Fatal Severe Fever with Thrombocytopenia Syndrome: An Autopsy Case Report

Natsumi Uehara¹, Takao Yano², Akira Ishihara³, Masayuki Saijou⁴ and Tadaki Suzuki⁵

Abstract

As of June 2014, among six patients who had severe fever with thrombocytopenia syndrome (SFTS) at our hospital, an 83-year-old man died despite receiving appropriate critical care. An autopsy revealed extensive ischemic damage of the intra-abdominal organs, including the liver, spleen, stomach and gut, due to severe celiac atherosclerotic stenosis and superior mesenteric arterial thrombosis. Many SFTS virus nucleoprotein antigen-immunoreactive cells were detected in a paraaortic node, where necrotizing lymphadenitis was seen, and in the spleen. Fewer such cells were seen in the liver, bone marrow and adrenals. Conclusion: Atherosclerosis, in addition to hemophagocytic lymphohistiocytosis syndrome, can be lethal in elderly SFTS patients.

Key words: severe fever with thrombocytopenia syndrome virus, autopsy, hemophagocytosis, necrotizing lymphadenitis, celiac artery and superior mesenteric artery thrombosis

Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease recently discovered in China that is caused by a novel bunyavirus, resulting in severe fever with thrombocytopenia syndrome virus (SFTSV) (1). The disease is characterized by the sudden onset of a fever, thrombocytopenia, leukocytopenia, gastrointestinal symptoms, neural symptoms and hemorrhagic tendency and has a 10-15% mortality rate, commonly due to multiorgan dysfunction (MODF). It has a seasonal occurrence from May to September and mainly targets those of ≥50 years of age (2). Cases of SFTS in Japanese patients with a higher fatality rate (55%) are very similar to the severe cases reported in Chinese patients (3), however, there have been only three published autopsy cases reporting pathological analyses for the disease progression to death of SFTS (3, 4). We herein report the autopsy findings of a SFTS patient who died in our hospital due to extensive ischemic damages of the intra-abdominal organs secondary to severe celiac atherosclerotic stenosis and superior mesenteric arterial thrombosis in addition to hemophagocytic lymphohistiocytosis syndrome (HPLS).

Case Report

Ethics statement

We obtained written informed consent from the responsible family members as well as institutional approval to carry out this study from the ethics committee of Miyazaki Prefectural Nobeoka Hospital. The clinical and laboratory data of the patients with SFTS were sent to the corresponding author without personal identifying information.

