ORIGINAL ARTICLE VIROLOGY

Probable aerosol transmission of severe fever with thrombocytopenia syndrome virus in southeastern China

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Abstract

Some clusters of severe fever with thrombocytopenia syndrome virus (SFTSV) infection were reported in China as of 2010. However, to date, there has been no epidemiologic evidence of aerosol transmission of SFTSV. Epidemiologic investigations were conducted after a cluster of 13 cases of SFTSV in May 2014. A total of 13 cases, including 11 confirmed cases and one clinically diagnosed case, were identified besides the case of the index patient. The index patient experienced onset of SFTSV on 23 April and died on 1 May. The patients with secondary cases had onset from 10 to 16 May, peaking on 13 May. Moreover, eight secondary cases occurred in family members of the index patient, and the other five cases occurred in neighbors of the index patient. According to epidemiologic investigations, patients 1, 3, 4, 5, 6, 7, 9 and 12 contracted the disease through contact with blood of the index patient. Notably, patients 8 and 10 did not have a history of contact with the blood of the index patient, but they stayed in the mourning hall for hours. SFTSV could be transmitted from person to person by direct contact and/or aerosol transmission, and it is important to consider aerosol transmission as a possible transmission route.

Keywords: Aerosol transmission, cluster, emerging infectious disease, person to person, severe fever with thrombocytopenia syndrome virus
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Introduction

Severe fever with thrombocytopenia syndrome (SFTS), with an average case fatality rate of 12%, is an emerging infectious disease caused by a newly discovered virus, severe fever with thrombocytopenia syndrome virus (SFTSV). SFTSV is classified in the family *Bunyaviridae*, genus *Phlebovirus*, and contains three segments of negative or ambisense polarity RNA, designated L, M and S segments. The major clinical symptoms and laboratory abnormalities of SFTS are fever, thrombocytopenia, leukopenia and elevated serum hepatic enzymes, and SFTS patients usually die of multiple organ failure [1]. The clinical symptoms, however, are less specific and need to be differentiated from various other infectious diseases, in particular hemorrhagic fever with renal syndrome caused by hantavirus and human anaplasmosis [2,3].

Knowledge of the transmission mode of SFTSV is fundamental to an understanding and control of the disease. SFTSV is believed to be transmitted by ticks because the virus has been detected in *Haemaphysalis longicornis* ticks. Some studies reported that SFTSV could also be transmitted from person to

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person. Bao and colleagues reported that SFTSV was transmitted from a 59-year-old man to his son and son-in-law in 2010, and another cluster showed that SFTSV was transmitted from an 80-year-old woman to six secondary patients including her daughters, nephews and sons-in-law in 2007 in Jiangsu Province [4,5]. Gai *et al.* [6] identified the person-to-person transmission of SFTSV with a cluster of six SFTS patients including intensive care unit physician, intensive care unit consultation physician, mortuary beautician and family members that occurred in 2010 in Shandong Province. Three other studies reported that person-to-person transmission of SFTSV occurred in Anhui Province, Henan Province and Hubei Province, respectively [7–9]. However, all secondary patients of these clusters contracted SFTSV infection through contact with the blood or bloody secretions of patients in the end stage of the disease. There was no epidemiologic evidence of aerosol transmission of SFTSV. In this study, we identified a cluster of person-to-person transmission of SFTSV and investigated the potential transmission routes, including aerosol transmission.

Methods

Case definition

According to "the diagnosis and treatment programs of severe fever with thrombocytopenia syndrome," issued by the Chinese Ministry of Health (http://www.moh.gov.cn/mohwsyjbgs/s8348/201010/49272.shtml), a suspected case of SFTS is defined as acute onset of fever ($\geq$38.0°C) with other symptoms (e.g. gastrointestinal symptoms, bleeding), epidemiologic risk factors (being a farmer or being exposed to ticks 2 weeks before onset of illness) and laboratory data consisting of thrombocytopenia and leukocytopenia. Confirmed SFTS cases were defined as meeting the criteria for suspected SFTS and also met one or more of the following criteria: (a) detection of SFTSV RNA by a molecular method from patient serum, (b) seroconversion or a fourfold or more increase of antibody titers between acute and convalescent sera collected at least 2 weeks apart or (c) isolation of SFTSV in cell culture.

The ethics committee of Zhejiang Provincial Centre for Disease Control and Prevention approved this research project. Human research was carried out in compliance with the Helsinki Declaration. All participants provided written informed consent to participate in this study.

Laboratory test assays

The sera of the suspected patients were tested for SFTSV RNA by real-time reverse-transcription PCR performed as described elsewhere [10] in the Zhejiang Provincial Centre for Disease Control and Prevention.

