Case Report
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Two Treatment Cases of Severe Fever and Thrombocytopenia Syndrome with Oral Ribavirin and Plasma Exchange

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Severe fever with thrombocytopenia syndrome (SFTS) is an emerging tick-borne disease. The primary symptoms associated with SFTS are fever, thrombocytopenia, leukopenia, nausea, and vomiting. Disease progression shows high mortality rate accompanied with multiple organ failure, bleeding tendency, and altered mentality. However, only supportive care has been the basis for the treatment of SFTS. We are reporting two patients who showed central nervous system manifestation, but cured them with ribavirin together with plasma exchange in an early state. The first case is a 60-year-old male, who was admitted to the hospital with a 7-day history of fever, chills, and thrombocytopenia. He was treated with empirical antibiotics; however, he experienced persistent high fever and an altered mentality has occurred. On hospital day 6, the SFTS virus (SFTSV) result from a real-time reverse transcription-polymerase chain reaction (RT-PCR) was confirmed positive. Therefore, ribavirin (30 mg/kg as initial loading dose, 15 mg/kg qid for 4 days and then 7.5 mg/kg qid as maintenance dose) was administered orally for 11 days and plasma exchange was performed for 5 days. The clinical outcome has improved. The second case is a 48-year-old male, who was admitted to the hospital with a 10-day history of fever, chills, myalgia, diarrhea, and thrombocytopenia. He was treated with empirical antibiotics. On hospital day 3, ribavirin (30 mg/kg as initial loading dose, 15 mg/kg qid as maintenance dose) was administered orally for 4 days and plasma exchange was performed for 4 days due to his high fever and altered mentality after a positive SFTSV result from a real-time RT-PCR. The patient had a successful recovery.

Key Words: Severe fever with thrombocytopenia syndrome; Bunyavirus; Ribavirin; Plasma exchange

Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging tick-borne disease that was first reported in China in 2011 [1]. There have been 2,047 cases reported in China, while 53 cases and 36 cases have been reported in Japan and Korea, respectively. It is known that SFTS occurs from May to August when the tick's activity is intense. However, in Korea, SFTS patients are increasing in September when people are mowing the grass around graves on the mountain [2]. Chief complaints include fever, thrombocytopenia, leukopenia, nausea, and vomiting. In a rapidly progressing SFTS, the fatal-

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ity rate becomes 6% to 30%, and it is accompanied by multiple organ failure, bleeding tendency, and altered mentality [3-5]. Treatment medicine has not been developed yet. Supportive treatment, such as transfusion, renal replacement therapy, and empirical antibiotics, has been the basis of treatment for SFTS [6, 7]. China has been using intravenous ribavirin as a guideline for the treatment of SFTS since 2012 [8]. There was a case wherein a patient of advanced age had a high probability of poor prognosis accompanied by clinical features, such as central nervous system (CNS) manifestation, bleeding tendency, disseminated intravascular coagulation, and multiple organ failure. The patient was treated with ribavirin and plasma exchange. Such cases that using of ribavirin and plasma exchange were few in Korea [9]. We are reporting two patients who showed CNS manifestation, and we treated them with ribavirin along with plasma exchange at an early stage.

