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【 CASE REPORT 】

Acute Myocarditis with Severe Fever and Thrombocytopenia Syndrome

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Abstract:
A 67-year-old man, hospitalized with fever and pancytopenia, experienced cardiogenic shock on the 3rd day of hospitalization. He complained of chest pain and exhibited cardiac dysfunction, upregulated serum troponin levels, and an ST elevation on electrocardiogram. Severe fever with thrombocytopenia syndrome (SFTS) was suspected based on the symptom course after a tick bite and was definitively diagnosed using the serum polymerase chain reaction (PCR) test. An endomyocardial biopsy performed in the convalescent phase revealed a sign of myocardial inflammation with increases in CD3- and CD68-positive cells. We herein report the first case of acute myocarditis complicated with SFTS.

Key words: myocarditis, severe fever with thrombocytopenia syndrome

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Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is a zoonosis characterized by high fever, leukopenia, thrombocytopenia, and multiple organ dysfunctions, resulting in a potentially fatal outcome (1). An emerging infectious disease-causing pathogen was reported in regions of central and northwest China in 2009, and it was confirmed as SFTS virus (SFTSV) in 2010 (1). The resulting disease manifested as a severe fever with joint pain, headache, vomiting, diarrhea, complicated hemophagocytic lymphohistiocytosis (HLH), renal dysfunction, cardiac dysfunction, encephalitis, and meningitis, and sometimes had a fatal progression (1). Previous studies have reported mortality rates of 10-30% (1, 2). The mortality rate of SFTS with heart disease is unknown, but Choi et al. reported that 6.7% of fatal cases of SFTS were clinically accompanied with myocarditis (2). For clinical treatment, the patient was diagnosed with SFTS and developed cardiogenic shock due to myocarditis. An endomyocardial biopsy (EMB) performed in the convalescent phase revealed a sign of myocardial inflammation, which suggested a resolving phase of myocarditis. To the best of our knowledge, this is the first case report of myocarditis due to SFTS with supportive EMB findings.

Case Report

A 67-year-old man had a history of mucosal resection for early gastric cancer and partial resection for left lung cancer. He did not have any heart disease and used conventional drugs. In April 201X, he had collected knee-high wild grass from a riverbed for 10 days. In late April, he developed systemic pain and fatigue, followed by the development of fever, chills, watery diarrhea, loss of appetite, and mildly disturbed consciousness within two weeks. In mid-May, he visited the department of internal medicine at a nearby hospital. The physician noted decreased white blood cells (WBC)

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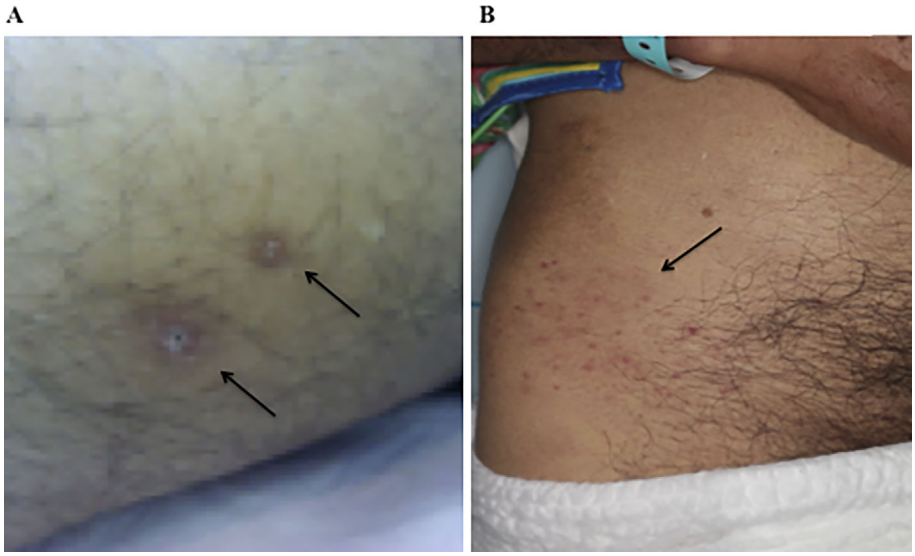

Figure 1. Skin findings. Observations of crusted skin lesions (arrows) (A) and aggregated papules (arrow) (B).

