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

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We investigated an outbreak of severe fever with thrombocytopenia syndrome (SFTS) that occurred during May and June 2010, to identify the mode of transmission. Contact with the index patient's blood was significantly associated with development of SFTS ($P = .01$, by the χ^2 test for linear trend); the frequency of contact with the index patient's blood increased the risk of SFTS in a dose-response manner ($P = .03$, by the χ^2 test for linear trend). We concluded that human-to-human transmission caused this cluster of cases.

Keywords. severe fever with thrombocytopenia syndrome virus (SFTSV); human-to-human transmission; blood.

In May 2007, a life-threatening disease characterized by the sudden onset of fever, thrombocytopenia, and leukopenia was first reported in several provinces in central and northeast China [1, 2]. A novel bunyavirus was identified as the causative agent of this disease. The disease is referred to as fever, thrombocytopenia, and leukopenia syndrome (FTLS) or as severe fever with thrombocytopenia syndrome (SFTS), and the virus is designated FTLSV or SFTSV, respectively [1, 2]. Tick bites were presumed to be the mode of transmission, although no definitive evidence associated with this hypothesis has been identified [1, 2].

During May–June 2010, a cluster of 5 suspected cases of SFTS occurred in Henan Province in central China, with 1 death. We investigated this cluster to confirm the diagnosis and identify the mode of transmission.

METHODS

We defined a laboratory-confirmed case of SFTSV infection as the presence of ≥1 of the following findings: a blood culture positive for SFTSV, identification of viral RNA through reverse transcription polymerase chain reaction (RT-PCR), and seroconversion or a 4-fold increase in anti-SFTSV immunoglobulin G (IgG) titers between acute- and convalescent-phase sera.

We collected acute-phase serum from the index patient and paired sera from the ill contacts, with acute-phase sera collected <7 days after onset and convalescent-phase sera collected >6 weeks after onset. Sera were also collected from the asymptomatic contacts of the index patient 6 weeks after exposure. Ticks were collected from the domestic animals (2 cows and 1 dog) kept by the index patient. An immunofluorescence assay was used to detect anti-SFTSV IgG [1], and RT-PCR (QIAamp viral RNA Mini Kit 52904, Qiagen, Hilden, Germany), using a specific RNA-dependent RNA polymerase gene primer set, was performed to detect SFTSV RNA [1]. Virus was isolated by inoculating acute-phase sera into 2 wells of Vero E6 cells.

In a retrospective cohort study, we performed a verbal autopsy of the deceased index patient by questioning his wife, younger son, and daughter; the village clinic doctors; the head of the village; and the doctors and nurses who treated the patient. We also interviewed the ill and asymptomatic contacts of the index patient about their symptoms of SFTS and possible risk factors for infection, including their exposure to the index patient, exposure to wild animals, and history of tick bites. All participants provided verbal informed consent for anonymous use of their specimens and clinical information for research. The institutional review boards of all participating institutions approved this study.

CASE REPORT

The index patient was a 58-year-old man, who, on 20 May 2010, experienced a sudden onset of fever (39.5°C), fatigue, myalgia, cough, and nausea. He initially received a diagnosis of influenza and was treated for 4 days in the village clinic with cefazolin, Shuanghuanglian (an herbal antiviral and antibiotic [3]), and dexamethasone (for fever reduction). On 25 May, his symptoms worsened, and he developed facial flushing and conjunctivitis and began vomiting, and he was transferred to municipal hospital A. On 26 May, he was transferred to municipal hospital B, where he received a diagnosis of suspected human granulocytic anaplasmosis [4] and was treated with doxycycline. However, his condition continued to deteriorate progressively; he developed nasal and oral bleeding at approximately 6:15 AM on 30 May and died at approximately 12:45 PM. During the verbal autopsy, the index patient's next of kin denied that the index patient had a history of tick bite before onset of illness. The index patient mostly worked in the field around his house during the 15 days prior to the onset of his illness. However, he often took cows to graze in the hills, and ticks were often found on the cows. During our investigation, we found that the index patient had 2 cows and 1 dog. We collected 9 ticks from the 2 cows, but no ticks were found on the family dog; all ticks, however, tested negative for SFTSV RNA by RT-PCR [1].

