

[CASE REPORT]

Plasma Exchange Did Not Reduce Viral Load in a Recovered Case of Severe Fever with Thrombocytopenia Syndrome

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Abstract:

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging tick-borne infectious disease caused by the SFTS virus (SFTSV). There is no specific treatment for SFTS, although several reports have indicated that plasma exchange (PE) can be an effective therapy for severe SFTS. However, whether or not PE can reduce the viral load is unclear. We herein report a woman with SFTS who had her SFTSV viral load measured just before and after PE. While the patient recovered, there was no significant difference in the SFTSV viral load after PE. Our results confirmed that PE itself does not reduce the SFTSV viral load.

Key words: severe fever with thrombocytopenia syndrome, viral load, plasma exchange, cytokine

(Intern Med 61: 253-256, 2022)

(DOI: 10.2169/internalmedicine.7075-21)

Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging tick-borne infectious disease caused by the SFTS virus (SFTSV) (currently *Dabie bandavirus*, belonging to the *Bandavirus* genus) (1). SFTSV is a spherically structured virus of approximately 100 nm in diameter (1). SFTS is endemic to East Asian countries, such as China, South Korea, and Japan. SFTS patients with neuropsychiatric symptoms or multiple organ dysfunction sometimes have a fatal course (2, 3).

Thus far, no specific treatment has been developed for SFTS, although several reports have indicated that plasma exchange (PE) can be an effective therapy for severe cases (4, 5). While double-filtration plasmapheresis of with average pore diameter of 30 nm can eliminate viruses such as hepatitis C (6), standard PE cannot eliminate viruses due to its pore size being larger than viruses. However, interestingly, previous report from South Korea have shown that SFTSV viral loads decreased after PE (5). Although viral loads are associated with disease severity and outcome, whether or not PE can directly decrease the viral load remains controversial (5, 7, 8).

We herein report a patient with SFTS who eventually recovered from a severe condition after PE, with SFTSV viral load measurements obtained immediately before and after PE.

Case Report

A 71-year-old woman with a fever, fatigue, and disturbed consciousness was brought to a hospital on day 4 after the disease onset. She reported no vomiting, diarrhea, or abdominal pain. She was engaged in agriculture and had no remarkable medical history nor any history of tick bites. She kept three dogs as domestic animals, but they were not ill.

Laboratory findings revealed thrombocytopenia (platelet count of $4.8 \times 10^3/\mu\text{L}$). On day 7 after the disease onset, SFTS infection was confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR), and she was transferred to our hospital. Her vital signs at this time were as follows: temperature of 37.2 °C, regular pulse of 72 bpm, blood pressure of 124/66 mmHg, oxygen saturation of 97% on 2 L/min oxygen, and disturbed consciousness [Glasgow coma scale (GCS) score 14 points, E3V5M6]. The auscultation of heart sounds was normal without murmur. Lung sounds and an abdominal examination were normal. She did

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Received: January 12, 2021; Accepted: June 3, 2021; Advance Publication by J-STAGE: July 30, 2021

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Table. Laboratory Data on Admission.

Day after the onset	4	5	6	7	8	9	10	11	12	13	14	15
WBC count (μL)	1,940	1,660	690	1,020	2,000	7,070	15,010	21,790	12,980	9,070	7,200	5,920
Platelet count ($\times 10^4/\mu\text{L}$)	14.5	9.9	8.2	5.0	3.9	5.1	4.8	7.9	13.9	21.8	27.8	36.7
Hemoglobin (g/dL)	14.4	14.4	15.4	13.6	13.1	11.8	11.6	11.6	11.3	11.3	10.0	9.8
Hematocrit (%)	43.0	42.7	46.2	40.0	38.2	35.0	34.5	34.2	32.7	32.8	29.2	29.6
ALT (IU/L)	63	56	91	97	51	41	40	45	46	48	51	58
AST (IU/L)	156	180	282	356	222	142	126	119	102	84	78	82
LDH (IU/L)	562	NA	1,139	1,654	1,141	737	591	571	439	418	384	421
CK (IU/L)	417	NA	558	583	713	592	393	236	180	135	86	78
Cre (mg/dL)	0.98	NA	0.67	0.50	0.47	0.41	0.40	0.36	0.37	0.39	0.40	0.42
C-reactive protein (mg/dL)	0.38	0.43	0.36	0.17	0.42	NA	0.99	1.17	1.58	1.01	0.57	0.44
APTT(s)	47.8	NA	52.6	81.9	46.4	NA	35.1	31.9	28.4	28.5	26.5	NA
PT-INR	1.08	NA	0.98	0.96	0.89	NA	0.89	0.89	0.95	0.96	0.97	NA

