with septic cardiomyopathy

Hematology			Biochemistry			Blood gases		
WBC	22,580	/µL	TP	4.5	g/dL	pH	7.070	
Neu	21,157	/µL	Alb	2.2	g/dL	PaCO ₂	64.0	mmHg
Ly	158	/µL	BUN	66.7	mg/dL	PaO ₂	83.0	mmHg
Mo	903	/µL	Cr	5.62	mg/dL	HCO ₃ ⁻	18.5	mmol/L
RBC	423 × 10 ⁴	/µL	Na	123	mEq/L	BE	-11.6	mmol/L
MCV	88.4	fL	K	3.9	mEq/L	Lactate	4.8	mmol/L
Hb	13.1	g/dL	Cl	84	mEq/L			
Ht	37.4	%	Ca	5.8	IU/L			
Plt	5.3 × 10 ⁴	/µL	AST	927	IU/L			
			ALT	252	IU/L			
			LDH	1,595	IU/L			
Coagulation			ALP	202	mg/dL			
APTT	77.5	s	T-Bil	4.0	mg/dL			
PT	20.5	s	BS	211	IU/L			
PT-%	42.9	%	CPK	35,695	IU/L			
PT-INR	1.72		AMY	511	IU/L			
Fibrinogen	551	mg/dL	CRP	0.97	mg/dL			
D-dimer	14.9	µg/mL	BNP	2,302.7	pg/mL			
			Tnl	238,349	pg/mL			

Blood gases were measured under 2 L/min O₂ given nasally. Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMY, amylase; APTT, activated partial thromboplastin time; AST, aspartate transaminase; BE, base excess; BNP, brain natriuretic peptide; BS, blood sugar; BUN, blood urea nitrogen; Ca, calcium; Cl, chloride; CPK, creatine phosphokinase; Cr, creatinine; CRP, C-reactive protein; Hb, hemoglobin; Ht, hematocrit; K, potassium; LDH, lactate dehydrogenase; Ly, lymphocyte; MCV, mean corpuscular volume; Mo, monocytes; Na, sodium; Neu, neutrophil; Plt, platelet count; PT, prothrombin time; PT-INR, prothrombin time – international normalized ratio; RBC, red blood cell count; T-Bil, total bilirubin; Tnl, troponin I; TP, total protein; WBC, white blood cell count.