Table. Laboratory Findings.

Complete blood cell count		Biochemistry	
White blood cell count	1,300 /μL	Total Protein	7.3 g/dL
Differential count of leukocytes		Albumin	3.9 g/dL
Neutrophils	69.2 %	BUN	17 mg/dL
Lymphocytes	26.3 %	Cr	0.84 mg/dL
Eosinophils	0 %	Total bilirubin	0.6 mg/dL
Monocytes	4.5 %	AST	230 U/L
Red blood cell count	473×10^4 /μL	ALT	90 U/L
Hemoglobin	16.3 g/dL	ALP	159 U/L
Platelet count	3.0×10^4 /μL	γ-GTP	83 U/L
PT	12.1 s	LDH	760 U/L
PT%	89 %	CK	746 U/L
PT-INR	1.05	Glucose	153 mg/dL
APTT	48.2 s	Sodium	132 mmol/L
Fibrinogen	315 mg/dL	Potassium	3.6 mmol/L
AT III activity	99 %	Chlorine	99 mmol/L
D-dimer	4.7 μg/mL	C-reactive protein	1.30 mg/dL

PT: prothrombin time, PT-INR: international normalized ratio for prothrombin time, APTT: activated partial thromboplastin time, AT: anti thrombin, BUN: blood urea nitrogen, Cr: creatinine, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyltranspeptidase, LDH: lactate dehydrogenase, CK: creatine kinase, BUN: blood urea nitrogen

and platelet counts and elevated hepatic enzyme levels in his blood test results, indicating hepatic dysfunction and referred him to our department for further examination. He was hospitalized on the same day.

He had a height of 169.0 cm, body weight of 52.3 kg, Glasgow Coma Scale of 14: E3, V5, M6, blood pressure of 130/79 mmHg, heart rate (HR) of 96/min with a regular pulse, respiratory rate (RR) of 20/min with O_2 saturation (SPO_2) of 94% in room air, and temperature of 38.9°C. He had no remarkable head-and-neck or chest abnormalities. He additionally presented with crusted skin lesions on the medial surface of the left thigh (Fig. 1A), a freely movable adenopathy of approximately 2 cm in size without tenderness, and aggregated papules in the right inguinal region (Fig. 1B). No remarkable neurological abnormalities were observed.

Laboratory findings: The blood count was 1,300/μL WBC, 30,000/μL platelets, neutrophil count was considerably low at 899/μL, and lymphocyte count was 342/μL. The activated partial thromboplastin time (APTT) of 48.2 seconds was prolonged. Biochemical findings showed a mild increase in the C-reactive protein (CRP) levels at 1.3 mg/dL and elevations in concentrations of aspartate aminotransferase (AST) at 230 U/L, lactate dehydrogenase (LDH) at 760 U/L, and creatine kinase (CK) at 746 U/L (Table).

