Person-to-Person Transmission of Severe Fever With Thrombocytopenia Syndrome Bunyavirus Through Blood Contact

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Severe fever with thrombocytopenia syndrome bunyavirus is a newly discovered bunyavirus with high pathogenicity to human. The transmission model has been largely uncharacterized. Investigation on a cluster of severe fever with thrombocytopenia syndrome cases provided evidence of person-to-person transmission through blood contact to the index patient with high serum virus load.

A novel bunyavirus designated severe fever with thrombocytopenia syndrome bunyavirus (SFTSV) was recently identified to be the etiological cause of severe fever with thrombocytopenia syndrome (SFTS) [1]. The SFTS bunyavirus was classified as a new member of genus Phlebovirus, family Bunyaviridae exception to pathogenic or nonpathogenic groups in the genus. Although ticks of the species Haemaphysalis longicornis were supposed to be the vector of SFTSV infection to humans [1], most patients reported none or unclear tick-bite history before their onset of SFTS. Thus, the risk factors of SFTS transmission remain unclear. A thorough review of literature did not find any reports on person-to-person transmission of phleboviruses. As for viruses in the family Bunyaviridae, person-to-person transmission of bunyavirus has so far been reported only for 2 viruses: Crimean-Congo hemorrhagic fever virus (CCHFV), a widespread tick-borne nairovirus spread through blood contacts [2, 3], and the human-to-human transmission of CCHFV, which occurs as nosocomial infections; and the Andes virus, a hantavirus causing hantavirus pulmonary syndrome in South America, which was documented to be transmitted through aerosol under certain circumstances [4, 5] (transmission occurred during the prodromal phase of the illness without bleeding of the index patient). The infected cases of SFTSV commonly showed a sporadic distribution with no relationship among cases. Here, we report results of an investigation into a cluster of SFTS patients occurred in Shandong province, a SFTS endemic area of China.

METHODS

Descriptive investigation of a cluster of 5 SFTS cases following exposure to an index patient who died from the disease was performed. A 77-year-old male farmer who died from SFTS was defined as the index patient in the cluster. Five other cases in the cluster included a 32-year-old male intensive care unit (ICU) physician (Case 1), a 48-year-old male ICU consultation physician (Case 2), a 42-year-old younger son of the index patient (Case 3), and a 45-year-old older son of the index patient (Case 4), as well as a 43-year-old male mortuary beautician (Case 5). The investigation included a review of circumstances and medical records, specimen collection, virus isolation, real-time polymerase chain reaction for viral RNA detection [6], and sequencing and serological tests (capture enzyme-linked immunosorbent assay [ELISA] for immunoglobin [Ig] M antibody, antigen sandwich ELISA for IgG antibody, and microneutralization tests [MNT]) [7]. As for risk assessment of transmission factors, all contactors of the index patient during the period from the beginning (25 September 2010) to the end (8 October 2010) were classified through 3 types of contacts, including blood, droplet, and possible airborne contacts. The investigation was reviewed and approved by the ethics committee of China Center for Disease Control and Prevention (CDC), which uses international guidelines to ensure confidentiality, anonymity, and informed consent.

RESULTS

The index patient was from an SFTS-endemic region and first had onset of illness on 25 September 2010; was admitted to a local hospital on 28 September with a high fever of 39.5°C and vomiting; and the infection was identified through initial
laboratory testing of thrombocytopenia, leukocytopenia, and elevated aspartate aminotransferase level. The patient was diagnosed as a suspected SFTS case, and transferred to the intensive care unit the next day, where he received ribavirin, dexamethasone, omeprazole, and cryoprecipitation for therapy. On 2 October 2010, his condition deteriorated with hypersomnia, shortness of breath, and mouth mucosal bleeding. On 3 October, he appeared confused and showed dyspnea, then was intubated and mechanical ventilated. On 4 October, the patient was in shock and comatose, developed disseminated intravascular coagulation and multiple organ dysfunction syndrome, and died the next day.