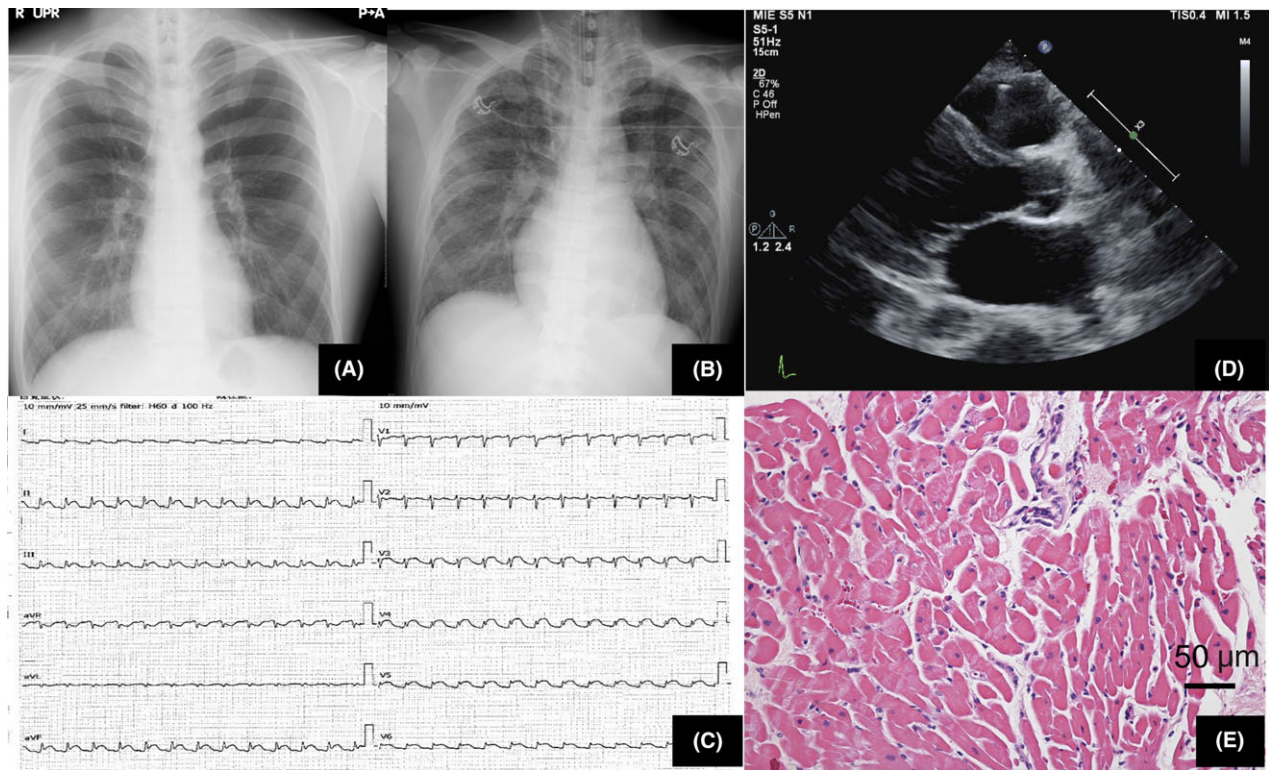


Fig. 1. Radiological studies, electrocardiogram, and transthoracic echocardiography on admission of a 34-year-old man with influenza-associated septic shock accompanied by septic cardiomyopathy. A, Chest X-ray taken at a previous hospital did not show pulmonary involvement. B, Chest X-ray on admission to our hospital shows rapidly progressed pulmonary edema with cardiomegaly. C, Electrocardiogram shows sinus tachycardia and diffuse ST segment elevation. D, Transthoracic echocardiography shows severely decreased left ventricular (LV) function and LV dilatation (ejection fraction, 20%; LV end-systolic diameter, 66 mm). However, unlike typical cases of fulminant myocarditis, myocardial edema was not detected. E, Myocardial biopsy findings do not show inflammatory cell infiltration or necrosis of cardiomyocytes and do not indicate fulminant myocarditis.

was restored, and LV dilatation returned to almost normal in the following 2 weeks. He moved back to a previous hospital for subsequent management in 4 weeks and achieved full rehabilitation in 8 weeks. We finally diagnosed him with influenza-associated septic shock accompanied by SC.

DISCUSSION

WE REPORT A case of SC that mimicked FM, but showed different features from FM, and was induced by influenza A infection in summer. Septic cardiomyopathy (also called sepsis-induced cardiomyopathy) is often diagnosed when there is acute perturbation in cardiac function in the setting of septic shock,² and is usually caused by bacterial infection. Influenza virus sometimes shows a significant interaction with the immune system.⁵ We searched PubMed (up to November 2018) for English articles for SC due to influenza virus infection. The keywords “septic

cardiomyopathy” OR “sepsis-induced cardiomyopathy” AND “influenza” were used, and we reviewed two articles. However, both reports were complicated by bacterial infection. A Japanese retrospective cohort study reported that SC developed in 13.8% (29/210) of patients with sepsis and septic shock.⁶ In this study, 37.9% (11/29) of patients with SC did not show pathogenic microorganisms and some of these patients has possible viral infections. Clinicians should take viral infection into consideration in the case of cardiac dysfunction with shock of unknown etiology.

