Case Report: Use of Plasma Exchange Followed by Convalescent Plasma Therapy in a Critically Ill Patient with Severe Fever and Thrombocytopenia Syndrome–Associated Encephalopathy: Cytokine/Chemokine Concentrations, Viral Loads, and Antibody Responses

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Abstract. We describe the case of a patient with severe fever with thrombocytopenia syndrome (SFTS) complicated by SFTS-associated encephalopathy who was successfully treated with 4-day plasma exchange followed by two-time convalescent plasma therapy. During plasma exchange, the plasma cytokines interferon- α and inducible protein-10 gradually decreased without change of plasma viral load. However, plasma viral load gradually decreased after convalescent plasma therapy. This case provides important insights for understanding the mechanisms of experimental therapy in severely affected SFTS patients.

INTRODUCTION

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging febrile disease caused by a novel SFTS virus (SFTSV) in the family *Bunyaviridae*, which was first reported from China in 2011.¹ There is no effective antiviral therapy for SFTS. The mainstay treatments are experimental therapies, including ribavirin administration which is effective in vitro, plasma exchange (PE),² convalescent plasma therapy,³ immunoglobulin and steroid administration,⁴ and conservative therapies such as hemodialysis. Here, we describe the use of experimental PE and convalescent plasma therapy in a patient with SFTS-associated encephalopathy and give detailed cytokine levels, viral loads, and antibody responses.

THE STUDY

A 65-year-old man with a history of hypertension and stroke was admitted to a tertiary hospital in Seoul, South Korea, with a 6-day fever, myalgia, and chill. He frequently went for knolls over the 2 weeks before admission. On admission, his temperature was 38.5°C and other vital signs were normal. No skin rashes or eschars were observed. His Glasgow coma scale (GCS) score was 13 points at admission. A peripheral blood test revealed leukopenia (white blood cell [WBC] count, 1,200/mm³; 48% neutrophil) and thrombocytopenia (platelet count, 42,000/mm³), and serum biochemistry showed mildly elevated aspartate transaminase (67 IU/L), lactate dehydrogenase (353 IU/L), creatine kinase (280 IU/L), and normal range of alanine transaminase (36 IU/L), blood urea nitrogen (7 mg/L), creatinine (0.66 mg/dL), and C-reactive protein (0.59 mg/dL). Lumbar puncture was performed, and analysis revealed no pleocytosis (WBC count, 4/ μ L; 51% neutrophils) and normal protein (58.2 mg/dL) and glucose (79 mg/dL; ratio of glucose concentration in the cerebrospinal fluid [CSF] to that in serum, 0.54) levels. No bacteria, virus, or fungi were isolated from CSF. The magnetic resonance imagining of

the brain was carried out, but gave no evidence of acute lesions such as stroke or hemorrhage.

Treatment began with empirical antibiotics (ceftriaxone and doxycycline) and ribavirin, and we planned emergent PE because the patient's mental deterioration had progressed to GCS score 11. We started PE from hospital day (HD) 1 and performed it a total of four times for about 120 minutes per session using a Cobe spectra (Terumo BCT, Lakewood, CO) because approximately 60–70% of the substances present in plasma are removed for each 1–1.5 plasma volumes exchanged, and more than 90% of substances can be removed when PE is performed more than three times.⁵ We analyzed 18 cytokines and chemokines in his serum, as described previously,⁶ and the levels of interferon (IFN)- α and inducible protein (IP)-10 significantly decreased after the start of PE (Figure 1 and Supplemental Figure 1). However, even after the fourth PE, when the level of IP-10 was further reduced from 6,427.8 pg/mL (HD 1) to 5,040.73 pg/mL (HD 3), the patient's consciousness had deteriorated further to GCS score 9 and there was no change in serum viral load (Figure 1).

A male patient who had recovered from SFTS in July 2016 agreed to donate plasma, and on HD 4, we performed the first convalescent plasma therapy. Approximately 500 mL of plasma (13% of the donor's blood) was collected using a Cobe spectra, and donor plasma was administered to the patient over a 4-hour infusion period. At the time of donation, the donor's indirect immunofluorescence antibody assay (IFA) SFTSV immunoglobulin G (IgG) titer which was detected as described previously⁷ was 1:640, whereas SFTSV immunoglobulin M and IgG were undetectable in the patient. On HD 5, quantitative reverse transcription polymerase chain reaction (RT-PCR) of serum SFTSV revealed that the viral load of the patient had not changed significantly (3.53 log copies/ μ L). He became comatose (GCS score 8) with persistent thrombocytopenia and leukopenia, and his oxygen demand increased because of accompanying pneumonia and required intubation and mechanical ventilation; he was therefore transferred to an intensive care unit. The SFTSV IgG titer was 1:80 after the first convalescent plasma therapy (Figure 1). On HD 6, follow-up quantitative RT-PCR for serum SFTSV revealed that viral load had decreased to 2.73 log copies/ μ L, but on HD 7, acute renal failure had progressed and ribavirin was discontinued. On

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FIGURE 1. Changes in viral RNA load, and IP-10, IFN- α , and IgG immunofluorescence antibody assay (IFA) titers with time. CSF = cerebrospinal fluid; SFTSV = severe fever with thrombocytopenia syndrome virus. This figure appears in color at www.ajtmh.org.

