J Infect Chemother xxx (2017) 1–6

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Case Report

A patient with severe fever with thrombocytopenia syndrome and hemophagocytic lymphohistiocytosis-associated involvement of the central nervous system

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ARTICLE INFO

Article history:
Received 30 August 2017
Received in revised form
24 September 2017
Accepted 19 October 2017
Available online xxx

Keywords:
Severe fever with thrombocytopenia syndrome
Hemophagocytic lymphohistiocytosis
Central nervous system involvement
Immunohistochemistry
Autopsy

ABSTRACT

Severe fever with thrombocytopenia syndrome (SFTS), a severe infectious disease caused by novel bunyavirus, SFTS virus (SFTSV), is endemic to China, Korea, and Japan. Most SFTS patients show abnormalities in consciousness. Pathological findings in the central nervous system (CNS) of SFTS patients are not reported. A 53-year-old Japanese man was admitted to Uwajima City Hospital with an 8-day history of fever and diarrhea. Laboratory tests revealed leukopenia, thrombocytopenia, and liver enzyme elevation. He was diagnosed as having severe fever with thrombocytopenia syndrome (SFTS) following detection of the SFTSV genome in his blood. Bone marrow aspiration revealed hemophagocytic lymphohistiocytosis. He suffered progressive CNS disturbance and died on day 13 from onset of first symptoms. The SFTSV genome load in blood and levels of certain cytokines increased over the disease course. Necrotizing lymphadenitis with systemic lymphoid tissues positive for nucleocapsid protein (NP) of SFTSV was revealed by immunohistochemical (IHC) analysis. SFTSV-NP-positive immunoblasts were detected in all organs examined, including the CNS, and in the vascular lumina of each organ. Parenchymal cells of all organs examined were negative for SFTSV-NP on IHC analysis. Microscopic examination of the pons showed focal neuronal cell degeneration with hemosiderin-laden macrophages around extended microvessels with perivascular inflammatory cell infiltration and intravascular fibrin deposition. Autopsy confirmed this patient with SFTS was positive for systemic hemophagocytic lymphohistiocytosis including in the CNS. This patient's neurological abnormalities may have been caused by both functional and organic abnormalities. These novel findings provide important insights into the pathophysiology of SFTS.

Abbreviations: CFS, cerebrospinal fluid; CNS, central nervous system; CNS-HLH, CNS involvement of HLH; HLH, hemophagocytic lymphohistiocytosis; IHC, immunohistochemical/immunohistochemistry; NP, nucleocapsid protein; RT-PCR, reverse-transcription polymerase chain reaction; SFTS, severe fever with thrombocytopenia syndrome; SFTSV, SFTS virus.

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https://doi.org/10.1016/j.jiac.2017.10.016
1341-321X/

1. Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is caused by a bunyavirus, SFTS virus (SFTSV), which belongs to the Family *Bunyaviridae*, Genus *Phlebovirus* [1]. SFTS was identified to be endemic to Japan in 2013 [2]. In the severe cases of SFTS, central nervous system (CNS) disturbance and hemophagocytic lymphohistiocytosis (HLH) generally appear, resulting in a poor prognosis [2,3]. The pathogenesis of CNS involvement associated with SFTSV infection remains obscure. An epidemiologic study of SFTS in 538 hospitalized patients with SFTS revealed that 19.1% had developed clinically diagnosed encephalitis with a fatality rate of 44.7%, although the definition of "encephalitis" was unclear [4]. SFTSV was isolated from the CSF sample of the only one surviving patient [4]. There were two reports in which pathological examination of the CNS was performed in patients with SFTS [5,6]. In these reports, microscopic examination of the brain revealed neither histopathological changes nor definitive evidence that CNS parenchymal cells were infected with SFTSV.

We report a patient who died of SFTS with rapidly progressive CNS disturbance and was examined pathologically including with immunohistochemical (IHC) analyses.

2. Case presentation

In July 2014, a 53-year-old male farmer who lived in a hilly rural area in Kochi prefecture, Japan, developed fever and diarrhea. He had been healthy without significant underlining illnesses, save for habitual alcohol consumption. He remained symptomatic and was transferred to Uwajima City Hospital on day 8, with day 1 considered the day on which symptoms first appeared. Laboratory tests performed at a local hospital revealed leukopenia, thrombocytopenia, and elevated levels of liver enzymes.

On admission, he was alert and well oriented. His body temperature was 39.3 °C and pulse rate, blood pressure, respiration rate, and oxygen saturation were 86 bpm with regular rhythm, 125/91 mmHg, 34 breaths/min, and 98% (ambient air), respectively. No tick bite wounds were observed. Laboratory tests yielded the following results: leukopenia, thrombocytopenia, liver and kidney dysfunctions, and coagulopathy (Table 1). The changes in these parameters from admission to discharge are also shown and indicate that all of the parameters worsened as the disease course progressed to death (Table 1).