Although our understanding of SC remains incomplete, recent studies have investigated its clinical pathophysiology. Despite the lack of diagnostic criteria, SC is considered to have the following three characteristics: (i) LV dilatation, (ii) depressed EF, (iii) recovery in 7–10 days.² At the early phase of sepsis, the EF is not impaired; however, stroke volume is low because of insufficient cardiac preload. After fluid loading, the EF is temporarily depressed because of LV

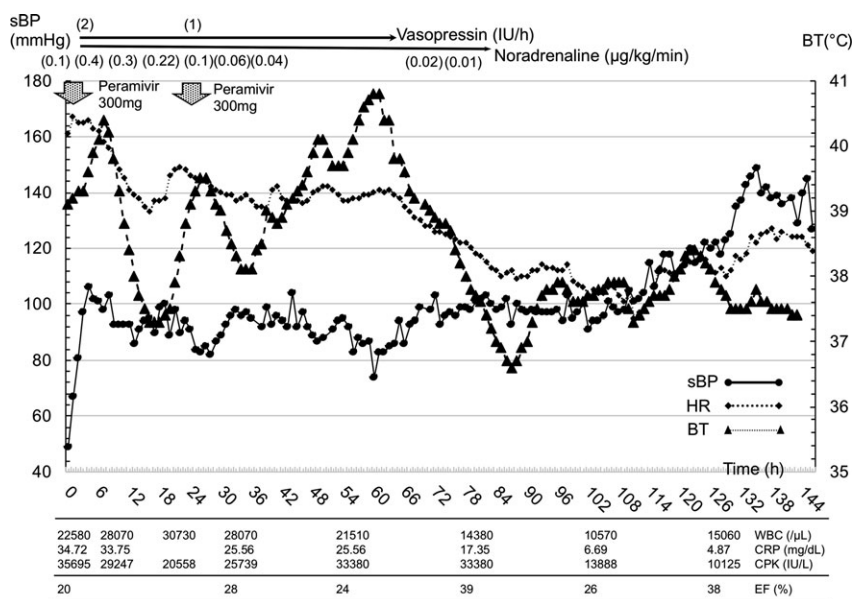


Fig. 2. Clinical course of the case of a 34-year-old man with influenza-associated septic shock accompanied by septic cardiomyopathy during the first week. Peramivir (300 mg/day for 2 days) combined with a vasopressor was initiated, and the patient was stabilized in the first 72 h. In contrast to fulminant myocarditis, his cardiac index was preserved on admission. Daily examination of the ejection fraction as measured by an echocardiogram showed gradual improvement and almost returned to normal in the following 2 weeks. BT, body temperature; CPK, creatine phosphokinase; CRP, C-reactive protein; EF, ejection fraction; HR, heart rate; sBP, systolic blood pressure; WBC, white blood cell count.

dilatation and stroke volume can be recovered in this phase.⁷ Because the EF is defined as stroke volume divided by end-diastolic ventricular volume, the denominator increases as the EF decreases.² Therefore, myocardial dysfunction is masked by a concomitant normal or elevated cardiac output in SC.^{8,9} A complicated and contradictory picture, such as hyperdynamic cardiac flow with hypodynamic cardiac movement, as observed in our case, is a characteristic response after preload optimization in SC.

Cardiac output is maintained by the compensatory mechanism of LV dilatation with tachycardia in SC, and this finding differs greatly from FM.^{4,7} Fulminant myocarditis is most often caused by a viral infection with a rapidly progressive course in severe heart failure and cardiogenic shock, and its initial features clinically resemble SC.¹ However, FM often requires mechanical circulatory support, such as intra-aortic balloon pumping and veno-arterial extracorporeal membrane oxygenation. Although SC sometimes requires such invasive mechanical support,² SC improves within a relatively short period with optimal treatment for sepsis. Moreover, management of patients who require extracorporeal membrane oxygenation is complex.^{6,10} A recent systematic MEDLINE database review of influenza myocarditis between 1946 and 2017 summarized 184 cases of patients suffering from influenza myocarditis.¹ However, patients with SC and those with

FM were not clearly distinguished in this study. We should carefully distinguish these diseases mainly by repeated echocardiography. Furthermore, the currently used indices of ventricular function are limited because the cardiac index and EF are load-dependent indices that do not reflect intrinsic myocardial contractile function during sepsis.¹¹ New approaches for detecting myocardial dysfunction with SC are warranted to make a certain diagnosis of SC.