Chest radiography and electrocardiography were normal

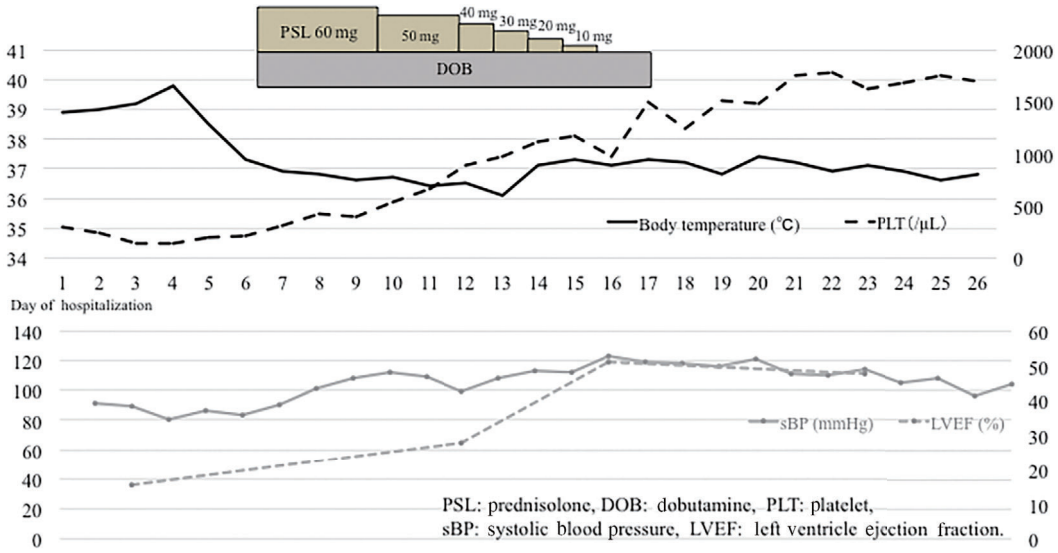

Figure 2. **The clinical courses during hospitalization.**

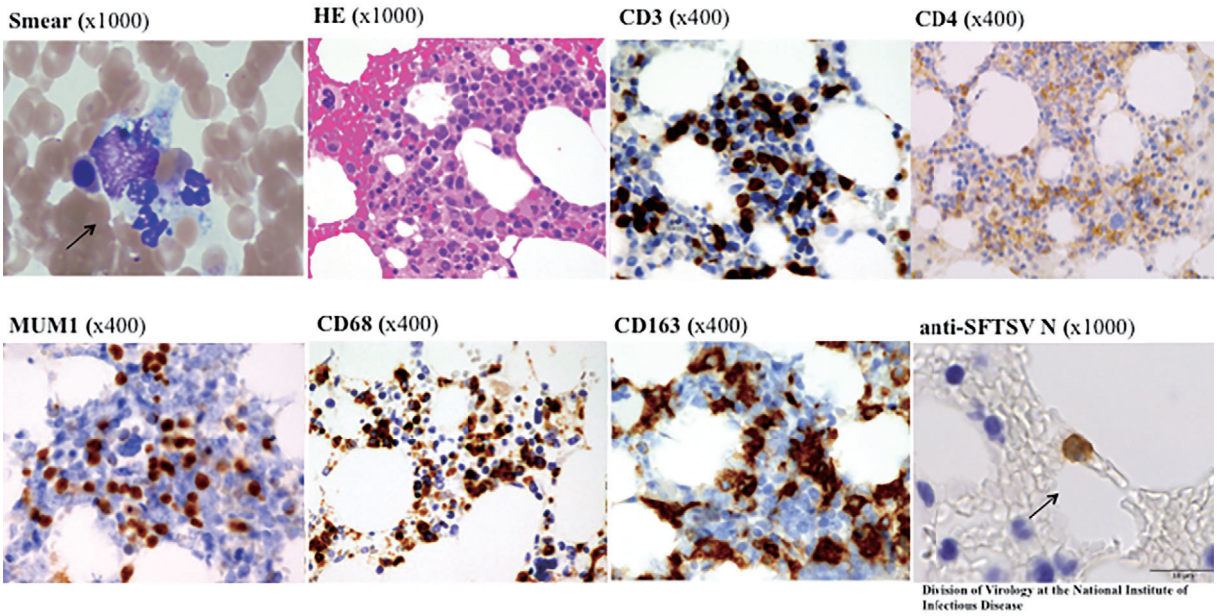

Figure 3. **Bone marrow biopsy. Bone marrow biopsy. Hemophagocytic image (arrow, ×1,000). Mature myeloid series cell counts were decreased, and monocytoid cells and lymphoid cell counts were increased. immunohistological examination; CD3- and CD4-positive T cells, MUM-1-positive lymphoid cells, and CD68- and CD163-positive histiomonocytes cell counts were increased (×400). Image of anti-SFTSV antibody staining was positive (arrow, ×1,000). HE: Hematoxylin and Eosin staining, MUM-1: multiple myeloma oncogene 1**

on the day of admission. A simple head-and-neck computed tomography (CT) scan revealed no remarkable abnormalities.