Epidemiologic investigation

All persons who had a history of contact with the body of the index patient from 1 to 3 May were interviewed. The aims of our study were explained to all patients, and their consent was obtained before inclusion onto this study. A standardized questionnaire was used to collect information about demographic features, such as age, gender, occupation, and residential address, exposure history, clinical signs and symptoms, date of onset and date of confirmation. Exposure history included taking care of the index patient in hospital, moving the corpse into a car and from the car to home, washing and wiping the corpse, dressing the corpse, moving the corpse to a coffin, keeping vigil beside the coffin and staying in the mourning hall with no contact with the corpse.

Results

A total of 13 SFTS cases, including 11 confirmed cases and one clinically diagnosed case, were identified besides the index patient during this outbreak. Of these patients, six were men and seven were women, and the median age of the patients was 60.5 years, ranging from 41 to 74 years (Fig. 1). The index patient experienced disease onset on 23 April and died on 1 May. The secondary cases occurred from 10 to 16 May, with a peak on 13 May (Fig. 2). Eight secondary cases occurred in family members of the index patient, and the other five cases occurred in neighbors of the index patient (Fig. 1).

The index patient and all secondary patients were hospitalized, and all patients had fever, fatigue and chills. The majority of patients had headache, anorexia, myalgia and conjunctival congestion. Four patients had nausea, three diarrhea, two vomiting and two gingival hemorrhage (Table 1). Symptoms were similar for the index patient and the secondary patients.

The index patient was 66-year-old female farmer with a history of hypertension for more than 15 years. She lived in a wooded, hilly upland area with shrubs and grasses (Fig. 3). She used to pick tea leaves before onset of illness and developed a fever on 23 April. She visited a clinic on 25 April, and her temperature was 40°C. She was treated with ribavirin and azlocillin, but symptoms were not alleviated. She thus continued seeking medical consultations at several hospitals. She was hospitalized on 29 April (Fig. 4). As her condition deteriorated, her family requested that the hospital discharge her. Her son, daughter and brother brought her home on 1 May. She died