Annual influenza epidemics affect 5–15% of the population, resulting in approximately 3–5 million cases worldwide.¹ Epidemics of influenza virus infections usually occur in winter, while it possesses a value as imported infections, especially during the summer break season. In fact, a small influenza epidemic was observed at the time that our patient presented to hospital in the area that he lived. Clinicians should consider influenza infection when they encounter highly febrile patients without infectious focus, even in summer.

CONCLUSION

WE REPORT A case of severe influenza A infection that highlights three important clinical insights: (i) influenza A infection sometimes can cause septic shock accompanied by SC, (ii) SC is confusing in clinical

appearance of FM, but shows critically different features of FM, (iii) SC due to influenza can occur in a non-epidemic period.

ACKNOWLEDGEMENTS

THE AUTHORS THANK all colleagues in the Emergency and Critical Center, Mie University Hospital (Drs. K. Ikejiri, R. Esumi, A. Ito, E. Kawamoto, K. Yokoyama, Y. Omori, K. Ishikura, and T. Takeda), Dr. A. Shindo (Department of Neurology, Mie University Hospital), and Dr. A. Nakamura (Department of Hematology and Oncology, Suzuka Chuo Hospital) for their assistance. We thank Ellen Knapp, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

DISCLOSURE

Approval of the research protocol: N/A.

Informed consent: Written informed consent was obtained from the patient.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

Conflict of interest: None.

REFERENCES

- Hékimian G, Jovanovic T, Bréchet N *et al.* When the heart get flu: fulminant influenza B myocarditis: a case-series report and review of the literature. *J. Crit. Care* 2018; 47: 61–4.
- Sato R, Nasu M. A review of sepsis-induced cardiomyopathy. *J. Intensive Care* 2015; 3: 48.
- Lu X, Wang H. Pathophysiology of sepsis-induced myocardial dysfunction. *Mil. Med. Res.* 2016; 3: 30.
- Parker MM, Shelhamer JH, Bacharach SL *et al.* Profound but reversible myocardial depression in patient with septic shock. *Ann. Intern. Med.* 1984; 100: 483–90.
- Florescu DF, Kalil AC. The complex link between influenza and severe sepsis. *Virulence* 2014; 5: 137–42.
- Sato R, Kuriyama A, Takada T, Nasu M, Luthe SK. Prevalence and risk factors of sepsis-induced cardiomyopathy: a retrospective cohort study. *Medicine (Baltimore)* 2016; 97: e0263.
- Kakihara Y, Ito T, Nakahara M, Yamaguchi K, Yasuda T. Sepsis-induced myocardial dysfunction: pathophysiology and management. *J. Intensive Care* 2016; 4: 22.
- Ehrman RR, Sullivan AN, Favot MJ *et al.* Pathophysiology, echocardiographic evaluation, biomarker findings, and prognostic complications of septic cardiomyopathy: a review of the literature. *Crit. Care* 2018; 22: 112.
- Price S, Anning PB, Mitchell JA, Evans TW. Myocardial dysfunction in sepsis: mechanism and therapeutic implications. *Eur. Heart J.* 1999; 20: 715–24.
- Combes A, Brodie D, Bartlett R *et al.* Position paper for the organization of extracorporeal membrane oxygenation programs for acute respiratory failure in adults patients. *Am. J. Respir. Crit. Care* 2014; 190: 488–96.
- Zaky A, Deem S, Bendjelid K, Treggiari MM. Characterization of cardiac dysfunction in sepsis: an ongoing challenge. *Shock* 2014; 41: 12–24.