Index patient

In the beginning of April 2014, an 82-year-old man with hypertension and hearing loss who lived in the wooded and hilly areas of Miyazaki prefecture of Japan exhibited an acute onset of symptoms, with a temperature of 38°C, chills and malaise, a high fever, vomiting, and watery diarrhea. At...
our hospital for further evaluation. On admission, his blood urea nitrogen level (2.1 mg/dL). He was immediately referred to the intensive care unit (ICU). The blood culture was negative for Scrub typhus (tsutsugamushi disease) and Japanese spotted fever. The level of serum soluble interleukin-2 receptor (1,120 U/mL) was elevated, and bone marrow aspiration revealed a mild increase in the levels of activated histiocytes and hemophagocytes (Fig. 3a). The patient’s serum ferritin level (106,600 ng/mL) was extremely elevated (normal range, 3-166 ng/mL). Although acute pancreatitis was initially suspected due to elevated serum amylase levels and the findings of abdominal CT, most of his clinical features suggested that infection-associated HPLS resulted in the main complication, including multiorgan dysfunction, coagulopathy, shock, and acute respiratory distress syndrome. He was treated with methylprednisolone (500-1,000 mg/day), human anti-thrombin III (1,500 IU/day), and recombinant human soluble thrombomodulin (7,800 U/day) and given antimicrobial therapy with ceftriaxone (4.0 g/day) beginning 7 days after the onset of symptoms. On the next day, continuous hemodiafiltration was started for oliguria below 500 mL/day, and high-dose dopamine and noradrenaline were required to maintain his hemodynamic state. His oxygenation status did not improve despite the use of more than 60% fractional inspired oxygen concentration and 10 cm H₂O positive end-expiratory pressure. A chest X-ray at this time revealed a prolonged activated partial thromboplastin time and a high D-dimer level (Table 1). Plain computed tomography (CT) of the abdomen showed mild hepatosplenomegaly (Fig. 1a) as well as diffuse pancreatic swelling with irregular pancreatic outline and obliterated peripancreatic fat (Fig. 1b). A chest X-ray was clear on admission (Fig. 1c). In the initial medical examination, it was difficult to distinguish the present case from a tick-borne infection, which is relatively common in this area; therefore, we continued to administer tetralcyline antibiotics (minocycline hydrochloride 200 mg/day) until a definitive diagnosis could be reached. The patient’s condition deteriorated rapidly on the following day after admission; he was not fully conscious (Glasgow coma scale score was 8: E2 V2 M4), and he had respiratory distress (PaO₂ <60 mmHg in ambient air). At 7 days after onset, SFTS viral infection was confirmed with the patient’s serum sample using reverse transcriptase-polymerase chain reaction (RT-PCR) with primer sets for the SFTS virus, and he was transferred to the intensive care unit (ICU). The blood culture was sterile, and the serum levels of (1-3)-β-D glucan (<3.0 pg/mL) and procollatin (0.68 ng/mL) were not increased. Serological tests were negative for Scrub typhus (tsutsugamushi disease) and Japanese spotted fever. The level of serum soluble interleukin-2 receptor (1,120 U/mL) was elevated, and bone marrow aspiration revealed a mild increase in the levels of activated histiocytes and hemophagocytes (Fig. 3a). The patient’s serum ferritin level (106,600 ng/mL) was extremely elevated (normal range, 3-166 ng/mL). Although acute pancreatitis was initially suspected due to elevated serum amylase levels and the findings of abdominal CT, most of his clinical features suggested that infection-associated HPLS resulted in the main complication, including multiorgan dysfunction, coagulopathy, shock, and acute respiratory distress syndrome. He was treated with methylprednisolone (500-1,000 mg/day), human anti-thrombin III (1,500 IU/day), and recombinant human soluble thrombomodulin (7,800 U/day) and given antimicrobial therapy with ceftriaxone (4.0 g/day) beginning 7 days after the onset of symptoms. On the next day, continuous hemodiafiltration was started for oliguria below 500 mL/day, and high-dose dopamine and noradrenaline were required to maintain his hemodynamic state. His oxygenation status did not improve despite the use of more than 60% fractional inspired oxygen concentration and 10 cm H₂O positive end-expiratory pressure. A chest X-ray at this time revealed a bilateral infiltrative shadow with right pleural effusion (Fig. 1d). Although the patient’s white blood cell and platelet counts started to improve, a marked increase in the AST, ALT, LDH and CKP levels indicated significant liver and intestinal damage (Table 1). Death occurred at 12 days after the onset of symptoms (Fig. 2).

