

Case Report

Severe fever with thrombocytopenia syndrome complicated with polyuria: report of a case and review of literature

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Abstract: Severe fever with thrombocytopenia syndrome (SFTS) is a fatal viral infection that is an important health problem in China, Japan, and Korea. SFTS is characterized by gastrointestinal symptoms, fever, leukopenia, thrombocytopenia, and multi-organ dysfunction. To our knowledge, patient with SFTS complicated with polyuria has never been reported and SFTS related-kidney involvement was remained largely uninvestigated. We present a case of SFTS complicated with fever, polyuria, increased Cystatin C (CysC) and urinary β_2 -microglobulin (β_2 -M) level, and a low electrolyte level.

Keywords: Severe fever with thrombocytopenia syndrome, polyuria, renal function, electrolyte disturbance

Introduction

A novel bunyavirus named severe fever with thrombocytopenia syndrome bunyavirus (SFTSV) was identified as the etiological cause of severe fever with thrombocytopenia syndrome (SFTS) reported in central China in 2009 [1]. In the past few years, cases of SFTS have also been identified and viruses were isolated from the sera samples of SFTS patients in Japan and Korea [2, 3]. With improved diagnosis and treatment, the fatality rate of SFTS has been reduced to 10-15% [4].

SFTSV infection was accompanied by gastrointestinal symptoms, myalgia, fever, lymphadenopathy, throat congestion, and multi-organ dysfunction with an initial reported fatality rate of up to 12-30% [1, 5]. A confirmed case with SFTS that had no fever during the course of the disease was reported in 2014 [6]. Laboratory findings of hospitalized cases with laboratory-confirmed SFTS on admission include decre-

ased leukocyte and platelet levels; increased aspartate aminotransferase (AST), alanineaminotransferase (ALT), lactate dehydrogenase (LDH), and creatine kinase (CK) levels; and an abnormality of serum K⁺, Na⁺, Cl⁻, and Ca⁺⁺ [1, 5, 7]. To the best of our knowledge, this is the first report of SFTS complicated with polyuria and a low electrolyte level. The incidence of SFTS with renal dysfunction was reported low and SFTS related-kidney involvement was remained largely uninvestigated. We also review the literature related SFTS related-kidney involvement.

Case description

A 60-year-old man was admitted to our hospital because of a sudden onset of fever (40.1°C) and fatigue starting 6 days before admission, and polyuria (urinating about 300-400 mL every 2 hours) for 1 days. He denied a history of a tick bite before onset of illness. He mostly worked in the fields in his village before her illness onset. There were animals in the fields,

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Table 1. Clinical features of the patient with SFTS

| | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 | Day 11 | Day 13 | Day 15 | Normal range |
|---------------------------------|-------|-------|-------|-------|--------|--------|--------|--------|--------------|
| <i>General data</i> | | | | | | | | | |
| 24-h urine volume (mL) | 4600 | 4580 | 4300 | 4180 | 3600 | 3480 | 3380 | 32800 | 400-2000 |
| MAP* (mmHg) | 70 | 72 | 73.33 | 74.33 | 80 | 83.67 | 86.67 | 86.67 | 70-105 |
| <i>Laboratory findings</i> | | | | | | | | | |
| WBC ($\times 10^9/L$) | 0.72 | 1.37 | 5.79 | 5.34 | 4.63 | 4.20 | 4.30 | 4.18 | 4-10 |
| Platelet ($\times 10^9/L$) | 45 | 40 | 48 | 60 | 79 | 94 | 130 | 223 | 100-300 |
| Serum K ⁺ (mmol/L) | 2.9 | 3.1 | 3.5 | N/A | 3.5 | 3.3 | 3.5 | N/A | 3.5-4.5 |
| Serum Na ⁺ (mmol/L) | 129 | 131 | 137.7 | N/A | 144.2 | 140.5 | 139.4 | 140 | 135-155 |
| Serum Cl ⁻ (mmol/L) | 90 | 90 | 100 | N/A | 104 | 103 | 102 | 101 | 95-105 |
| Serum Ca ⁺⁺ (mmol/L) | 1.59 | 1.75 | 1.90 | N/A | 2.06 | 2.11 | 2.10 | 2.2 | 2.0-2.7 |
| Serum Mg ⁺⁺ (mmol/L) | N/A | N/A | 0.56 | N/A | 0.64 | N/A | 0.76 | 0.79 | 0.67-1.04 |
| Serum P (mmol/L) | N/A | N/A | 0.60 | N/A | 0.76 | N/A | 0.86 | 1.12 | 0.80-1.61 |
| CysC (mg/L) | N/A | 1.98 | N/A | N/A | N/A | 1.28 | N/A | N/A | 0.5-1.15 |
| Creatinine (umol/L) | 53 | 54 | 51 | 76 | 55 | 40 | N/A | 56 | 40-97 |
| BUN (mmol/L) | 4.0 | 4 | 2.2 | 2.6 | N/A | 1.4 | N/A | N/A | 1.40-7.80 |
| ALT (U/L) | N/A | 48 | 43 | 38 | 47 | 68 | 85 | N/A | 0-40 |
| AST (U/L) | N/A | 92 | 108 | 89 | 95 | 91 | 82 | N/A | 0-40 |
| CK (U/L) | N/A | 243 | 206 | 198 | 125 | 88 | 66 | N/A | 0-170 |
| Proteinuria | 1+ | 1+ | 2+ | 2+ | N/A | N/A | N/A | - | - |
| Hematuria | 1+ | 1+ | 1+ | - | N/A | N/A | N/A | - | - |
| Urinary β_2 -M (mg/L) | N/A | 1.88 | N/A | N/A | N/A | N/A | 0.62 | N/A | <0.5 |