An important observation was that the index patient had unique hemorrhagic symptoms, including bleeding from mouth mucosa, gastrointestinal lumen, and lungs, which was rare in previously identified SFTS patients [1]. The patient’s fever remained high (39°C–40°C) until death, although lowered somewhat by giving dexamethasone. Clinical laboratory values (Table 1) showed unusually high level of tissue enzymes, blood urea nitrogen, and creatinine, which might indicate impaired liver, heart, and kidney functions. Consistent with the largely reduced platelet count, the index patient had a significantly elongated activated partial thromboplastin time, which represented a largely impaired coagulation function. Immediately after death, the corpse was transferred to the patient’s home in a local village for a funeral ceremony, then transferred to a crematorium 3 days later.

Epidemiologic investigations began with interviews with 5 secondary SFTS patients and 58 other individuals who had exposure to the index patient from onset of the illness until cremation. We found that all 5 secondary cases had possible blood contact through skin or mucosa. Case 1, the local ICU doctor, performed the intubation for the index patient, resuscitating the patient before his death. He had general surgical protection but without a protective face shield or goggles. Case 2, the consultant doctor, traveled from a nonendemic area to the local hospital for a medical consult with the patient, and the patient’s blood dropped on his hand when he was helping an ICU nurse draw

| Table 1. Laboratory Analysis of a Cluster of Severe Fever With Thrombocytopenia Syndrome Patients in China |
|--------------------------------------------------|-----------------|-----------------|------------------|-----------------|-----------------|-----------------|
| Clinical tests | Index Patient | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
| Platelet count | 21 | 69 | 32 | 38 | 77 | 84 |
| White-cell count | 1.03 | 2.18 | 1.23 | 1.54 | 1.35 | 2.30 |
| ALT | 126 | 89 | 146 | 166 | 107 | 92 |
| AST | 543 | 57 | 140 | 186 | 66 | 64 |
| LDH | 2213 | 207 | 578 | 606 | 210 | 199 |
| Proteinuria | ++ | + | + | + | -- | -- |
| Hematuria | ++ | + | + | + | -- | -- |
| APTT | 101.2 | 47.0 | 63.5 | 87.1 | 44.7 | 45.2 |
| Laboratory findings | | | | | | |
| Virus isolation | Yes | No | Yes | Yes | No | No |
| Viral RNA (copies/mL) | $3.55 \times 10^9$ | $2.42 \times 10^4$ | $9.00 \times 10^3$ | $4.10 \times 10^3$ | $7.13 \times 10^3$ | $3.43 \times 10^3$ |
| Virus load (TCID$_{50}$/mL) | $9.67 \times 10^7$ | $6.60 \times 10^1$ | $2.45 \times 10^1$ | $1.12 \times 10^1$ | $1.94 \times 10^1$ | $9.33 \times 10^0$ |
| IgM antibody | <10 | 640 | 5120 | 5120 | 640 | 5120 |
| IgG antibody | N/A | 640 | 5120 | 2560 | 2560 | 640 |
| MNT | N/A | 40 | 40 | 40 | 40 | 10 |
| Risk factors | Blood (P < .001) | N/A | Yes | Yes | Yes | Yes | Yes |
| Droplet (P = .192) | N/A | Yes | No | No | No | No |
| Possible airborne (P = .434) | N/A | No | No | No | No | Yes |

a ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; APTT, activated partial thromboplastin time.

b –, negative; +, weak positive; +++, strong positive.

c Viral RNA copies were calculated according to standard reaction curves, which were established using serially diluted in vitro RNA transcripts as standard samples.

d Virus load was determined based on an average conversion coefficient between virus copies and virus titer presented as 50% tissue culture infective dose (TCID$_{50}$/mL).

e Serum samples collected in the acute phase were subjected to immunoglobulin (Ig) M detection with IgM antibody capture enzyme-linked immunosorbent assay (ELISA), with horseradish peroxidase–conjugated recombinant severe fever with thrombocytopenia syndrome bunyavirus (SFTSV) nucleoprotein as the detection agent.

f Serum samples collected in the convalescent phase were subjected to IgG detection with sandwich ELISA by using recombinant SFTSV nucleoprotein as the detection agent.