**Table 1. Laboratory Data.**

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference range, adult (on admission)</th>
<th>5 days after onset</th>
<th>7 days after onset</th>
<th>9 days after onset</th>
<th>11 days after onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>38.6–50.9</td>
<td>37.5</td>
<td>41.5</td>
<td>41</td>
<td>34.2</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.9–17.4</td>
<td>14.2</td>
<td>15.8</td>
<td>14.8</td>
<td>10.8</td>
</tr>
<tr>
<td>White-cell count (×10⁹/L)</td>
<td>2,970–9,130</td>
<td>9.30</td>
<td>2.810</td>
<td>7.370</td>
<td>4,590</td>
</tr>
<tr>
<td>Platelet count (×10¹²/L)</td>
<td>14.3–33.3</td>
<td>1.9</td>
<td>3.3</td>
<td>4.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Lymphocyte count (×10⁴/μL)</td>
<td>1,000–4,000</td>
<td>316</td>
<td>183</td>
<td>627</td>
<td></td>
</tr>
<tr>
<td>Neutrophil count (×10⁹/μL)</td>
<td>1,000–7,500</td>
<td>567</td>
<td>2,585</td>
<td>6,449</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase (IU/L)</td>
<td>8–40</td>
<td>303</td>
<td>405</td>
<td>1,472</td>
<td>18,720</td>
</tr>
<tr>
<td>Alanine aminotransferase (IU/L)</td>
<td>3–35</td>
<td>96</td>
<td>110</td>
<td>243</td>
<td>2,639</td>
</tr>
<tr>
<td>Lactate dehydrogenase (IU/L)</td>
<td>117–205</td>
<td>831</td>
<td>1,212</td>
<td>4,870</td>
<td>18,900</td>
</tr>
<tr>
<td>Creatine phosphokinase (IU/L)</td>
<td>30–200</td>
<td>794</td>
<td>2,554</td>
<td>8,983</td>
<td>15,380</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>8.0–20.0</td>
<td>53.1</td>
<td>46.9</td>
<td>76.8</td>
<td>42.2</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.6–1.1</td>
<td>1.6</td>
<td>1.4</td>
<td>3.7</td>
<td>2.9</td>
</tr>
<tr>
<td>Na(mEq/L)</td>
<td>135–148</td>
<td>134</td>
<td>133</td>
<td>139</td>
<td>145</td>
</tr>
<tr>
<td>Amylase(IU/L)</td>
<td>42–158</td>
<td>217</td>
<td>210</td>
<td>393</td>
<td>689</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>&gt;0.3</td>
<td>0.75</td>
<td>0.72</td>
<td>1.31</td>
<td>0.88</td>
</tr>
<tr>
<td>Prothrombin time (%)</td>
<td>70–120</td>
<td>82.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activated partial thromboplastin time (seconds)</td>
<td>26.1–35.6</td>
<td>45.3</td>
<td>47.9</td>
<td>63.8</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>150–450</td>
<td>153</td>
<td>123</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Fibrin/fibrinogen degradation products (μg/mL)</td>
<td>&lt;5.0</td>
<td>21.2</td>
<td>35.8</td>
<td>15.6</td>
<td>8.3</td>
</tr>
<tr>
<td>D dimer (μg/dL)</td>
<td>&gt;0.01</td>
<td>11.03</td>
<td>21.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ferritin level (ng/mL)</td>
<td>3–166</td>
<td>106,600</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>soluble interleukin 2 receptor (U/mL)</td>
<td>122-496</td>
<td>1,120</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Figure 1.** Clinical images. a: Plain abdominal computed tomography at 5 days after the onset of symptoms shows mild hepatosplenomegaly. b: Plain abdominal computed tomography at 5 days after the onset of symptoms shows diffuse pancreatic swelling with irregular pancreatic outline and obliterated peripancreatic fat. c: A chest X-ray at 5 days after the onset of symptoms shows clear lung fields. d: A chest X-ray at 9 days after the onset of symptoms shows a bilateral infiltrative shadow with right pleural effusion.

**Figure 2.** Clinical course of the patient while in the intensive care unit.
Pathological findings

At autopsy, a subcutaneous hemorrhage was observed in the left inguinal regions and bilateral lower limbs. The aorta was moderately atheromatous and tortuous. The celiac arterial trunk revealed severe atherosclerotic stenosis at the site of orifice (Fig. 3b). The superior mesenteric artery (SMA) had moderate atherosclerotic stenosis, and although patent, there was a small amount of mural thrombus. The gastrointestinal (GI) mucosa was severely hemorrhagic, edematous and congested over its entire length, and the stomach was filled with 250 mL of bloody fluid. The liver was rather small (890 g) and had irregular bright lesions on the external surface. When sectioned, grossly visible multiple yellowish white patches with geographic borders with hyperemic rims were seen. These patches were confirmed to be massive hepatocyte necrosis with peripheral hyperemia, thought histologically to indicate hepatic infarction (Fig. 3c).
Table 2. Results of Immunohistochemistry (IHC) and RT-PCR for Severe Fever with Thrombocytopenia Syndrome Virus SFTSV.

