Severe Fever with Thrombocytopenia Syndrome Mimicking Scrub Typhus: Three Case Reports

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Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease in South Korea with clinical features similar to those of scrub typhus. Infected patients with these two diseases usually visited the emergency department (ED) complaining of fever that was not responsive to treatment in a local clinic. Aggressive management of SFTS is required in order to prevent rapid progression and human-to-human transmission, thus rapid and accurate differential diagnosis of the two diseases in the ED is important. We reported three laboratory confirmed cases of SFTS during 2013-2014 in a single center, with fever, skin lesions, and history of outdoor activities in order to help in differential diagnosis between SFTS and scrub typhus in the ED.

Key Words: Severe fever with thrombocytopenia syndrome, Scrub typhus, Fever

Introduction

Severe fever with thrombocytopenia syndrome (SFTS) and scrub typhus share several similarities in clinical manifestations. They are both transmitted via tick or mite bites with present comparable clinical features such as fever, cutaneous symptoms, and cytopenia. Differential diagnosis between the two diseases is not simple. Whereas scrub typhus can be treated with antibiotics, SFTS currently has no known definitive treatment and is known for its high mortality rate. SFTS has also been reported to have human-to-human transmission. Therefore, it is important to understand characteristic clinical features associated with SFTS and scrub typhus for an early and accurate diagnosis in patients and to prevent spreading secondary infection, especially in emergency department (ED) where these febrile patients usually visited at first. Herein, we report our experiences with three patients visiting ED who had been initially suspected of scrub typhus but subsequently confirmed with SFTS. The study protocol was approved by the institutional review board (IRB No. 13-10-010).

Case Report

1. Case 1

In May 2013, a 73-year-old man presented with fever, diarrhea, myalgia and chilling persisting for a week to be transferred to our ED from local clinic. Four days prior to admission, the patient identified a tick embedded in the right flank and removed it. Clinical symptoms did not improve upon administration of doxycycline under a clinical suspicion of scrub typhus but rather rapidly worsened. Physical examination revealed a healing ulcer with peripheral erythema on the right flank at the insect-bite site (Fig. 1A). Initial laboratory results indicated thrombocytopenia (30,000/μL), leukopenia (1,500/μL), elevated levels of aspartate aminotransferase (AST) (392 IU/L), alanine aminotransferase (ALT) (136 IU/L), and lactate dehydrogenase (LDH) (136 IU/L), prolonged activated partial thromboplastin time (aPTT) (74 seconds), and microscopic hematuria. Serological examination for scrub typhus was negative, but SFTS virus (SFTSV) was identified from serum using real time-polymerase chain reaction (PCR). Despite continuous
blood transfusion, clinical condition and laboratory parameters declined. Upon transfer to intensive care unit, mechanical ventilation and continuous renal replacement therapy were applied. On the 6th hospital day, diffuse symmetric ecchymosis on forearms, knee, and foot were observed indicating disseminated intravascular coagulation (DIC). On the 8th hospital day, the patient died of multiple organ failure and massive hemorrhage.

2. Case 2

In October 2013, a 70-year-old man was referred to our ED due to thrombocytopenia along with persisting fever of 38°C, generalized myalgia, and chilling for ten days. Physical examination revealed a crusted erythematous ulcer on the lateral side of left knee accompanied with left inguinal lymphadenopathy (Fig. 1B). Initial laboratory results showed thrombocytopenia (58,000/μL), leukopenia (3,700/μL), elevated levels of AST (116 IU/L), ALT (64 IU/L), and LDH (858 IU/L), and prolonged aPTT (42 seconds). Even though doxycycline and cefepime were empirically used for clinical possibility of scrub typhus, an initial serologic test for tsutsugamushi indicated low titer (1:40), but serial tests showed no changes in the titer. Furthermore, SFTS viral RNA was detected from the patient’s serum. Conservative management was able to control fever and normalize laboratory parameters. On the 7th hospital day, the patient was discharged without other symptom complain.

3. Case 3

In June 2014, a 78-year-old woman was referred to our ED due to fever of 39°C persisting for two days and thrombocytopenia accompanied by anorexia, diarrhea, and a suspicious eschar-like skin lesion of tick bite on left buttock (Fig. 1C). Physical examination indicated multiple cutaneous eruptions on abdomen, back, and face. Initial laboratory results revealed thrombocytopenia (12,800/μL) and leukopenia (2,000/μL) along with elevated levels of AST (78 IU/L) and LDH (601 IU/L) and prolonged aPTT (42 seconds). Empirical antibiotics of cefepime and azithromycin were administered for neutropenia and clinical suspicion of scrub typhus, respectively, and microbiological identification was performed upon suspicion of SFTSV infection. On the 2nd hospital day, SFTSV was confirmed by polymerase chain reaction (PCR), and upon initiation of plasmapheresis for three days for SFTS infection, clinical symptoms and laboratory parameters continued to improve. After eight days of conservative treatment, the patient was discharged healthy.

Discussion

SFTS is a recently reported fatal tick-borne viral disease in some countries such as China, Korea, Japan and the USA with an average mortality rate of 10~15%7,8). Patients with SFTS require immediate symptomatic ther-

Table 1. Clinical features in differential diagnosis between severe fever with thrombocytopenia syndrome and scrub typhus.