We identified 31 contacts with the index patient during his illness, including 16 healthcare workers, 10 family members, 4 relatives and friends, and the village funeral director. During 6–8 June, 4 of these individuals (13%) developed secondary SFTSV infection, with clinical signs and symptoms consistent with SFTS (Supplementary Figure 1) [1]. Of these 4 individuals, 3 were members of the index patient's family. Since 2006, one son (son 1) had resided in another city (Ninbo, Zhejiang Province), approximately 1300 km away, in which SFTSV infection has never been reported [1, 2]. Hearing of his father's grave illness, son 1 went directly to the hospital on 29 May and stayed at the bedside for 2 days, until his father's death. Son 1 became ill on 6 June. The index patient's other son (son 2) resided in the same village as the index patient, and he had visited his father every 3–5 days before his father became ill [1]. Son 2 began caring for the index patient on 25 May. The index patient's daughter resided in another county, approximately 20 km away, and went to the hospital to care for her father during 26–30 May. She had not seen her father during the 30-day period before 26 May. Son 2 and the daughter both became ill on 7 June. The only nonfamilial secondary case was the village funeral director, who resided in the same village and had unprotected contact with the index patient's blood from 1:00–4:00 PM on 30 May, after he sustained a cut on his right index finger while washing and clothing the body with his bare hands. He became ill on 8 June. All secondary cases denied tick bites, contact with wild animals, or exposure to other patients with SFTS during the 15-day period before the onset of their illness.

During the index patient's final hours of life, while he bled profusely from his mouth and nose, 5 of 10 family members were at the bedside; none wore rubber gloves or gowns. Three of these family members helped to wipe off the index patient's blood without wearing personal protection, and blood splashed onto their faces. All 3 became ill, showing clinical signs and symptoms consistent with SFTS [1]. The other 2 family members had no contact with the patient's blood but were only present in the ward; neither became ill. Four relatives and friends visited the index patient and talked with him during the early stages of his illness, when there was no bleeding, and none became ill.

The 16 healthcare workers with contact with the index patient consisted of 8 doctors and 8 nurses. Before the index patient was transferred to hospital B, 2 village doctors and 2 doctors in hospital A had unprotected contact with him during physical examinations, including taking his temperature and testing for coated tongue and lymph node enlargement, and intramuscular injection; none wore wear rubber gloves or gowns and none became ill. Following transfer of the index patient to hospital B, 4 healthcare workers had protected contact with the index patient before he developed bleeding, during physical examinations, including taking his temperature and testing for coated tongue and lymph node enlargement, and intravenous injections; none became ill. When he was bleeding on 30 May, 8 healthcare workers provided care, including wiping off his blood and administering intravenous injections, but only 1 did not wear rubber gloves, surgical masks, and gowns. None of these workers became ill.

RESULTS

Overall, contact with the index patient's blood was significantly associated with developing secondary illness ($P = .01$, by the χ^2 test for linear trend), whereas contact with the index patient's respiratory secretions, urine, and feces was not (Table 1). Of the various modes of exposure, contact with the index patient's blood on mucous membranes or skin wounds ($P < .01$, by the χ^2 test for linear trend) and not wearing personal protective equipment while providing care ($P = .01$, by the χ^2 test for linear trend) were significantly associated with disease risk. Additionally, frequency of contact with blood was associated with disease risk in a dose-response fashion ($P = .03$, by the χ^2 test for linear trend; Table 2).