<table>
<thead>
<tr>
<th>Tissue-block</th>
<th>IHC (anti-SFTSV-NP)</th>
<th>RT-PCR (SFTSV-RNA, copy/cell)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>+</td>
<td>1.95 x 10^2</td>
</tr>
<tr>
<td>Spleen</td>
<td>++</td>
<td>3.45 x 10^2</td>
</tr>
<tr>
<td>Kidneys</td>
<td>-</td>
<td>2.20</td>
</tr>
<tr>
<td>Adrenals/Spinal cord</td>
<td>+/-</td>
<td>1.53 x 10^3/under detection limit</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>+</td>
<td>4.19</td>
</tr>
<tr>
<td>Bronchus</td>
<td>-</td>
<td>0.513</td>
</tr>
<tr>
<td>Lung</td>
<td>-</td>
<td>2.12</td>
</tr>
<tr>
<td>Brain</td>
<td>-</td>
<td>under detection limit</td>
</tr>
<tr>
<td>Tongue/Palatine tonsil</td>
<td>-</td>
<td>under detection limit</td>
</tr>
<tr>
<td>Lymph node</td>
<td></td>
<td></td>
</tr>
<tr>
<td>paraaortic</td>
<td>++</td>
<td>3.11 x 10^5</td>
</tr>
<tr>
<td>right hilar</td>
<td>-</td>
<td>under detection limit</td>
</tr>
</tbody>
</table>

The results were graded as follows: - no positively-stained cells, +: under 10 cells, ++: 10–100 cells, +++: 100–500 cells,

Similar ischemic lesions were observed in the spleen (Fig. 3d), kidneys, adrenals and testes. The thick and dark-colored mucosa of the intestine was microscopically eroded with focal necrosis and was markedly edematous and congested, raising the suspicion of circulatory disturbance (Fig. 3e). A purulent and hemorrhagic exudate was seen in the tracheobronchial mucosa (left view of Fig. 3f) with a mixed Candida and Aspergillus infection (right lower inset of Fig. 3f). The lungs were edematous and congested (left, 525 g; right, 640 g), with bloody pleural efluxion on the right side (800 mL). The alveolar spaces were diffusely flooded with edema fluid where extravasated red blood cells were seen (right upper inset of Fig. 3f). A hyaline membrane was not seen. These observations were consistent with the initial stage of diffuse alveolar damage. Hemophagocytosis was occasionally identified throughout the sections examined. One of the paraaortic lymph nodes, which was not enlarged but was firmer than the others, showed histologic features of necrotizing lymphadenitis, where the basic lymph nodal architecture was lost and replaced by massive necrosis leaving cell debris. Surrounding the necrotic area was a mononuclear cell infiltrate including lymphocytes, immunoblasts and histiocytes (Fig. 3g). The palatine tonsil and the other lymph nodes did not show any necrotizing lymphadenitis. The central nervous system showed no pathological changes. A gross examination of the pancreas revealed mild congestion. There was no necrotic change in the parenchyma, fat or vessels in the pancreatic interstitium or peripancreatic space under microscopy.

Paraffin-embedded blocks of various tissues (e.g., liver, spleen, adrenals, kidneys, lymph nodes, palatine tonsil, tongue, brain, spinal cord and bone marrow) were sent to the Department of Virology 1 at the National Institute of Infectious Diseases (NIID) for immunohistochemistry (IHC) and virological analyses. IHC was performed as previously described (3). Rabbit anti-SFTSV-nucleoprotein (NP) serum and peroxidase-labeled polymer-conjugated anti-rabbit immunoglobulin [En Vision horseradish peroxidase (HRP), Dako, Glostrup, Denmark] were used (3). SFTSV RNA was extracted from the paraffin-embedded tissue blocks using a Pure Link FFPE RNA isolation kit (Invitrogen, Thermo Fisher Scientific, Waltham, USA) at the NIID. The SFTSV copy number was determined by performing quantitative real-time RT-PCR on the tissue extracts as previously described (3, 5). The amount of human β-actin mRNA in the RNA extracted from each section was also determined and used as an internal reference for normalization (5). Ten tissue-blocks were analyzed using IHC (Table 2). SFTSV-NP antigen-positive immunoblasts were detected in the liver, adrenals, and the bone marrow. A large number of such cells was also seen in a solitary paraaortic lymph node (Fig. 3h) and the spleen. The parenchymal cells of each organ, including hepatocytes (Fig. 3i), were negative for SFTSV-NP antigen. In contrast to the IHC results, low copy numbers (<40 copies/cell) of SFTSV-RNA were detected in the adrenals and bone marrow (Table 2). Very little or no SFTSV-RNA was detected in the spinal cord, brain, tongue, palatine tonsil and right hilar lymph node (Table 2).