Clinical course (Fig. 2): Given the physical and laboratory findings, on day 1 of hospitalization, we suspected sepsis and febrile neutropenia (FN) associated with hemophagocytosis. We therefore administered antibiotics until the neutropenia resolved. On day 2 of hospitalization, his blood test results revealed elevated ferritin levels of 15,165 ng/mL (normal range, 39.9-465 ng/mL). He was screened closely for potential antibodies specific for cytomegalovirus and Epstein-Barr virus (EBV), which could have resulted from his prior infections. His blood culture was also negative. On the same day, we performed a bone marrow biopsy to investigate the cause of pancytopenia, and the sample revealed hemophagocytosis with fewer mature myeloid series cells and more monocytoid and lymphoid cells. Additionally, an immunohistological examination revealed a high number of CD3- and CD4-positive T cells, multiple myeloma oncogene 1 (MUM-1)-positive lymphoid cells, and CD68, CD 163-positive histiomonocytes. No EBV-encoded small RNAs (EBERs)-positive cells were detected (Fig. 3). He was then

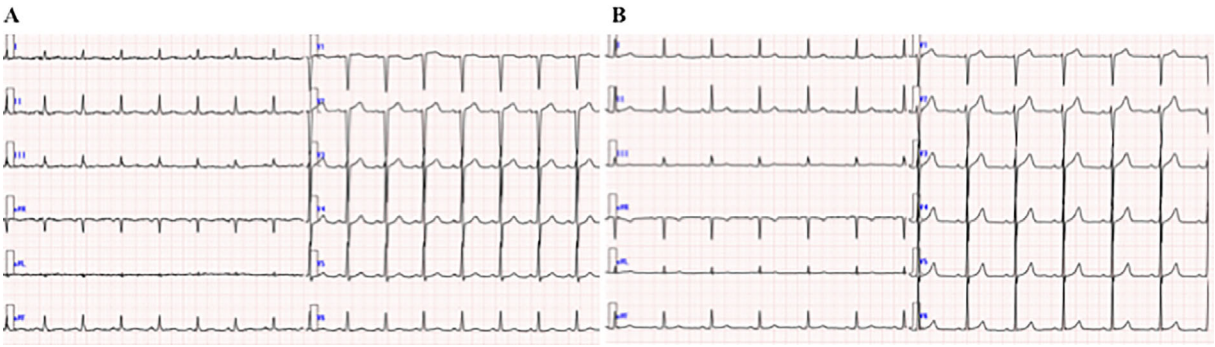

Figure 4. ECG data obtained on day 3 of hospitalization. The ECG shows a slight ST elevation in the V1-2 leads (A), and it recovered to the normal level on day 14 of hospitalization (B).

diagnosed with HLH, for which we administered prednisolone (PSL) at 60 mg/day (1 mg/kg/day) according to the guidelines (3), which was gradually tapered along the clinical course, and stopped on day 12 of administration.

On day 3 of hospitalization, He developed chest pain, shivering, and fever of 39.2°C, with blood pressure at 88/52 mmHg, HR at 89/min, RR at 24/min and SPO_2 at 94% (6-L mask for oxygen administration). Concurrent blood test results revealed elevated CK levels at 953 U/L (normal range, 59-248 U/L), LDH at 1,405 U/L (normal range, 124-222 U/L), and high-sensitivity troponin I (TnI) at 271 pg/mL (normal range, <30 pg/mL). Transthoracic echocardiography showed severe left ventricular dysfunction [left ventricular ejection fraction (LVEF) of 15%], while an electrocardiogram (ECG) showed a slight ST elevation in the V1-2 leads (Fig. 4A). Contrast-enhanced CT of the chest and abdomen showed no remarkable abnormalities. He fulfilled the diagnostic criteria of clinically suspected myocarditis with chest pain, cardiac dysfunction, troponin elevation, and ST elevation (4). Acute myocarditis was suspected rather than ischemic heart disease because of the absence of a mirror image on the ECG indicated local asynergy. We did not perform coronary angiography (CAG) or EMB at this moment because an unknown infection was suspected with a severe bleeding tendency. Moreover, we continued respiratory and circulatory management and infection control in the intensive care unit (ICU), and TnI peaked at 82.6 pg/mL. We suspected SFTS because of the possibility of tick bites as well as digestive symptoms, polymyalgia, thrombocytopenia, and liver function impairment. Therefore, we submitted his serum and urine samples and throat swabs to a responsible public health center. We moved him to negative-pressure room. A reverse transcription polymerase chain reaction (RT-PCR) analysis of the submitted serum detected 1.77×10^6 SFTSV RNA copies/mL. We also submitted pathological sections of his bone marrow to the Division of Virology at the National Institute of Infectious Disease to request an examination of the involvement of SFTSV. The researchers found infected cells that were stained positively by an anti-SFTSV-nucleoprotein (N) antibody (Fig. 3).