ALT: alanine aminotransferase, AST: aspartate aminotransferase LDH: lactate dehydrogenase, CK: creatine phosphokinase, Cre: creatinine, APTT: activated partial thromboplastin time, PT-INR: prothrombin time international normalized ratio, NA: not analyzed

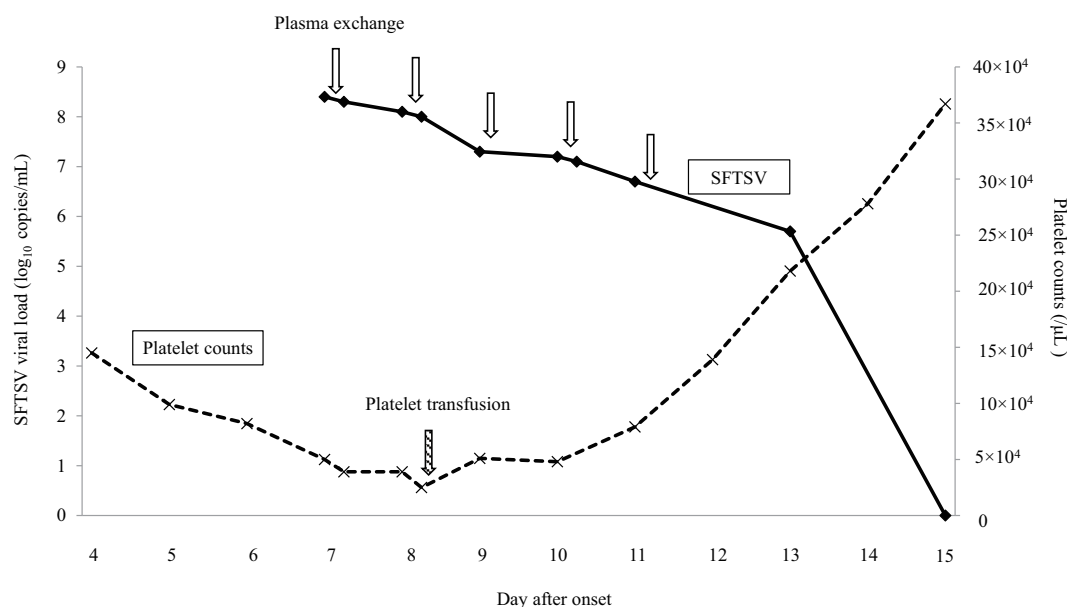


Figure. Changes in SFTSV viral loads and platelet counts during the patient's clinical course. White arrows indicate the timing of plasma exchange. The black arrow indicates the timing of platelet transfusion. SFTSV: severe fever with thrombocytopenia syndrome virus

not exhibit a skin rash or eschar. Lymph nodes were not palpable. Laboratory tests showed leukopenia [white blood cell (WBC) count of $1,020/\mu\text{L}$], thrombocytopenia (platelet count of $5.0 \times 10^4/\mu\text{L}$), and elevated serum levels of alanine aminotransferase (ALT) of 97 IU/L, aspartate aminotransferase (AST) of 356 IU/L, lactate dehydrogenase (LDH) of 1,654 IU/L, and creatine phosphokinase (CK) of 583 IU/L (Table). Serum creatinine (Cre) levels were normal (0.5 mg/dL). Other laboratory data included an activated partial thromboplastin time (aPTT) of 81.9 seconds, prothrombin time international normalized ratio of 0.96, D-dimer of 18.3 mg/L, and C-reactive protein level of 0.17 mg/dL.