Discussion

This report described the case of an elderly man who had no underlying conditions or other infectious disease or traveled outside of this area for many years. Furthermore, we interviewed his family members and all hospital staff members who provided him with medical assistance, however, no other cases of this illness were identified. Although tick bite wounds or other kinds of skin lesions were not observed, it was difficult to distinguish the present case from a rickettsial infection, which is relatively common in this area; therefore, we continued to administer tetracycline antibiotics, until a definitive diagnosis could be reached. Scrub typhus (tsutsugamushi disease) and Japanese spotted fever are representative of rickettsial disease in Miyazaki. The infection is acquired through bites from an infected tick during outdoor activities. A fever, exanthema and eschar are the major clinical signs of both infections. A shorter incubation time and a smaller eschar characterize Japanese spotted fever. An exanthema of Japanese spotted fever tends to spread from the extremities to the trunk, while that of scrub typhus ap-
pears mainly in the trunk. Despite these different clinical pictures, the laboratory differential diagnosis is indispensa-
ble in distinguishing them from one another. Cases of Japa-
nese spotted fever were reported from Chiba, Shimane, and
Miyazaki Prefectures, and the male to female ratio was 1:1.

As of June 24, 20XY, six patients with SFTS were admit-
ted to our hospital, including the present case. The epidemi-
ological and clinical features observed in these SFTS cases
are summarized in Table 3. They were ≥60 years of age
(range, 62-92 years), and the male to female ratio was 1:1.
The disease onset occurred in all cases between the months
of April and November. There was clear evidence of tick
bites in two of six cases. All cases showed nonspecific feb-
rile symptoms, gastrointestinal tract symptoms, and leuko-
penia and thrombocytopenia in the early phase of the dis-
ease. Deterioration in the level of consciousness, as charac-
terized by dysphasia, dysarthria, disorientation, and altered
consciousness, was observed in four of six cases, and gener-
alized convulsions were seen in the late stages of the disease
in two cases, including the present case. Mechanical ventila-
tory support was needed in two cases, including the present
case. Hyponatremia was noted in four of six cases, includ-
ing the present case. Blood urea nitrogen and creatinine lev-
els were elevated in two of six cases, and only the present
case required continuous hemodialfiltration. The liver plays a
central role in the pathogenesis of SFTSV infection (1, 3).
An elevation in liver markers (AST, ALT, and LDH) was
observed in five of six cases as found in a majority of SFTS
patients (8), and abnormalities were observed in the labora-
tory tests in four of six cases (including the present case)
with regards to coagulopathy, prothrombin time, activated
partial thromboplastin time, fibrin/fibrinogen degradation
products, fibrinogen, and/or D-dimer, all of which could re-
fect underlying disseminated intravascular coagulation
(DIC). In four of five cases, including the present case, for
which a bone marrow examination was performed, hemopha-
gocytosis was observed, and the serum ferritin level was
 Elevated. These are many of the systemic features of
HPLS (9), and affected patients received corticosteroids for
the management of hemophagocytosis. The symptoms re-
solved by 1 week after onset in the survivors, and the serum
enzymes began to decline toward normal levels and showed
signs of recovery after 2 weeks of disease onset. Only the
present case was fatal.