*MAP, mean arterial pressure; WBC, white blood cell count; BUN, blood urea nitrogen; N/A, not applicable.

including cattle, goats, and voles, and ticks were often found on these animals. None of his family members had similar symptoms before his illness onset. He was initially diagnosed with influenza and was treated for 6 days with levofloxacin and dexamethasone (for fever reduction) at the village clinic before admission. However, there was no improvement in his symptoms.

Physical examination showed a high fever of 39.4°C, a pulse of 102 beats/min and blood pressure of 94/58 mmHg. Left axillary lymphadenopathy was found. Electrocardiogram and non-contrast high-resolution computed tomography of the chest and abdomen showed no abnormal findings. Routine blood tests showed leukopenia and thrombocytopenia. Clinical laboratory values showed increased levels of liver-associated enzymes, serum Cystatin C (CysC) and urinary β_2 -microglobulin (β_2 -M), a decreased level of electrolytes, and proteinuria (**Table 1**), indicating impaired liver, heart and kidney. Blood cultures were negative as were serological tests for human immunodeficiency virus (HIV), cytomegalovirus, the Epstein-Barr virus,

adenovirus, respiratory syncytial virus, Mycoplasma, Chlamydia, Coxiella, Bartonella, Strongyloides, spotted fever group (rickettsiae), filariasis, hemorrhagic fever with renal syndrome (HFRS) and Toxoplasma. Thus, fluid resuscitation and supportive therapy were initiated.

He received minocycline capsules, ribavirin, fluid resuscitation and supportive therapy. Intravenous compound glycyrrhizin and reduced glutathione were administered to protect the liver and reduce the transaminase levels. A hypodermic injection of recombinant human granulocyte colony stimulating factor (200 mg) was administered to increase the white blood cell level. He recovered gradually and serum electrolytes gradually became normal. His temperature returned to normal on the ninth day. On the fifth day, he was discharged from the hospital with mild polyuria. Urine volume became normal after 2 months of follow-up.

To investigate the viral pathogen that caused the patient's disease, a serum sample was collected on the first day of admission and used

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Figure 1. The phylogenetic tree of the virus strain (QD49).



for laboratory tests. Total RNAs were purified and complementary DNAs were generated by reverse transcript polymerase chain reaction (RT-PCR) according to the manufacturer's instructions (Invitrogen). Fragments of the S and L segments of SFTSV RNAs were detected by nested polymerase chain reaction as described previously (Shu, et al. In submission) and then sequenced, which confirmed the case as an SFTS patient. The viral load was also quantified by quantitative RT-PCR, as described before [8], which equals $2.1 \pm 1.2 \times 10^8$ copies/mL in the serum sample. Unfortunately, the attempt to isolate this virus failed. Viral RNAs could not be detected in the supernatant after four blind passages (data not shown). However, the partial sequence of the S segment of QD49 (1-1250 nt) was amplified and sequenced (Genbank accession number: KU315174). The phylogenetic tree was constructed by Mega (version 5.0), showing that this strain (QD49)

was close to other strains from the Hubei and Shandong Provinces (Figure 1).