Case Report

1. Case 1

A 60-year-old male mowed the grass near a grave on a mountain 3 weeks before the hospital admission, and then he developed and lower abdominal rash, fever, chills, myalgia, cough, and mucopurulent sputum 1 week before the hospital admission. He visited the local hospital 2 days before the admission, and the blood test showed abnormal liver function test and thrombocytopenia. He had no vomiting, diarrhea and abdominal pain. The patient drank 1-2 bottles of alcohol per day. He stopped smoking 30 years ago (10 pack-year history). He had dyspnea at modified medical research (mMRC) grade 1-2. On admission to the hospital, his blood pressure was 110/70 mmHg, pulse rate was 75/min, respiratory rate was 20/min, and body temperature (tympanic membrane) was 37.3°C. The auscultation of heart sound was regular without murmur. Crackles are noted in both lower lung fields. The patient was conscious. There was no eschar on the skin; however, a lower abdominal popular rash has developed. He had a 1.0 cm right inguinal lymph node, which was movable and non-tender. The physical examination of the abdomen was normal. Laboratory findings revealed white blood cell (WBC) 2,510/mm^3, hemoglobin (Hb) 13.6 g/dL, platelet 49,000/mm^3, Na/K 122/3.6 mEq/L, C-reactive protein (CRP) 1.05 mg/dL, aspartate transaminase (AST)/alanine transaminase (ALT) 188/88 U/L, lactate dehydrogenase (LDH) 1,136 U/L, creatinine kinase-MB (CK-MB) 3.4 ng/mL, activated partial thromboplastin time (aPTT) 50.1 sec, international normalized ratio (INR) 1.12, and D-dimer 17.06 mg/L. Urinalysis revealed red blood cell (RBC), 10-20/ high-power-field (HPF), and albumin 2+. Stool occult blood was negative. Electrocardiogram showed sinus rhythm and right bundle branch block. Chest radiography showed no active lung lesion. However, chest computed tomography (CT) showed peripheral emphysema on both lungs. Multiple enlarged lymph nodes (size 0.7-1.0 cm) on the abdomen CT was observed in the right common iliac area and right inguinal area. Clinical features and blood test showed suspected SFTS. On the 3rd day of his hospital stay, SFTSV real-time RT-PCR was taken by using Viral Genespin Viral DNA/RNA Extraction kit (iNtRON, Seongnam-si, Gyeonggi-do, Korea) for RNA isolation and using DiaStar™ 2X OneStep RT-PCR Pre-Mix (SolGent, Daejeon, Korea) for RNA detection. Intravenous ceftriaxone (2.0 g qd) injection was started as empirical antibiotics for fever, and doxycycline (100 mg bid) was administered orally. He experienced high fever and mental confusion. The blood test indicated deterioration, which revealed WBC 1,960/mm^3, platelet 37,000/mm^3, AST/ALT 1,813/477 U/L, and LDH 2,462 U/L. Considering the probability of superimposed bacterial infection, empirical antibiotics have been replaced by intravenous piperacillin/tazobactam (4.0 g/0.5 g tid), and plasma exchange was started due to a suspicion of SFTS accompanied by CNS manifestation (based on weight and hematocrit, approximately 2,800 mL for 120 min, 23 mL/min, lumen size 11.5 Fr, COBE Spectra Apheresis System, Lakewood, CO, USA). On the 6th day of his hospital stay, hemoptysis occurred. The chest radiograph showed an increased opacity on both middle-lower lung fields. We thought of the possibility of acute pulmonary distress syndrome (ARDS) or pulmonary edema, secondary bacterial pneumonia, thus antibiotics were replaced by intravenous meropenem (1.0 g tid), and ventilator treatment was performed. The SFTSV real-time RT-PCR result confirmed positive, and ribavirin 2,000 mg (30 mg/kg) loading dose was started on the 6th day of his hospital stay. On the 7th day of his hospital stay, laboratory findings revealed WBC 6,110/mm^3, Hb 8.8 g/dl, platelet 71,000/mm^3, and AST/ALT 33/27 U/L. His fraction of inspired oxygen (FiO_2) of ventilator remained in stable status, thus the plasma exchange was discontinued and ribavirin 1,000 mg (15 mg/kg qid) was tapered orally. On the 10th day of his hospital stay, ribavirin 500 mg (7.5 mg/kg qd) was tapered orally. On the 13th day of his hospital stay, mental instability has improved, and the patient recovered consciousness and good breathing. The ventilator treatment was discontinued, and antibiotics were de-escalated by intravenous moxifloxacin (400 mg qd). On the 16th day of his hospital stay,

oral administration of ribavirin was discontinued. On the 18th day of his hospital stay, the patient was discharged in improved condition (Fig. 1).