Among 11 cases of the first identification and retrospec-
tive study of SFTS in Japan, macrophages with phagocytosis
of bone marrow cells were observed in all patients in whom
a bone marrow examination was performed. The ferritin
level was extremely elevated in the sera of all patients who
were tested. SFTSV infections induce a cytokine storm,
which is associated with hemophagocytosis and DIC in ad-
dition to MODF, all of which indicate a poor prognosis (3).
The clinical course of SFTS has largely been divided into
four stages: 1) incubation stage: 5 to 14 days after the tick
bite, 2) fever stage: flu-like symptoms develop, such as a fe-

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### Table 3. Epidemiological and Clinical Features of 6 Severe Fever with Thrombocytopenia Syndrome (SFTS) Patients of Our Hospital.

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Date of admission (year/month/day)</th>
<th>Clinical symptoms</th>
<th>Laboratory findings (nadir or peak)</th>
<th>Hemophagocytosis in bone marrow</th>
<th>Management</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>male</td>
<td>20XX/May/18</td>
<td>anorexia/vomiting/diarrhea</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>Alive</td>
</tr>
<tr>
<td>62</td>
<td>female</td>
<td>20XX/July/22</td>
<td>disturbance of consciousness</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
<td>Alive</td>
</tr>
<tr>
<td>70</td>
<td>male</td>
<td>20XX/Nov/19</td>
<td>tick bite wound</td>
<td>(+)</td>
<td>(-)</td>
<td>(+)</td>
<td>Alive</td>
</tr>
<tr>
<td>84</td>
<td>female</td>
<td>20XX/June/9</td>
<td>AST:Aspartate aminotransferase</td>
<td>LDH:Lactate dehydrogenase</td>
<td>BUN: Blood urea nitrogen</td>
<td>CHDF: Continuous hemodialfiltration</td>
<td></td>
</tr>
<tr>
<td>92</td>
<td>female</td>
<td>20XX/June/25</td>
<td>WBC: White-cell count</td>
<td>Plt: Platelet count</td>
<td>Creatinine</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>82</td>
<td>Male</td>
<td>20XX/April/15</td>
<td>D dimer (µg/dL)</td>
<td>36.92</td>
<td>Unexamined</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>male</td>
<td>20XX/June/25</td>
<td>ferritin level (µg/mL)</td>
<td>736.3</td>
<td>(+)</td>
<td>Alive</td>
<td></td>
</tr>
</tbody>
</table>

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WBC: White-cell count  
AST: Aspartate aminotransferase  
ALT: Alanine aminotransferase  
LDH: Lactate dehydrogenase  
BUN: Blood urea nitrogen  
Creatinine  
CHDF: Continuous hemodialfiltration
ver, headache, malaise, muscular pain, and diarrhea, 3) MODF stage, and 4) convalescence stage. Most patients generally shift into the MODF stage after a fever stage of 5 to 11 days. Severe leukocytopenia and thrombocytopenia have been reported during the MODF stage when DIC is common, causing several fatalities (1, 3, 10, 11). The present case was hospitalized at 5 days after the onset of the fever, and his condition deteriorated on the next day. He already had been in the MODF stage with markedly elevated AST, LDH and CPK levels, abnormal neurological findings, acute kidney injury and DIC. At that time in the present case, the clinical signs and laboratory data nearly met the clinical criteria for the diagnosis of HPLS (9). HPLS is a life-threatening clinicopathological condition with an overwhelming inflammatory reaction with prominent hemophagocytosis in the bone marrow and lymph nodes (10). It is accompanied by excessive activation and expansion of macrophages and T cells, mainly CD8* cells. These cells may infiltrate nearly every organ in the body and may account for many of the systemic features of HPLS. SFTSVs belong to the Bunyaviridae family, which includes Rift valley fever virus, Hantaan virus and Heartland virus (12), which infect monocytes/macrophages (13, 14). These infected monocytes/macrophages may control the spread of viruses to cells within other organs. SFTSV infections induce a cytokine storm, the level of which correlates with the severity of SFTS (15). HPLS may play an important role in the disease progression, disease severity, and clinical outcomes of SFTS. Some lethal SFTS cases have been treated with corticosteroids (dexamethasone, methylprednisolone or prednisolone) to suppress the hemophagocytic reaction (16). Since this treatment may not always prevent the poor outcomes, the use of corticosteroids for SFTS patients is controversial and requires further experience and evaluation to determine its overall utility (17, 18).