Two isolates of SFTSV were obtained, one from the acute-phase sera of the index patient and the other from son 1. Whole-genome sequencing showed that the 2 isolates (GenBank accession numbers: HN01: HQ642766, HQ642767,

Table 1. Risk Factors for Secondary Severe Fever With Thrombocytopenia Syndrome Among 31 Close Contacts of the Index Patient, Henan Province, China, May–June 2010

| | Close Contacts, No. | | | | |
Secretion	Overall	Developed Secondary Case	Attack Rate, %	P^a	OR (95% CI)[a]
Blood					
Exposed	12	4	33.33	.01	…
Unexposed	19	0	0		
Respiratory secretion					
Exposed	4	1	25.00	.44	2.67 (.21–34.56)
Unexposed	27	3	11.11		
Urine					
Exposed	5	1	20.00	.52	1.92 (.16–23.35)
Unexposed	26	3	11.54		
Feces					
Exposed	2	0	0	>.99	…
Unexposed	29	4	13.79		

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Calculated using the 2-sided Fisher exact test.

and HQ642768; HN69: JF682776, JF682777, and JF682778) were nearly identical (99.99% similarity). These 2 isolates showed slightly less similarity (99.83% and 99.83%, respectively) with an isolate obtained from a patient in Xinyang City on 23 June 2009 (GenBank accession numbers: HN20: JF682773, JF682774, JF682775).

Table 2. Risk Factors for Secondary Severe Fever With Thrombocytopenia Syndrome Among 12 Close Contacts Exposed to the Index Patient's Blood, Henan Province, China, May–June 2010

| | Close Contacts, No. | | | |
Variable	Overall	Developed Secondary Case	Attack Rate, %	P
Exposure route				
Mucosa, mouth, nose, wound	4	4	100.00	<.01[a]
Skin, clothes, shoes	8	0	0	
Personal protective equipment				
Did not use	5	4	80.00	.01[a]
Use	7	0	0	
Exposure frequency, no. of episodes				
≥3	4	3	75.00	.03[b]
2	5	1	20.00	
1	3	0	0	

[a] Calculated using the Fisher exact test.

[b] Calculated using the 2-sided χ^2 test for trend.

The acute-phase sera from all 5 disease-positive patients were positive for SFTSV RNA by RT-PCR and negative for IgG to the virus. The convalescent-phase sera from the 4 secondary patients had IgG to SFTSV. The sera IgG titers were 1:80 (for son 1), 1:160 (for son 2), 1:640 (for the daughter), and 1:160 (for the funeral director). Sera from all 27 asymptomatic contacts tested negative for both viral RNA (by RT-PCR) and IgG to the virus.

Although contact with the index patient's blood was a point source of exposure, other exposures were also possible. We estimated that the incubation period of SFTSV for this mode of transmission was 7–13 days. However, our sample size was small, and this incubation period might not apply to other modes of transmission, such as tick- or mosquito-borne infection.

The index patient was treated with dexamethasone for fever reduction, during the first 4 days after onset of illness. Dexamethasone and other glucocorticoids lower innate immunity and increase the severity of viral infections [5, 6]. Although it was impossible to determine the role of dexamethasone in the severity of the index patient's illness, it is nonetheless advisable that dexamethasone not be used to treat simple fever. Steroids may have increased the number of circulating virions in his blood and excreted into other body fluids. This may have led to human-to-human transmission of SFTSV.

DISCUSSION

In summary, we have documented an outbreak of infection with the recently identified SFTSV and provided strong

epidemiologic and viral genomic evidence that SFTSV can be transmitted between humans through contact with infected blood. This finding underscores the importance of protecting healthcare workers and patients' family members from exposure to blood. Our data also indicated that practicing standard isolation precautions [7] may minimize the risk of virus transmission by blood.

Since the submission of this manuscript, probable human-to-human transmission of SFTSV has been reported in patients who were not treated with steroids [8, 9]. We recommend that healthcare workers and family members caring for patients with suspected SFTS, as well as persons handling the bodies of those who have died of this disease, wear personal protective equipment, including gloves, gowns, eye protection, and masks, and avoid touching patients' blood and other body fluids. Patients with SFTS should be isolated until they no longer have detectable viremia, and all who come in contact with these patients should be monitored for fever until the end of the incubation period (>13 days). Those who develop symptoms should be isolated and tested.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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