g MNT, microneutralization test.

h Values for IgM antibodies, IgG antibodies, and MNT are the reciprocals of the serum dilution.

i Risk factors were assessed using logistic regression analysis; P < .05 was considered to be statistically different. Definition of risk factors was described in the Results section.
blood without wearing gloves. Case 3, the younger son of the index patient, was a long-distance truck driver not living in the same village, and directly touched the blood flowing from the deceased patient’s mouth and nose when he cried on the corpse. Case 4, the older son of the index patient, was also a long-distance truck driver, and took care of the dead body and was wiping off the blood from the face of the corpse. Case 5, a local mortuary beautician, did the make-up for the corpse with gloves and mask, but took them off twice during the procedure. The above 5 cases all developed the disease 7–15 days after exposure, with only 3 of them having contact with blood after death. In comparison with the index patient, all 5 secondary cases had minor clinical features (Table 1), without obvious hemorrhagic manifestations, so they did not receive dexamethasone therapy. Except for the major risk factor of blood contact, droplet contact (N = 4), which included 3 medical staff who were involved in the intubation and the index patient’s daughter who cared for him before death, was assessed as the second possible risk factor. In addition, the risk factor of possible airborne transmission (being in the ICU room or funeral room without mask protection) was also assessed among all 63 exposed individuals. Of them, the medical doctors and nurses (N = 16) were with protection; and the others were without (N = 47), including ICU patients who were staying in the same room (N = 8), family members (N = 3), and visitors to the funeral room where the corpse was kept (N = 35). The multivariate analysis (logistic regression analysis) showed that blood contact was the most likely mode of transmission (P < .001; Table 1).

It is noticeable that the serum collected from the index patient on the day he died contained a relatively high amount of SFTSV, which reached about 3.55 × 10^{10} viral RNA copies/mL (calculated as 9.67 × 10^7 50% tissue culture infective dose [TCID_{50}]/mL). This number was about 100 000-fold higher than viral copies detected in the serum samples of the 5 secondary patients, which ranged from 10^3 to 10^5 copies/mL. It is notable that the level of virus copies in the index patient’s serum was extremely high, but with no detectable IgM or IgG antibodies, which suggested that his immune responses to limit the replication of SFTSV were severely impaired. The patient had no immune system disease, thus the minimal immune responses might be due to the early and sustained application of glucocorticoid, which has a side effect of depressing immune functions [8]; clinical physicians should take note of this finding.

Clinically, SFTS is easily confused with hemorrhagic fever with renal syndrome caused by hantavirus [9] and human anaplasmosis [10]. The hantavirus-specific IgM antibodies were not detected in the SFTS patients’ serum samples (data not shown). Due to the limitation of our study, we were not able to detect Rickettsia infection, which was previously reported in outbreaks of nosocomial infections [10]. However, the methods we used for diagnosis of SFTS patients were well validated [1], and the human-to-human transmission of SFTSV we described in this study could not simply be classified as being nosocomial transmission; specially, 3 of the 5 secondary cases that occurred in the household. Additionally, the lessons of person-to-person transmission of SFTSV we learned from this study highlighted the necessity of establishing standard precautions for avoiding direct contact and blood-based transmission.

**DISCUSSION**

Here, we reported the person-to-person transmission of SFTSV with a cluster of 6 SFTS patients that occurred in Shandong Province of eastern China. Investigation studies revealed that all 5 secondary infected patients had possible contact with the index patient’s blood. Of them, only Case 1 (ICU doctor) had evidence of droplet contact contamination (during intubation) but not blood contact, but we included him also as a blood contactor because he performed intubation without protective face shield and goggles, therefore he had an extremely high risk of blood contact through unprotected skin and mucosa. The risk assessment revealed that blood contact was the major risk factor for the human-to-human transmission of SFTSV. Additionally, 3 secondary patients who only had contact with the index patient after death were still infected, which indicated that SFTSV-infected blood may remain infectious for a long time, even after patient death.

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**Notes**

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