Chest radiography showed no active lung lesions. On the day of admission to our hospital, PE using the Plasmaflo OP-05w (Asahi Kasei Medical, Tokyo, Japan) was started

and repeated for 5 days because her consciousness and laboratory findings were suggestive of severe disease. Neither corticosteroid nor ribavirin were used.

To clarify the SFTSV reduction effect by PE, we measured the SFTSV viral load using RT-PCR just before starting PE and just after ending PE. At the first PE session, the SFTSV loads before and after PE were 8.36 log copies/mL and 8.26 log copies/mL, respectively (Figure). For neutropenia, granulocyte-colony stimulating factor was administered for 3 days. On day 2 of hospitalization (day 8 after the onset), the WBC counts and AST, ALT, and LDH levels were slightly improved (Table). However, her consciousness deteriorated, and the platelet count decreased. At the second PE session, the SFTSV viral loads before and after PE were 8.09 log copies/mL and 7.99 log copies/mL, respectively.

Her platelet count further decreased to $2.5 \times 10^4/\mu\text{L}$ after the second PE session, and then she received a platelet transfusion.

Her GCS score was 10 points (E3V3M4) on day 5 of hospitalization (day 11 after the onset). To exclude the possibility of meningitis, lumbar puncture was performed, and an analysis revealed no pleocytosis (WBC count $6/\mu\text{L}$; 17% neutrophils) and normal levels of protein (80.7 mg/dL) and glucose [100 mg/dL; ratio of glucose concentration in the cerebrospinal fluid (CSF) to that in serum, 0.54]. No bacteria, viruses, or fungi were isolated from the CSF. Brain magnetic resonance imaging did not show acute lesions such as stroke or hemorrhaging. Furthermore, chest radiography showed consolidation in the right lung field. Considering the probability of superimposed bacterial infection, meropenem as empirical therapy was initiated. On day 9 of hospitalization (day 15 after the onset), the right lung consolidation had almost disappeared, and the patient's consciousness had improved. At that time, the SFTSV viral load was undetectable. The patient was finally discharged on day 19 of hospitalization (day 25 after the onset).

Discussion

A recent nationwide study in Japan showed that the mortality rate of SFTS is 27% (2, 9). Liu et al. showed that some clinical signs, including neurological manifestations, skin bleeding, and multiple organ dysfunction, predict fatal cases of SFTS (3). In addition, some laboratory data, including AST, CK, LDH, blood urea nitrogen (BUN), Cre, and APTT, are associated with a poor outcome (3, 10-12). The present patient had neuropsychiatric manifestations, prolonged aPTT, and elevated levels of ALT, AST, LDH, and CK, which suggested a severe condition and poor outcome. In addition to these markers, Yang et al. reported that the viral load was an independent predictor and that a viral load $> 10^7$ copies/mL indicates a severe disease outcome (13). Kwon et al. reported a significant difference in the plasma viral RNA level at admission between survivors and non-survivors [3.70 ± 1.03 log copies/ μL (6.7 log copies/mL) vs. 6.51 log copies/ μL (9.5 log copies/mL), respectively] (14). These findings support the notion that a high viral load is associated with fatality. Our case can be considered to have had a high viral load (approximately 8 log copies/mL), which also suggests a severe case, although the use of RT-PCR may be different from the PCR methodology applied in other cases.

Although there is no specific treatment for SFTS, PE has been performed for severe cases (4). However, the kinetics of the SFTSV viral load throughout PE have not been elucidated. Several reports examined the changes in viral loads and serum cytokine levels following PE (4, 5, 7). Yoo et al. measured SFTSV viral loads within 48 hours before PE using the COBE Spectra Apheresis System and compared the findings with those within 48 hours after PE (5). They concluded that the SFTSV viral load decreased after PE; there-