2. Case 2

A 48-year-old male is a farmer who had a 10-day history of fever, chills, myalgia, and diarrhea, which appeared 10 days prior to his hospital visit. He had diabetes and also had a 45-pack-year smoking history. On hospital admission, the patient's blood pressure was 130/80 mmHg, pulse rate was 80/min, respiratory rate was 20/min, and body temperature (tympanic membrane) was 38.0°C. The patient was alert. The auscultation of heart sound was normal without murmur. His lung sounds were normal. There was no skin rash or eschar. Abdominal examination was normal. Laboratory findings revealed WBC 1,280/mm^3, Hb 15.3g/dL, platelet 45,000/mm^3, Na/K 132/3.6 mEq/L, CRP 1.01 mg/dl, AST/ALT 110/38 U/L, LDH 983 U/L, creatinine phosphokinase (CPK) 268 U/L, prothrombin time (PT) 12.5 sec, aPTT 47.7 sec, and INR 1.13. Urinalysis revealed RBC 0-2/HPF and albumin 2+. Stool occult blood was negative. SFTSV real-time RT-PCR was conducted on admission day and on hospital day 3, which were both confirmed positive. Chest radiography showed no active lung lesion. Abdomen CT was conducted as he had a history of diarrhea, and the result showed fatty liver and mild splenomegaly. The patient was suspected of having SFTS form clinical manifestation and laboratory finding. SFTSV real-time RT-PCR were taken using the same method as described above on admission day. Intravenous ceftriaxone (2.0 g qd) and oral doxycycline (100 mg bid) were administered as empirical antibiotics for the fever. On the 2nd day of his hospital stay, high fever (38.3°C, tympanic membrane) has continued and the blood test result indicated deterioration, showing WBC 2,030/mm^3, Hb 16.1 g/dL, platelet 43,000/mm^3, AST/ALT 252/52 U/L, LDH 2,764 U/L, and CPK 592 U/L. The patient experienced a confused mental state, and he was transferred to intensive care unit. We performed brain non enhancement CT and brain diffusion magnetic resonance imaging, and consulted with department of neurology. There was no evidence of organic brain lesion. His antibiotics were replaced by intravenous piperacillin/tazobactam (4.0 g/0.5 g tid). On the 3rd day of his hospital stay, the SFTSV real-time RT-PCR was confirmed positive. Ribavirin 2,600 mg (30 mg/kg) loading dose and 1,200 mg (15 mg/kg qid) maintenance dose were administered orally, and plasma exchange was performed (based on weight and hematocrit, approximately 3400 ml for 150 min, 22 ml/min, lumen size 11.5 Fr, COBE Spectra Apheresis System, Lakewood, CO, USA). On the 4th day of his hospital stay, his condition has improved. His laboratory findings revealed WBC 4,300/mm^3, Hb 13.8 g/dL, platelet 44,000/mm^3, AST/ALT 122/35 U/L, LDH 1,181 U/L, and CPK 461 U/L. The patient's fever has subsided. On the 6th day of his hospital stay, laboratory findings revealed WBC 3,600/mm^3, Hb 13.3 g/dL, platelet 59,000/mm^3, AST/ALT 101/42 U/L, LDH 768 U/L, and CPK 492 U/L. Due to the remarkable improvement of the patient's clinical course, plasma exchange and ribavirin treatment were all discontinued on the 6th day of his hospital stay. And de-escalation of antibiotics was done by intravenous levofloxacin (750 mg qd). On the 10th day of his hospital stay, the patient showed improved condition; therefore, the antibiotics were discontinued. On the 14th day of his hospital stay, the patient's mental state has fully recovered, and he was discharged on the 17th day of his hospital day (Fig. 1).

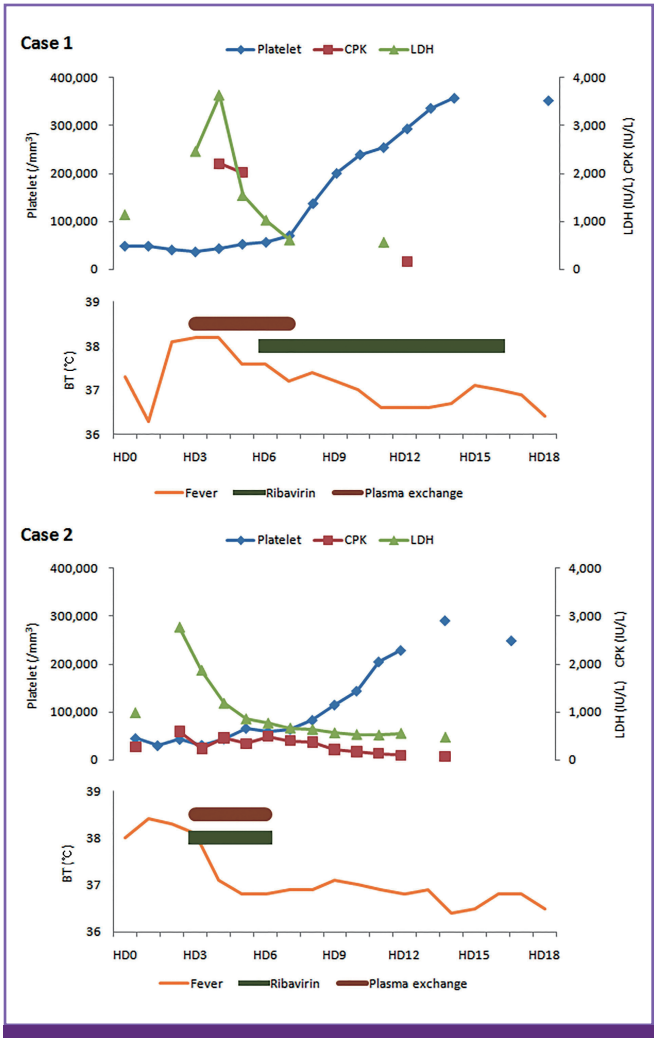

Figure 1. Laboratory findings and fever of two patients with severe fever with thrombocytopenia syndrome.
CPK, creatinine phosphokinase; LDH, lactate dehydrogenase; HD, hospital day.

