INTRODUCTION

Severe fever with thrombocytopenia syndrome (SFTS) is a fatal infectious disease caused by the SFTS virus (SFTSV), which is a novel Phlebovirus in the family Bunyaviridae. The major clinical features of patients with SFTS are high fever, thrombocytopenia, leukopenia, and gastrointestinal symptoms. Elevated serum levels of alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, lactate dehydrogenase, creatine kinase, and ferritin are also common laboratory findings in patients with SFTS. However, the pathological mechanism of thrombocytopenia and leukopenia in patients with SFTS is not fully understood until now; it is unclear whether production failure or peripheral destruction/sequestration is the main mechanism of cytopenia in these patients.

In the present study, therefore, we investigated the bone marrow (BM) findings of patients with SFTS to understand the pathogenesis of SFTS.

CASE REPORT

Case 1

Abdominal pain developed in a 73-year-old man. He was transfused with packed red blood cells due to low hemoglobin (Hb) (7.6 g/dL) at a local hospital 10 days later. Fever, neutropenia, and elevated liver enzymes were observed. He was referred to our hospital for further evaluation and treatment. SFTSV was confirmed by reverse-transcription polymerase chain reaction (RT-PCR) analysis at Division of Arboviruses, National Institute of Health, Korea Centers for Disease Control and Prevention. The laboratory and clinical findings are summarized in Table 1 and 2. A BM biopsy was performed. Hemophagocytic histiocytes were observed in an aspirate (Fig. 1A), and hypocellular marrow was noted in the BM section (Fig. 1B). However, mega-
karyocytes were relatively preserved in the section (Fig. 1C). He was treated with antibiotics and plasmapheresis. However, he died 3 weeks after the initial symptoms (3 days after BM biopsy) due to metabolic acidosis and multi-organ failure.

**Case 2**

Fever and enlargement of the left inguinal lymph node developed in a 53-year-old man, and he was treated with antibiotics at a local hospital. However, pancytopenia was detected (Hb, 12.9 g/dL; white blood cell, 3.77×10^9/L; platelet, 24.0×10^9/L) at local hospital, and he was referred to our hospital for further evaluation and treatment. SFTSV was confirmed by RT-PCR analysis at Division of Arboviruses, National Institute of Health, Korea Centers for Disease Control and Prevention. The laboratory and clinical findings at our hospital are summarized in Table 1 and 2. Severe hypocellular marrow was noted in an aspirate and section (Fig. 1D and E). Megakaryocytes were rarely found. He was treated with antibiotics; however, he died 10 days after admission due to multi-organ failure.

**Case 3**

An 86-year-old woman was admitted to our hospital for a 3-day fever. She had been with antibiotics at local hospital; however, pancytopenia was detected, and she was referred to our hospital for further evaluation and treatment. SFTSV was confirmed by RT-PCR analysis at Division of Arboviruses, National Institute of Health, Korea Centers for Disease Control and Prevention. The laboratory and clinical findings at our hospital are summarized in Table 1 and 2. Hemophagocytic histiocytes were observed in an aspirate (Fig. 1F). The megakaryocytes were normally observed in an aspirate (Fig. 1G). Normocellular marrow with focal hypocellular area was noted in the BM section (Fig. 1H). The patient was successfully treated with antibiotics and ribavirin.

**DISCUSSION**

Thrombocytopenia and leukopenia are prominent features in
patients with SFTS. Viral replication in a mouse model mainly occurs in splenic macrophages. However, SFTSV is not found in mice BM, but the numbers of megakaryocytes increase in the spleen and BM of mice. In vitro cell assays show that SFTSV adheres to mouse platelets and facilitates phagocytosis of platelets by primary macrophages, suggesting that the cause

Fig. 1. Findings of bone marrow (BM) aspirate and section of case 1 (A, B, and C), 2 (D and E), and 3 (F, G, and H). (A) The hemophagocytic histiocytes were increased in the aspirate [Wright-Giemsa (W-G), ×400]. (B) Hypocellular area was noted in the BM section [hematoxylin and eosin (H&E), ×100]. (C) The number of dysplastic megakaryocytes increased slightly in the cellular area (CD61 immunohistochemistry, ×400). (D) Hypocellular particles (W-G, ×40). (E) Severe hypocellular marrow is noted (H&E, ×40). (F) The hemophagocytic histiocytes are increased in the aspirate (W-G, ×400). (G) Megakaryocytes are normally observed in the aspirate (W-G, ×200). (H) Normocellular marrow for age (86 years) with a focally hypocellular area is noted (H&E, ×100).
They reported two patients treated with ribavirin and plasma
destruction/sequestration and BM suppression.

However, hypocellular marrow with an increased number of
hemophagocytic histiocytes is observed in Japanese patients
with SFTS, whereas megakaryocytes are relatively preserved
in BM. Consistent with these findings, our Korean patients also
showed moderate to severe hypocellular marrow with an in-
creased number of hemophagocytic histiocytes and/or relat-
ively preserved megakaryocytes. The reason for the different
BM findings between Chinese and Japanese or Korean patients
with SFTS is unclear. The Chinese patients with SFTS were
relatively young age (30–50 years) and all of them recovered
successfully. However, our Korean patients with SFTS (53–86
years) and the Japanese patients with SFTS were older (>50
years), and two of our Korean patients died. Therefore, age and
clinical status/severity may be the cause of the different BM
findings.