fore, the PE-induced reduction in viral loads is a potential treatment for patients with severe SFTSV infection. However, whether the decreased viral load can be attributed to PE or is a spontaneous decrease is unclear, as the blood collection did not occur immediately after PE. Choi et al. reported that levels of plasma cytokines, such as interferon-alpha and interferon-gamma inducible protein-10, were decreased after PE, whereas the viral load was not changed (7). In the present case, the SFTSV viral load was measured just before and after PE, but there was no significant difference in the viral loads after PE despite the patient's recovery. Our results confirmed that PE did not reduce the SFTSV viral load. We believe that this result may be due to the pore size of PE being larger than the virus diameter (300 nm for PE vs. 100 nm for SFTSV). A smaller pore size, such as double-filtration plasmapheresis, which has an average pore of 30 nm, would be able to eliminate the virus (6). Unfortunately, cytokine levels could not be measured in our case; however, PE may be involved in eliminating inflammatory cytokines. Alternatively, our patient may have recovered spontaneously through self-remission. Further studies are required to elucidate changes in cytokines and viral loads before and after PE in cases of SFTSV infection.

In conclusion, this case suggests that PE may be an effective treatment for severe cases of SFTS; however, its mechanism of action does not depend on a reduction in the SFTSV viral load. A further investigation is necessary to elucidate the mechanism underlying PE for SFTS patients.

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

References

- Saijo M. Pathophysiology of severe fever with thrombocytopenia syndrome and development of specific antiviral therapy. *J Infect Chemother* **24**: 773-781, 2018.
- Wang L, Zou Z, Hou C, Liu X, Jiang F, Yu H. Score risk model for predicting severe fever with thrombocytopenia syndrome mortality. *BMC Infect Dis* **17**: 42, 2017.
- Liu J, Fu H, Sun D, et al. Analysis of the laboratory indexes and risk factors in 189 cases of severe fever with thrombocytopenia syndrome. *Medicine (Baltimore)* **99**: e18727, 2020.
- Park I, Kim HI, Kwon KT. Two treatment cases of severe fever and thrombocytopenia syndrome with oral ribavirin and plasma exchange. *Infect Chemother* **49**: 72-77, 2017.
- Yoo JR, Kim SH, Kim YR, Lee KH, Oh WS, Heo ST. Application of therapeutic plasma exchange in patients having severe fever with thrombocytopenia syndrome. *Korean J Intern Med* **34**: 902-909, 2019.
- Ishikawa T, Abe S, Kojima Y, et al. Prediction of a sustained viral response in chronic hepatitis C patients who undergo induction therapy with double filtration plasmapheresis plus interferon-beta/ribavirin. *Exp Ther Med* **9**: 1646-1650, 2015.
- Choi S, Kim MC, Kwon JS, Kim JY, Lee KH, Kim SH. 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. *Am J Trop Med Hyg* **99**: 1466-1468, 2018.

8. Nakamura S, Iwanaga N, Hara S, et al. Viral load and inflammatory cytokine dynamics associated with the prognosis of severe fever with thrombocytopenia syndrome virus infection: an autopsy case. *J Infect Chemother* **25**: 480-484, 2019.
9. Kobayashi Y, Kato H, Yamagishi T, et al. Severe fever with thrombocytopenia syndrome, Japan, 2013-2017. *Emerg Infect Dis* **26**: 692-699, 2020.
10. Kato H, Yamagishi T, Shimada T, et al. Epidemiological and clinical features of severe fever with thrombocytopenia syndrome in Japan, 2013-2014. *PLoS One* **11**: e0165207, 2016.
11. Jia B, Yan X, Chen Y, et al. A scoring model for predicting prognosis of patients with severe fever with thrombocytopenia syndrome. *PLoS Negl Trop Dis* **11**: e0005909, 2017.
12. Chen Y, Jia B, Liu Y, Huang R, Chen J, Wu C. Risk factors associated with fatality of severe fever with thrombocytopenia syndrome: a meta-analysis. *Oncotarget* **8**: 89119-89129, 2017.
13. Yang ZD, Hu JG, Lu QB, et al. The prospective evaluation of viral loads in patients with severe fever with thrombocytopenia syndrome. *J Clin Virol* **78**: 123-128, 2016.
14. Kwon JS, Kim MC, Kim JY, et al. Kinetics of viral load and cytokines in severe fever with thrombocytopenia syndrome. *J Clin Virol* **101**: 57-62, 2018.

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Intern Med 61: 253-256, 2022