HD 10, follow-up CSF examination detected no leukocytes; protein (68 mg/dL) and glucose (68 mg/dL; CSF/blood glucose ratio, 0.57) were normal and viral load was 0.08 log copies/ μ L, significantly lower than at admission. We performed a second convalescent plasma therapy on HD 13, with plasma from a woman who had recovered from SFTS in September 2016, because his mental status had not recovered. The second donor's and patient's titers of SFTSV IgG were both 1:640 before the second plasma therapy. On HD 14, the patient's SFTSV IgG titer was 1:1,280 and the serum SFTSV viral load was 0.10 log copies/ μ L. After that, virus RNA was no longer detectable by RT-PCR (Figure 1). On HD 17, his mental status had improved sufficiently for him to obey a simple request such as eye closure, and from HD 23, his platelet count was maintained above 100,000/ mm^3 without blood transfusion. By HD 37, his level of consciousness was sufficient to allow him to move his limbs by himself, and on HD 60, he was transferred to a general ward, and on HD 76, he was discharged after discontinuation of dialysis. Six months later, all the test results including renal function were normal and there were no neurologic sequelae.

CONCLUSIONS

As antiviral agents for SFTSV have not yet been developed and there is no effective treatment, conservative therapy including transfusion and renal replacement therapy are the main treatments currently available. It is known that specific cytokines and chemokines are elevated in fatal SFTS patients,⁸ and the cytokine storm involved in the inflammatory response during the acute phase of SFTS is associated with disease progression and severity.⁹ Therefore, because PE has been shown to lower cytokine levels in several viral

infections,^{10,11} we performed PE on this patient in the early course of the disease. Although serum viral load did not change significantly during PE, the levels of IP-10 and IFN- α decreased significantly (Figure 1 and Supplemental Figure 1). A recent article from South Korea reported that early implementation of PE within 7 days of symptom onset was independently associated with 30-day mortality (adjusted hazard ratio 0.05, P value = 0.02).² Because PE reduces cytokine levels rather than viral loads (Figure 1), we believe that PE to reduce initial cytokine levels might be more beneficial during the early course of disease than during the later course. Further studies are needed to determine whether early PE can prevent organ damage by lowering cytokines in animal models mimicking human SFTS infection, as well as in clinical studies.

The use of convalescent plasma therapy in some viral infectious diseases such as those involving coronavirus, influenza A (H1N1), A (H5N1), and Ebola virus has led to clinical improvement.^{12–15} Hung et al.¹⁵ showed that respiratory tract viral load, serum cytokine levels, and mortality were significantly lower in a convalescent plasma therapy group than in the control group in severe H1N1 2009-infected patients. Although a recent phase 2 randomized study of convalescent plasma therapy for severe influenza infections did not produce statistically significant effects, clinical status improved in the plasma therapy group and the procedure seemed safe and well tolerated.¹⁶ Based on these studies, we provided convalescent plasma therapy because there was no clinical improvement after early PE. We suppose that convalescent plasma therapy reduces viral loads via neutralizing antibodies that it may contain. It could therefore be considered a rescue or salvage therapy after PE. The patient's serum viral load decreased rapidly after the convalescent plasma therapy and

the clinical course improved (Figure 1), consistent with our findings in a previous SFTS case³ and with the observations of Zhou et al.¹² in influenza A (H5N1)-infected patients. It is worth noting that we did not have the data on viral load kinetics and IFA titers on HD 13 at the time we decided on the second convalescent plasma therapy. These data were obtained later from assays using the blood samples that have been collected. Because the patient's viral load was already low on HD 13, it is possible that the second convalescent plasma therapy did not actually contribute to his recovery.

In summary, our experience with this patient suggests that PE may play a role in quashing the cytokine storm, especially during the early course of disease, and that convalescent plasma therapy as a salvage therapy may reduce viral load. These treatments may be considered as forms of bridging therapy to be used in patients with severe SFTS while we wait for their humoral and cell-mediated immune responses to control the disease. However, this is a single case report and no controls not given these experimental therapies were included. Therefore, the outcome should be interpreted with caution because of the possibility of overtreatment of the SFTS because these treatments may have had nothing to do with the patient's recovery. Further studies of the mechanisms of SFTS-associated encephalopathy and ways to treat it are warranted.

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