<table>
<thead>
<tr>
<th>SFTS</th>
<th>Scrub typhus</th>
<th>Skin eruption</th>
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<tbody>
<tr>
<td>No specific skin rash</td>
<td>Ecchymosis, and purpura of extremities (&lt;7%)</td>
<td>Diffuse ill-defined, erythematous maculopapules on trunk and proximal extremities</td>
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<tr>
<td>Eschar</td>
<td>Rare (&lt;6%)</td>
<td>Present (50~70%)</td>
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<tr>
<td>Sustained fever (&gt;38°C), gastrointestinal symptoms (vomiting, nausea, diarrhea), leukopenia, thrombocytopenia, multiple organ failure, disseminated intravascular coagulation, central nervous system complications, and hematuria</td>
<td>Fever, peripheral lymphadenopathy, arthralgia/myalgia, headache, transitory leukopenia, transitory or rare thrombocytopenia, hepatic dysfunction, pneumonia, and pleurisy</td>
<td></td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>No</td>
<td>Resolution within 48 hours after oral admission of doxycycline</td>
</tr>
<tr>
<td>Therapeutic responses to doxycycline</td>
<td>1st and 2nd weeks after onset</td>
<td>None</td>
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<tr>
<td>Risky periods related to death</td>
<td></td>
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SFTS: sever fever with thrombocytopenia syndrome
apy and close monitoring in order to prevent severe complications such as multiple organ dysfunction, DIC, altered mental change, and shock. In first case, the patient had not been suspected of SFTS in an early disease course, proceeded to fulminant multiorgan failures and death without response to antibiotics and conservative managements. However, in second and third case, the patients were suspected of SFTS early enough to be fully recovered by conventional treatment.

Scrub typhus is rare happened secondary infection and does not need any protection when coming into contact with patient. On the other hand, SFTS was known to be usually infected by tick exposure, however, some articles reported about human-to-human transmission in cases of unprotected contact with blood and body fluid of patients. Recently, nosocomial transmission of SFTS in Korea was reported an ED is the place where emergency physicians have first contact with these febrile patients and had risk of exposure to their blood and body fluid without proper protective equipment.

Due to similar initial clinical manifestations between SFTS and scrub typhus, it is critical for emergency physicians to differentiate the two diseases in order for determining follow-up plans, such as hospitalization or

**Fig. 1.** Eschar-like skin lesions. (A) a healing ulcer with peripheral erythema on the right flank at the insect-bite site in case 1. (B) a crusted erythematous ulcer on the lateral side of left knee in case 2. (C) a crusted pinkish ulcer lesion on the left buttock area in case 3.
outpatient follow-up and treatment, and for prevention of person-to-person transmission. It was not easy for emergency physicians to distinguish between the two diseases. We reviewed previous literature and would like to share our experiences to provide differences between the diseases (Table 1). Firstly, all patients had a history of outdoor activities, and their occupations is famred. This history is not help a differential diagnosis to physicians, because tsutsugamushi disease is tick borne disease. Also tick bite history and skin lesion is similar. In terms of cutaneous manifestations, petechiae or skin rash was found in only 9% of SFTS patients, whereas rash and erythematous flushes were evident in 90% and 50%, respectively, in scrub typhus. In addition, eschar was found in less than 6% and 88% in SFTS and scrub typhus, respectively, and eschar in scrub typhus was associated with regional lymphadenopathy in 60%. In SFTS, typical clinical manifestations include abrupt onset of fever and gastrointestinal symptoms along with hematologic abnormalities, and it generally begins with mild clinical manifestations, leading to fatal multiple organ failure, shock, and coma. In scrub typhus, characteristic clinical signs consist of abrupt fever, chill, peripheral lymphadenopathy, abdominal pain, and myalgia; in addition, following complications include acute respiratory distress syndrome, pneumonia, encephalitis, myocarditis, pericarditis, acute renal failure, and acute hepatic failure. Thrombocytopenia was evident in all SFTS patients, but in only 19% in scrub typhus. In addition, another study has reported that thrombocytopenia and leukopenia was shown in only 4.6% and 0.8%, respectively, which indicates that cytopenia is less severe and less common in scrub typhus than in SFTS infection. In scrub typhus, response to doxycycline is reported to occur within 3 days along with defervescence. However, such a response to doxycycline is absent in SFTS. In addition, even though systemic symptoms generally resolve within two weeks after onset, this is a critical period in determining clinical progress in SFTS infection with known risk factors such as elevated hepatic enzymes, central nervous system complications, hemorrhagic manifestation, DIC, and multiple organ failures. Because no specific treatment is available until now, even if diagnosis was confirmed in severe cases, patients were already progressing to fatal condition or death. Fatal caseses was showed thrombocytopenia, leukopenia, abnormality liver enzymes, LDH (>1,200 IU/L), and CK (> 800 IU/L). And if patients were a above descripted laboratory finding, hemorrhagic signs and altered mental change, caution of physicians were more need. Some SFTS patients, as like first case, said that they saw the tick, because Haemaphysalis longicornis was seen by naked eye. But, species of trombiculid mites (“chiggers”, particularly Leptotrombidium delicense), which transmit Orientia tsutsugamushi to the scrub typhus patient, was not seen.

**Conclusion**

It is necessary for the emergency physicians, especially working in endemic areas for SFTS and scrub typhus, should include theses two infectious diseases as differential diagnosis in patients with fever, hematologic abnormalities, and cutaneous symptoms and try to differentiate between SFTS and scrub typhus earlier. Our report provides some clinical insights in differential diagnosis between the two infectious diseases; different peak season, response to the antibiotics, rapidly worsening leukopenia and thrombocytopenia. Rapid diagnosis along with intensive conservative management such as plasma exchange offer the chance to recover from SFTS and early recognition can prevent secondary infection of SFTS.

**Conflicts of interest**

The authors have no conflicts of interest in relation to this article.

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