Discussion

The patient has normal serum creatinine and increased serum CysC, we speculated he was in the early stage of decreased glomerular filtration rate (GFR). Because meta-analysis revealed that serum CysC is clearly superior to serum creatinine as a marker of GFR measured [9]. Most serum β_2 -M is filtered by the glomeruli and 99.9% reabsorbed by proximal tubular cells. Therefore, urinary β_2 -M been considered an ideal biomarker for proximal tubular function. The patient has a high fever, increased urine output, serum CysC and urinary β_2 -M level, and decreased electrolytes, we speculate that the patient might have decreased GFR and the disorder of renal tubule reabsorption. The latter was major which results in the loss of water and many electrolytes

in the urine. Maybe like many mild cases of HFRS patients without abnormality of renal function, oliguria stage, directly into diuretic stage.

There are no previous reports concerning polyuria in SFTS patients. Because SFTS patients usually have fever and lose large amounts of water from the body surface, respiratory tract and gastrointestinal tract, they should be relatively less urine output. It is abnormal for them having polyuria. Maybe polyuria is mild which didn't attract enough attention. Moreover, the character of SFTS patients involved kidney were not elucidated. A systematic search of the following electronic biomedical databases from 2007 to January 1, 2016 was performed: PubMed, Embase, China Academic Journals Full-text Database, Wanfang Database. Only studies recording data on nephritic laboratory parameters (proteinuria or renal function) were included. Cases which were not diagnosed

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Table 2. Laboratory parameters related kidney, clinical factors associated with output and input on admission

| Publication | Fever | Anorexia | Nausea | Vomiting | Diarrhea | Proteinuria | Hematuria | Renal function impairment | Low sodium | Low potassium | Low chloride | Low calcium |
|-------------------------------|---------|----------|---------|----------|----------|-------------|-----------|---------------------------|------------|---------------|--------------|-------------|
| Yu XJ [1] | 81/81 | 61/81 | 56/81 | 38/81 | 34/81 | 36/43 | 27/46 | NA | NA | NA | NA | NA |
| Deng B [11] | 115/115 | 74/115 | 59/115 | 38/115 | 65/115 | 64/110 | 25/115 | 32/115 | 44/115 | 36/115 | 22/115 | 86/115 |
| Xu B [7] | 232/238 | 219/238 | 181/238 | 153/238 | 156/238 | 205/238 | NA | NA | 113/238 | NA | NA | 206/238 |
| Zhang YZ [12] | 33/33 | NA | 13/33 | 12/33 | 14/33 | 14/20 | 7/13 | 9/30 | NA | NA | NA | NA |
| Han L [13] | 22/22 | 18/22 | NA | 11/22 | 7/22 | 15/22 | 15/22 | 12/22 | NA | NA | NA | NA |
| Zhou L [14] | 68/68 | 68/68 | 48/68 | 36/68 | 36/68 | 64/68 | 41/68 | 4/68 | 23/68 | 29/68 | NA | 36/68 |
| Gai ZT [15] | 59/59 | 51/59 | 38/59 | 18/59 | 16/59 | 45/59 | 36/59 | NA | NA | NA | NA | NA |
| Weng Y [16] | 12/12 | NA | 8/12 | 8/12 | 11/12 | 12/12 | 12/12 | 0/12 | NA | NA | NA | 12/12 |
| Li S [17] | 5/5 | 5/5 | 4/5 | 4/5 | 3/5 | 5/5 | 5/5 | 2/5 | 5/5 | 5/5 | NA | NA |
| Guo FL [18] | 7/7 | 5/7 | 5/7 | 1/7 | 6/7 | 6/7 | 3/7 | 2/7 | 7/7 | 7/7 | 7/7 | 7/7 |
| Zhang ZP [19] | 12/12 | 10/12 | NA | NA | 2/12 | 6/12 | 5/12 | NA | NA | NA | NA | NA |
| Shen AH [20] | 6/6 | 6/6 | 4/6 | 2/6 | 5/6 | 4/6 | 4/6 | NA | NA | NA | NA | NA |
| Yuan C [21] | 253/253 | 235/253 | 205/253 | 106/253 | 76/253 | 243/253 | 221/253 | 58/253 | 46/253 | 42/253 | 14/253 | NA |
| Yu B [22] | 61/61 | NA | NA | NA | 19/61 | 41/48 | NA | NA | NA | NA | NA | NA |
| Case number/total case number | 966/972 | 752/866 | 621/877 | 427/899 | 450/972 | 760/903 | 401/618 | 119/512 | 238/686 | 119/448 | 43/375 | 347/440 |

NA: not available.