Discussion

SFTS is an emerging tick-borne disease which normally occurs in Korea from May to August. There have been constant reports after the first patient was identified through the retrospective isolation of the virus in May 2013 [2, 10]. Laboratory confirmation of SFTSV is established through the isolation of SFTSV in cell culture, viral identification through the RT-PCR or DH82 cells from the patient's serum, or serologic detection of 4-fold increase in anti-SFTS virus immunoglobulin G titers between acute and convalescent phases [6]. Laboratory diagnosis takes times so long from several days to weeks, even if RT-PCR takes approximately minimum 5-7 days to know the results from Korean Centers for Disease Control and Prevention. Thus on the basis of the clinical manifestation performing a diagnostic test as soon as possible is most important thing. Supportive care, such as transfusion of fresh frozen plasma or platelet for hematologic abnormalities, methylprednisolone for acute lung injury or ARDS, albumin replacement for hypoalbuminemia, intravenous immunoglobulin for severe infection or encephalitis, granulocyte colony stimulating factor for leukopenia, and antibiotics for bacterial superinfection, would be the most important part of the treatment process.

The antiviral effect of ribavirin and plasma exchange can be considered in SFTS patients with poor prognosis factor, such as old age, altered mentality, high level of LDH (>1,200 U/L), and CPK (>800 U/L) [8], and progression to multiple organ failure in spite of traditional supportive care [11]. In Korea, two cases reported that early plasma exchange and ribavirin administration were applied for the treatment of rapidly progressive SFTS. A 66-year-old farmer and a 62-year-old farmer were transferred from community hospital to tertiary care hospital due to septic shock. Positive SFTSV real-time RT-PCR and clinical manifestation such as low blood pressure, thrombocytopenia were indication of combination of oral ribavirin and plasma exchange [9]. Our treatment is done based on the above cases. In our cases, among clinical manifestations associated with fatal outcome, CNS involving symptoms such as confused or altered mentality were remarkably shown. Laboratory findings and other symptoms did not shown a significant difference from previous cases. Our patients had common history of the exposure to a rural environment by occupation or by accident in endemic season. For the better prognosis, physicians need to have a suspicion from the characteristic clinical manifestations and epidemiologic history, and make early decision when to start antiviral treatment and plasma exchange.

Since 2012, intravenous ribavirin has been introduced for the treatment of SFTS in China because it has been proven that ribavirin is as effective on the Crimean-Congo hemorrhagic fever (CCHF) virus, Bunyaviridae, as the SFTSV [12], and ribavirin exerts its antiviral effects through various mechanisms, including the reduction of viral RNA-dependent RNA polymerase activity, mutagenesis in the viral genome, inhibition of RNA capping, reduction of cellular inosine monophosphate dehydrogenase activity, and modulation of the host immune response [13]. Since then, ribavirin has been used for the SFTS treatment in Korea and abroad [9, 14]. Intravenous ribavirin has some advantages that time to therapeutic effect is relatively faster than oral ribavirin and it can be used for patients who are not allowed to be administered orally. Thus intravenous ribavirin is used to more severe viral infection. But it did not show significant difference between intravenous ribavirin and oral ribavirin for treatment cases in other viral infections, such as respiratory syncytial virus, CCHF [15, 16]. Although antiviral effect of ribavirin on SFTS was confirmed only in vitro [13, 17], because of previously reported positive efficacy of ribavirin and oral ribavirin's inexpensive price [12, 13, 15-17], we are able to use oral ribavirin as treatment for severe SFTS and it may be currently the only treatment medication.

The pathogenesis of the disease has not been established yet. It has been known that several cytokines (interleukin (IL)-1β, IL-8, macrophage inflammatory protein 1β, and interferon-gamma) are elevated in patients with SFTS, and the serum levels of cytokines are correlated with serum viral loads and disease severity. As a result, the cytokine-mediated inflammatory response may play an important role in the disease progression in patients with SFTS [5, 6, 9]. Based on this theory, several cases have reported that the plasma exchange were able to remove the immune complexes correlated with disease severity, such as cytokines, reduce serum cytokines, and improve the clinical courses in patients with ARDS or hemodynamic shock [11, 12]. We performed plasma exchange with references to the reason mentioned above.

However, there are some limitations of the combination of plasma exchange and ribavirin. Plasma exchange is not guaranteed by health insurance review and a few hospitals can do this technically. In addition, there are side effects such as hypocalcemia, hypokalemia, severe anaphylactic reactions, and transfusion related acute lung injury [18]. For ribavirin, only oral administration is approved in Korea, we cannot use for patients who are impossible to be administered orally. Also we do not have enough reference about the treatment dura-

tion of oral ribavirin. The significant adverse effects of the ribavirin, such as reversible hemolytic anemia can occur [19]. Most reported cases are the result from intravenous ribavirin, not orally [3, 8, 20]. Moreover, there were only a few cases reported that were treated with both route of administration [9]. In order to establish how ribavirin and plasma exchange works on SFTS patients, further in-depth research on its efficacy will be necessary.

Conflicts of Interest

No conflicts of interest.

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