Deng, et al. also observed that two patients expired of SFTS
presented with empty marrow. These two cases and our cases
(case 1 and case 2) suggest that BM hypocellularity is associat-
ed with severity of SFTS. However, further studies are needed.

Considering the results of animal experiments and those of
pathological examinations of patients with SFTS, hemoph-
agocytosis appears to be common in patients with SFTS, and
the laboratory findings of most patients with SFTS are compat-
ible with hemophagocytic lymphohistiocytosis (fever, cytopenia,
high ferritin level, etc.). Moreover, one study revealed that
increased cytokine levels are correlated with viral load/clini-
"cally parameters in patients with SFTS. Since dysregulation of
the immune system with hypercytokinemia is an underlying me-
chanism of hemophagocytic lymphohistiocytosis, SFTSV may
produce hemophagocytic lymphohistiocytosis. Therefore, cy-
topenia in patients with SFTS may result from both peripheral
destruction/sequestration and BM suppression.

Based on the “cytokine storm” and “immune-mediated plate-
let consumption in the spleen” concepts, some authors have
reported cases treated with plasmapheresis to reduce cytokine
levels as well as other pathological immune-mediating agents.
They reported two patients treated with ribavirin and plasma-
pheresis and they recovered from SFTS. However, plasm-
apheresis does not have demonstrated therapeutic efficacy until
now. Our Patient 1 died after a plasmapheresis treatment. Th-
therefore, further studies are needed to define the exact patho-
genesis and the therapeutic implications.

In conclusion, our results together with other studies indi-
cate that BM suppression and hemophagocytic histiocytes are
common findings in patients with SFTS. Although a limited
number of cases were available, our observations may help un-
derstand the pathogenic mechanism of SFTSV and aid in fu-
ture therapeutic applications.

REFERENCES

1. Yu XJ, Liang MF, Zhang SY, Liu Y, Li JD, Sun YL, et al. Fever with
thrombocytopenia associated with a novel bunyavirus in China.
N Engl J Med 2011;364:1523–32.
2. QuanTai X, FengZhe C, XiuGuang S, DongGe C. A study of cytological
changes in the bone marrow of patients with severe fever with
thrombocytopenia syndrome. PLoS One 2013;8:e83020.
3. Takahashi T, Maeda K, Suzuki T, Ishido A, Shigeoka T, Tominaga T,
et al. The first identification and retrospective study of Severe Fe-
ver with Thrombocytopenia Syndrome in Japan. J Infect Dis 2014;
209:816–27.
4. Jin C, Liang M, Ning J, Gu W, Jiang H, Wu W, et al. Pathogenesis of
emerging severe fever with thrombocytopenia syndrome virus in
C57/BL6 mouse model. Proc Natl Acad Sci U S A 2012;109:10053–8.
5. Kim WY, Choi W, Park SW, Wang EB, Lee WJ, Jee Y, et al. Nosoco-
cial transmission of severe fever with thrombocytopenia syndrome
in Korea. Clin Infect Dis 2015;60:1681–3.
6. Ding S, Niu G, Xu X, Li J, Zhang X, Yin H, et al. Age is a critical risk
factor for severe fever with thrombocytopenia syndrome. PLoS One
2014;9:e111736.
7. Gai ZT, Zhang Y, Liang MF, Jin C, Zhang S, Zhu CB, et al. Clinical
progress and risk factors for death in severe fever with thrombo-
cytopenia syndrome patients. J Infect Dis 2012;206:1095–102.
8. Deng B, Zhou B, Zhang S, Zhu Y, Han L, Geng Y, et al. Clinical fea-
tures and factors associated with severity and fatality among pa-
tsients with severe fever with thrombocytopenia syndrome Bunya-
ivirus infection in Northeast China. PLoS One 2013;8:e80882.
9. Jordan MB, Filipovich AH. Hematopoietic cell transplantation for
hemophagocytic lymphohistiocytosis: a journey of a thousand
miles begins with a single (big) step. Bone Marrow Transplant 2006;
42:433–7.
10. Sun Y, Jin C, Zhan E, Wang X, Liang M, Zhang Q, et al. Host cytokine
storm is associated with disease severity of severe fever with throm-
bocytopenia syndrome. J Infect Dis 2012;206:1085–94.
11. Usmani GN, Woda BA, Newburger PE. Advances in understanding
the pathogenesis of HLH. Br J Haematol 2013;161:609–22.
12. Oh WS, Heo ST, Kim SH, Choi WJ, Han MG, Kim JY. Plasma ex-
change and ribavirin for rapidly progressive severe fever with throb-
ocytopenia syndrome. Int J Infect Dis 2014;18:84–6.