We considered steroid pulse therapy for HLH with SFTS but did not proceed with it due to concerns regarding the risks of further immune deficiency and secondary infections. On the day 14 of hospitalization, he withdrew from circulatory agonist and ventilator management. ECG showed improvement of ST elevation in the V1-2 leads (Fig. 4B). On day 17 of hospitalization, we re-submitted his serum and confirmed negativity for viremia and released him from quarantine.

On day 24 of hospitalization, we performed CAG and EMB due to an insufficient improvement in his LVEF. Although no coronary artery stenosis was observed on CAG, pathological evaluation of the EMB specimen revealed that the myocardium was mildly hypertrophic with mild myofibrillar loss and disarrangement. Active mononuclear cell infiltration adjacent to the damaged myocardium was not observed. However, immunohistochemistry revealed increases in the number of CD3-positive T cells ($10/mm^2$) and CD68-positive macrophages ($18/mm^2$) with tenascin-C expression in the stroma, suggesting an ancillary diagnosis of myocardial inflammation (Fig. 5). We further subjected the myocardial tissues to immunostaining with an anti-SFTSV antibody but could not identify any infected cells. He was discharged on day 29 of hospitalization. On a follow-up visit 1 month after discharge, transthoracic echocardiography showed a slight improvement with an EF of 52.5%, and there was no heart failure thereafter.

Discussion

SFTS is caused by SFTSV, a *phlebovirus* in the family *Bunyaviridae*, which is carried by *Haemaphysalis longicornis* and should be suspected when there is an exposure to ticks in its endemic areas (1). The adverse prognostic factors of SFTS have been reported to include delayed hospitalization, an older age, a decline in consciousness, respiratory and cardiovascular symptoms, elevated LDH or AST levels, severe thrombocytopenia, and prolonged APTT and this infection has reported mortality rates of 10-30% (1, 2). The infection should be detected in the early stage, using an RT-PCR analysis of viral RNA in serum to establish a diagnosis of SFTSV infection (5). Our patient had collected knee-high wild grass from a riverbed for 10 days. Thereafter, he developed systemic pain and fatigue, fever, chills, watery diar-