A non-contrast whole-body computed tomography scan revealed hepatosplenomegaly and swollen axillary and inguinal lymph nodes. Cefotaxime and minocycline were administered empirically. The serum ferritin level on day 9 was elevated at 50,889 ng/mL. The patient exhibited limb tremor and slurred speech, and then his condition worsened with progressive disturbance of consciousness from day 10. Bone marrow aspiration revealed hemophagocytosis (Fig. 1). The patient met 5 of the 8 diagnostic criteria of the HLH-2004 guidelines [7], including fever, cytopenia, increased levels of liver enzymes and serum ferritin, and bone marrow hemophagocytosis, and was therefore diagnosed as having HLH. Methylprednisolone was therefore started at the dose of 1000 mg/day.

A serum sample collected on day 8 was confirmed to be SFTSV genome-positive by reverse-transcription polymerase chain reaction (RT-PCR) with primer sets for the SFTSV [8,9]. On day 9, his consciousness was impaired (Glasgow coma scale score 5: E1, V2, M2), and oral hemorrhage and melena became evident. Laboratory tests indicated worsening of liver damage, a markedly elevated serum ferritin level, and coagulation abnormality. He died on day 13. The patient's serum was tested for SFTSV genome quantification with quantitative RT-PCR [8], which revealed that the SFTSV-RNA copy number on day 8 was 1.46×10^6 copies/mL, and then increased thereafter, eventually reaching 1.41×10^9 copies/mL (Table 2).

Table 1
Laboratory findings of the patient over the time course of SFTS from day 8 to day 12.

Laboratory findings	Normal range	Days after onset of illness				
		8	9	10	11	12
WBC ($\times 10^9$/L)	4.0–9.0	0.57	0.93	0.65	3.01	5.56
Hemoglobin (g/dL)	12–16 (men)	15.9	15.8	15.4	15.3	14.3
Platelets ($\times 10^9$/L)	150–450	23	22	9	29	60
AST (IU/L)	13–33	785	785	1258	1568	1585
ALT (IU/L)	8–42	218	224	297	350	327
LDH (IU/L)	100–200	1139	1603	2195	3516	5263
Amylase (IU/L)	33–120	235	NA	357	500	908
Lipase (IU/L)	13–49	NA	NA	730	981	2533
CRP (mg/dL)	0–0.3	0.52	0.37	0.39	0.46	0.32
BUN (mg/dL)	5–23	37	41	46	53	60
Creatinine (mg/dL)	0.36–1.06	1.33	1.87	2.21	2.15	2.78
CK (IU/L)	62–287	2357	3665	5859	8244	12565
CK-MB (IU/L)	0–24	NA	NA	131	NA	NA
Ferritin (ng/mL)	122–496	NA	50889	61560	87101	>100000
Sodium (mmol/L)	135–149	127	134	135	137	141
PT/INR	0.8–1.3	1.06	0.91	0.96	NA	1
aPTT (s)	24–36	39.8	NA	NA	NA	49.5
FDP (μg/mL)	0–5	41.3	NA	23.5	NA	11.9
D-dimer (μg/mL)	0–1	7.8	8.5	6.4	NA	3.7
Urine protein (mg/day)		NA	NA	NA	5024.3	6150.3

SFTS: severe fever with thrombocytopenia syndrome, WBC: white blood cells, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, NA: not available, CRP: C-reactive protein, BUN: blood urea nitrogen, CK: creatine kinase, PT/INR: prothrombin time/international normalized ratio, aPTT: activated partial thromboplastin time, FDP: fibrin/fibrinogen degradation products.

Serially collected serum samples were tested for 30 cytokines and chemokines by use of the Luminex™ Cytokine Human Magnetic 30-Plex Panel (Thermo Fisher Scientific K.K., Yokohama, Japan). High levels of IP-10, IFN-γ, IL-8, and MCP-1 were found in the late stage of the disease. RANTES was not elevated before clinical deterioration (Table 2).

3. Pathological findings

A postmortem examination including autopsy was performed with the informed consent of the patient's family. The CNS was included in the organs for pathological examination to investigate the mechanism behind the neurological symptoms and rapid deterioration in consciousness. The study was conducted in accordance with the guiding principles of the Declaration of Helsinki.

Autopsy was performed 1.5 hours after death. Subcutaneous hemorrhage was observed in the bilateral flanks and limbs. The lungs were mildly edematous and congested and weighed 270 g (left) and 300 g (right). In some alveolar spaces, edema fluid with extravasated red blood cells and focal hyaline membrane formations were observed, suggesting diffuse alveolar damage. The liver weighed 1590 g. Microscopic examination showed mild interlobular inflammatory cell infiltration with hepatocyte degeneration and congestion around the central venules. Hemophagocytosis was evident in the bone marrow, spleen, and systemic lymph nodes. Histologic features were those of necrotizing lymphadenitis as reported previously [2,5,6,10]. The basic lymph nodal architecture was lost and replaced by massive necrosis with cell debris. The necrotic area was surrounded by mononuclear cell infiltration including lymphocytes, immunoblasts, and histiocytes.

The brain was examined for gross pathological changes after fixation in 10% buffered formalin for 4 weeks. The fixed brain was then sliced into standard coronal plane sections. Pigmented lesions

Please cite this article in press as: Masahiko K, et al., A patient with severe fever with thrombocytopenia syndrome and hemophagocytic lymphohistiocytosis-associated involvement of the central nervous system, J Infect Chemother (2017), https://doi.org/10.1016/j.jiac.2017.10.016