A high viral load in the serum is characteristic of fatal SFTS infection (19, 20), and the main pathological finding of SFTSV infection are necrotizing lymphadenitis with both numerous apoptotic cells and nuclear debris (16). However, the present case had typical necrotizing lymphadenitis strongly positive for the SFTSV-NP antigen only in a solitary paraaortic lymph node. The pathological and virological observations of the present case suggest that SFTSV replicates predominantly in the affected lymph node, where immunoreactive cells for SFTSV are numerous. The SFTSV RNA copy numbers in the paraaortic lymph node sections were the highest among the tissues tested, while the bone marrow and adrenals showed lower copy numbers (<100/cell) with weakly antigen-positive cells as assessed by IHC analyses. The other specimens, such as the brain, bronchus, lung, right hilar lymph node, kidneys, tonsil and tongue, showed low copy numbers, consistent with antigen-negative cells (Table 2), which could be due to the influence of the SFTSV-infected cells in the peripheral blood or cell-free circulating SFTSV. We performed only qualitative real-time PCR on serum specimens obtained from this case during the treatment course while in hospital. When the results of the SFTSV RNA copy numbers in all specimen examined at NIID were noted, a sufficient amount of appropriate blood or serum specimens had not been prepared ahead of time and, as a result, we were unable to perform quantitative real-time RT-PCR on either the serum or SFTSV-infected cells from the peripheral blood of this case.

To the best of our knowledge, this case is the 4th autopsy case report to describe the pathologic findings of a patient with SFTS. The clinical course of the patient, who was dead at 12 days after the onset of multiorgan failure, including liver dysfunction, acute renal failure, acute respiratory distress syndrome and DIC, was similar to those of fatal cases described in previous reports (1-4). Notably, in the present case, the peak levels of AST, ALT, and LDH were observed at the time of death, and the liver showed multiple lobular necroses. Although some SFTSV-NP antigen-positive cells were observed in the liver, hepatocytes were not infected, as previously reported (4). These observations suggest that the liver damage in the present case may be due to a secondary pathological process (e.g., shock status, hypercytokinemia, and hemophagocytosis) rather than due to a direct disturbance by SFTSV. Furthermore, the autopsy of the present case demonstrated severe atherosclerotic stenosis of the celiac arterial trunk at the site of orifice as well as moderate atherosclerotic stenosis (partially patent) of the SMA with the presence of a small amount of mural thrombus (Fig. 3b). As the blood supply of the liver has many collateral pathways (mainly from the portal venous system and hepatic arterial system), true hepatic infarction in man is extremely rare. Nevertheless, a severe blood flow reduction (from the celiac trunk and the proximal superior mesenteric artery) may produce hepatic infarction (21). Autopsy studies have shown that the incidence of more than 50% stenosis in at least one mesenteric artery occurs in 6-10% of the population (22). Risk factors for arterial thrombosis includes low flow states (such as shock), atherosclerosis, congestive cardiac failure, recent myocardial infarction, advanced age, vasculitis and intra-abdominal malignancy. Half of those risk factors were present in this case. Unlike embolic events, which affect the distal arterial branches and result in limited bowel ischemia, thrombosis of the celiac artery occurs at the vessel origin and may result in extensive bowel involvement, including the liver and spleen (22). This case report could show an example of an acute mesenteric ischemic event involving the celiac artery distribution.

This case showed that shock and DIC initiated by SFTSV-associated HPLS in an elderly patient resulted in life-threatening severe ischemia of the liver, spleen and GI tract, which was accompanied by severe atherosclerotic stenosis with thrombosis at the celiac trunk and SMA.

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References