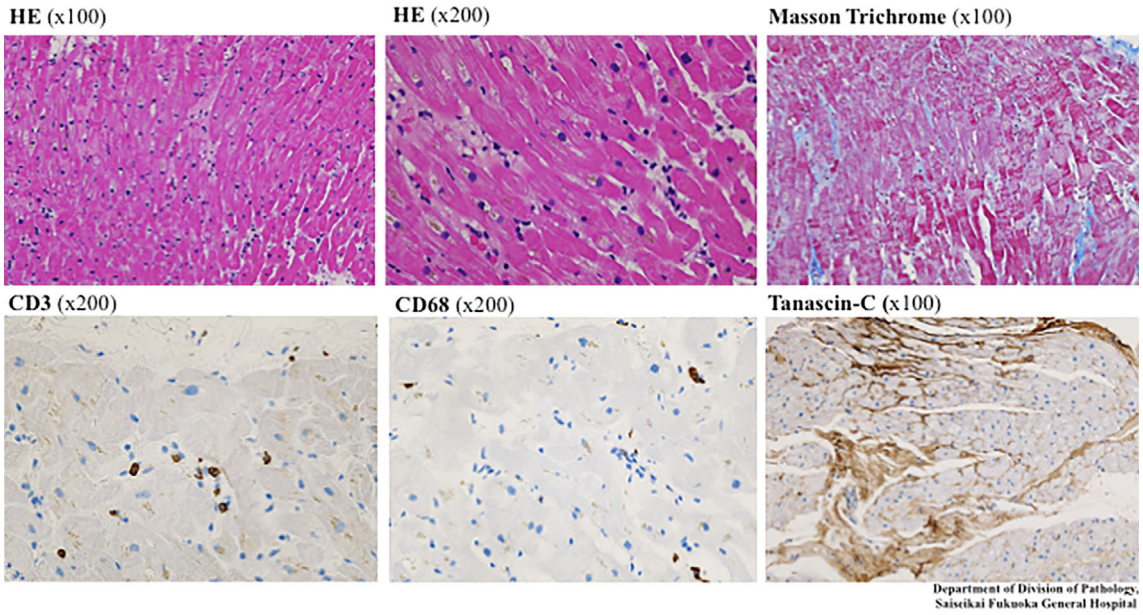

Figure 5. Endomyocardial biopsy of the right ventricle. It revealed a non-specific pathology with mild/indefinite inflammatory infiltration (×100). Mild myocardial hypertrophy and nuclear swelling relative to the myocardial size are present (×200), with areas of marked regularization and mildly crude myofibrils (×100). Intrinsic deflection or explicit active inflammatory cell infiltration are not detectable. Immunostaining reveals increases in CD3-positive (T-cells), CD68-positive cells (macrophages) (×200), and tenascin-C expression (×100).

rhea, and mildly disturbed consciousness. Moreover, his decreased WBC and platelet counts, elevated hepatic enzyme and CK levels, LV dysfunction, dysfunction of the kidneys and liver, and disturbance of consciousness were observed. His bleeding tendency presented as disseminated intravascular coagulation. This clinical course is typical of SFTS.

Secondary HLH has been identified as relevant to SFTS; as this patient exhibited hyperferritinemia and findings of hemophagocytosis in the bone marrow, we were able to successfully identify SFTS-infected cells in this tissue (6).

The patient's bone marrow specimens showed higher number of CD3-, CD4-positive T cells, MUM-1-positive lymphoid cells, and CD68- and CD163-positive histiomonocytes. Suzuki et al. reported that B cells differentiating into plasmablasts and macrophages in the secondary lymphoid organs were targets for SFTSV at the end stage of lethal infection, and the majority of SFTSV-infected cells were B cell-lineage lymphocytes that were widely distributed in both lymphoid and non-lymphoid organs. In our patient, MUM-1-positive cells indicated some differentiation from germinal-center B lymphocytes to plasma cells and CD68- and CD163-positive histiomonocytes cells; this is consistent with a previous report (7). Moreover, CD4-positive T cells were more predominant than CD8-positive T cells. However, increased CD8-positive T cells in the bone marrow are a typical finding in HLH, which was not the case here (8). Sun et al. reported that counts of CD3- and CD4-positive T lymphocytes were significantly diminished in SFTS compared to normal controls (9). It has been shown that the number of CD4-positive T cells in peripheral blood decreases in the acute phase, but there are few references on CD4-positive T cells in the bone marrow, and thus the details are unknown (10).

This case was treated under ventilation management, and his cardiorespiratory status was stabilized using inotropic agents and water balance management in the ICU. The efficacy of high-dose steroid therapy for acute myocarditis remains controversial; some studies have reported no effects on mortality; however, we used high-dose steroid therapy for HLH due to SFTSV, which consequently may have been effective in treating hypercytokinemia accompanying SFTS (3, 11)

He was clinically diagnosed with myocarditis (4) because of new onset of chest pain and unexplained cardiogenic shock, an elevated TnI level, severe left ventricular dysfunction on echocardiography, and ST elevation in the V1-2 leads on electrocardiography. In addition, an EMB was performed in the convalescent phase. Although we could not detect SFTSV pathologically, Choi et al. reported that 6.7% of fatal cases of SFTS had been complicated with myocarditis (2). For the pathological definition of myocarditis, we might consider the indication of EMB in the acute period, but it was difficult in this case due to the risk of horizontal transmission of unknown infection and bleeding tendency in SFTS. In the present case, EMB revealed mild mononuclear infiltration in the myocardium without active inflammatory infiltration adjacent to the necrotic myocardium. However, immunostaining revealed increases in CD3- and CD68-positive cells, which is consistent with the unspecified immunohistochemical criteria for myocarditis (4). Furthermore,

tenascin-C expression was upregulated in the interstitium, suggesting inflammatory stromal remodeling (12). The immunological criteria of myocarditis were defined in the guidelines proposed by the European Society of Cardiology (ESC) but not in those established by the Japanese Circulation Society (JCS) (13). The significance of chronic myocarditis has not been clearly identified, and there should thus be room for further investigation (14). Whereas it is still unclear whether SFTSV causes myocarditis indirectly or directly through the immune response against SFTS (15, 16), myocarditis caused by SFTS could be suggested in the convalescent phase by an EMB.

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

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