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according to the criteria set by the China CDC [10] or data with cases numbering <5 were also excluded. Laboratory parameters related kidney, clinical factors associated with output and input, level of blood electrolyte, were recorded [11-22] (Table 2).

The main data was fever (pooled rate 99.8%, 95% CI 99.4-100), followed by digestive tract symptom covering anorexia (pooled rate 86.5%, 95% CI 80.4-92.7), nausea (pooled rate 66.8%, 95% CI 58.7-74.9), vomiting (pooled rate 45.2%, 95% CI 36.2-54.2) and diarrhea (pooled rate 49.8%, 95% CI 38.7-60.8), and low level of blood electrolyte including low calcium (pooled rate 81.9%, 95% CI 69.3-94.5), low potassium (pooled rate 55.5%, 95% CI 27.3-83.6), low sodium (pooled rate 53.8%, 95% CI 32.8-74.8) and low chloride (pooled rate 39.6%, 95% CI 32-76). But disturbance of serum phosphate and magnesium didn't reported. SFTS related-kidney involvement was characterized by proteinuria (pooled rate 82.2%, 95% CI 75.6-88.8) and hematurias (pooled rate 63.5%, 95% CI 46.6-80.4), damaged renal function (pooled rate 22.8%, 95% CI 12.3-33.3) were relatively rare (mostly BUN which might be associated with gastrointestinal bleeding). Only Shen et al. reported that 5 of 6 SFTS patients had elevated serum CysC [20]. But the deaths have multiple organ failure [11].

The intake of majority of SFTS patients was reduced, and losing too much liquid from the body surface and the gastrointestinal tract. Kidney damage was mild and characterized by hematuria and proteinuria. SFTS patients were very prone to low electrolyte level. But there was no further report of kidney damage, including urine output and urinary β_2 -M level.

SFTSV sharing aspects of its molecular and cellular biology with all Bunyaviridae family members, they might have similar symptoms. Most SFTS patients had proteinuria and renal impairment is slight, some have low electrolyte concentration, and probably have similar haemorrhagic fever-like diuretic symptoms. The patient had proteinuria, polyuria, increased urinary β_2 -M level, and a low electrolyte level, we speculated he had dysfunction of proximal tubular reabsorption that led to the inability of the kidney to concentrate urine. But slight polyuria did not attract attention. Due to seri-

ous loss of water and electrolytes in the urine and peptic tract and failure to compensate for these losses in a timely manner, our patient suffered from a low blood pressure and low electrolyte level on admission.

Potassium, sodium, chloride, calcium, magnesium, and phosphate have many physiological functions: phosphate participates in cell synthesis, and calcium and phosphate are involved in blood coagulation, etc. Many patients with SFTS have concomitant multiple organ dysfunction, a blood coagulation disorder, and the phenomenon of bleeding at the end of the last stage of the clinical course. Severely low potassium, sodium, and phosphorus levels in those with a viral infection can cause an elevated CK level and rhabdomyolysis [23]. It was reported previously that the levels of CK increased in SFTS patients, and they suffered from muscle pain, muscle tremors, and even rhabdomyolysis [15]. Physicians can prevent further deterioration of the patient's condition through fluid resuscitation and timely electrolyte supplementation.

Current knowledge of SFTS is limited. No specific therapeutic strategy has been recommended in clinical practice. One study showed that in vitro experiments of ribavirin were effective for treating bunyavirus [24]. However, clinical studies found that outcome was not improved in the group of SFTS patients taking ribavirin compared with the control group not taking ribavirin [8], although the occurrence of anemia and hyperamylasemia was increased [25]. Recent study found that one of the risk factors associated with fatal outcome of patients with SFTS is a longer delay from illness onset to hospitalization [26, 27]. Detecting SFTS in patients early, and providing timely supportive and systematic treatment, including fluid resuscitation, and electrolyte and nutritional supplementation, are essential to prevent a low blood volume, and low potassium and sodium levels. Since serum electrolytes can be closely monitored and corrected, symptomatic and supportive treatment is critical for SFTS like epidemic hemorrhagic fever in the early stage [28].

Disclosure of conflict of interest

None.

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