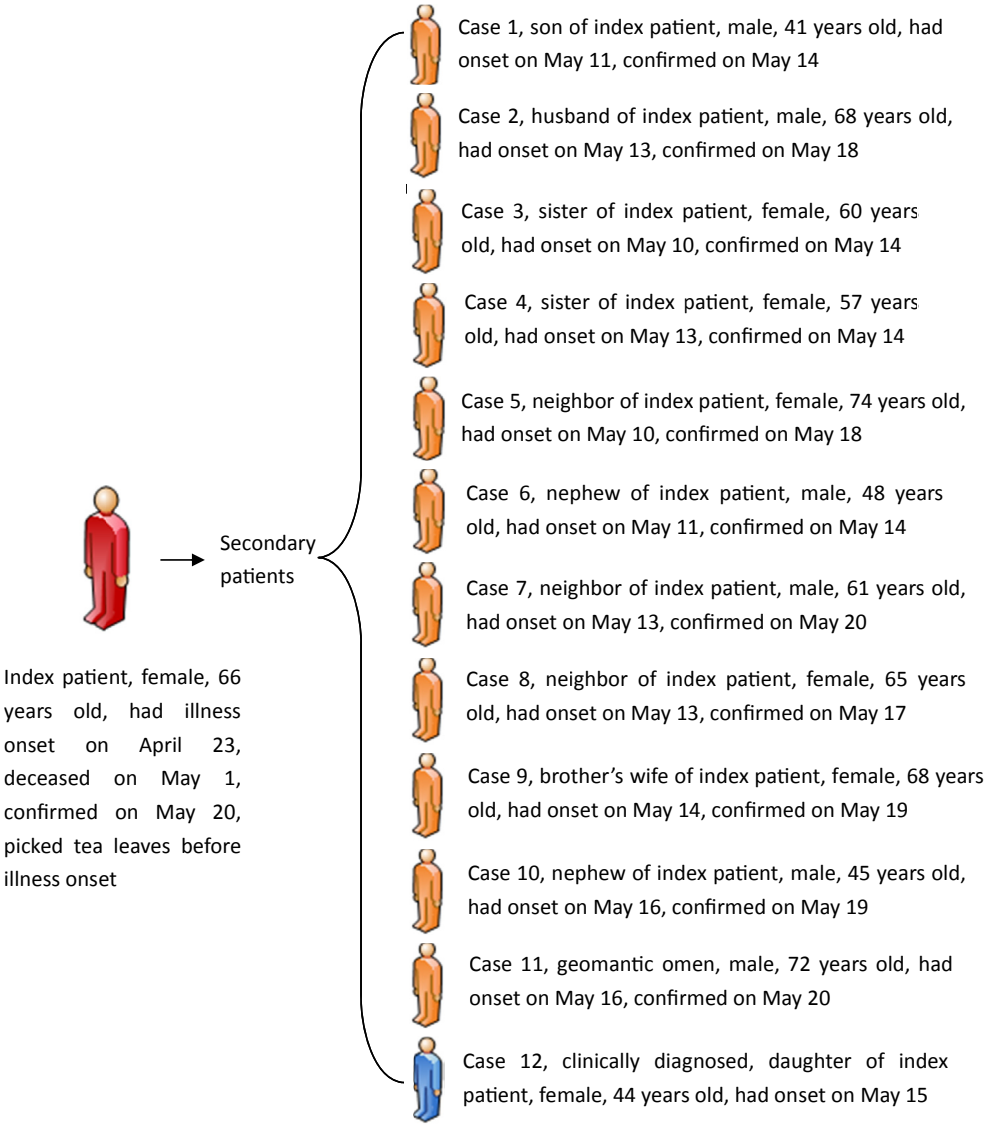

FIG. 1. Demographic features and date of illness onset of patients with severe fever with thrombocytopenia syndrome.

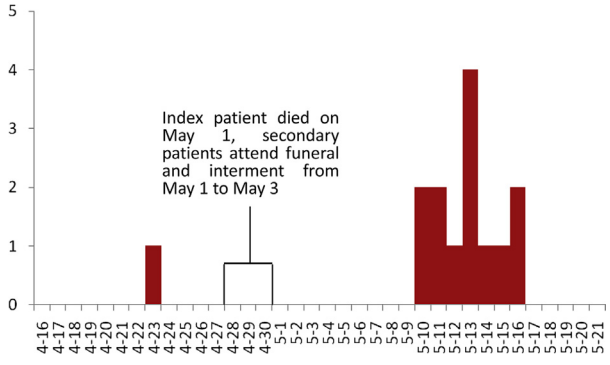

FIG. 2. Timelines of index patient and key event of severe fever with thrombocytopenia syndrome outbreak in southeastern China.

during the trip home. Because the corpse had already been buried when the outbreak occurred, blood samples were not collected from the index patient. Fortunately, we collected seven blood spot samples on the walls of her home on 18 May, and two of the samples were positive for SFTSV. The minimum platelet count of the patient was 20 × 10^9/L on 29 April.

Patient 1, the son of the index patient, developed fever on 11 May. He took care of the index patient in hospital, participated in moving the corpse into a car and from the car to home, moved the corpse to a coffin and kept vigil beside the coffin (Table 2).

Patient 2, the husband of the index patient, experienced onset of illness on 13 May. He did not have contact with the corpse, but he stayed in mourning hall for hours. Similarly,

TABLE 1. Clinical characteristics of index patient and secondary patients

Characteristic	Index	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
Fever	√	√	√	√	√	√	√	√	√	√	√	√	√
Fatigue	√	√	√	√	√	√	√	√	√	√	√	√	√
Chills	√	√	√	√	√	√	√	√	√	√	√	√	√
Headache	√	√		√	√	√	√		√				
Anorexia	√	√	√	√	√	√	√	√	√				
Nausea								√	√	√			√
Myalgia	√	√		√	√		√	√	√			√	√
Diarrhea	√						√		√				
Vomiting									√	√			
Gingival hemorrhage	√								√				
Conjunctival congestion	√	√		√	√					√	√	√	√

FIG. 3. House where index patient lived.

patients 8 and 10 also did not have history of contact with the corpse, although they too stayed in the mourning hall for hours.

Patients 3 and 4 were sisters of the index patient. Both of them participated in washing and wiping the corpse, and they dressed the corpse. Patients 5 and 9 dressed the corpse but had no other contact. Patient 12 was the daughter of the index patient; she had taken care of the index patient in hospital, moved the corpse into the car, washed and wiped the corpse, dressed the corpse and kept vigil beside the coffin. Three persons, patients 3, 4 and 12, participated in washing and wiping the corpse, and five people, patients 3, 4, 5, 9 and 12, participated in dressing the index patient. All these persons were infected with SFTSV.

Patients 6 and 7 participated in moving the corpse from the car to home and moving the corpse to a coffin, along with patient 1. Of note, patients 1, 6 and 7 had contact with the index patient's blood when they carried the corpse from the car into the house.

Of interest, patient 11 was a geomantic omen, and he did not have history of contact with the corpse; nor did he stay in the mourning hall for hours. However, he went to hilly areas to select the burial site for the index patient. We collected ticks in hilly areas near the cemetery, indicating that patient 11 had a history of exposure to ticks.

Discussion

In this study, we identified a cluster of person-to-person transmission of SFTSV including the index patient and 12 secondary patients. Notably, two secondary patients probably contracted the disease through aerosol transmission and/or direct contact.

A fatal outcome of SFTS was associated with high virus load in blood at admission and sustained high virus load during different illness stages [11–13]. These findings indicated that

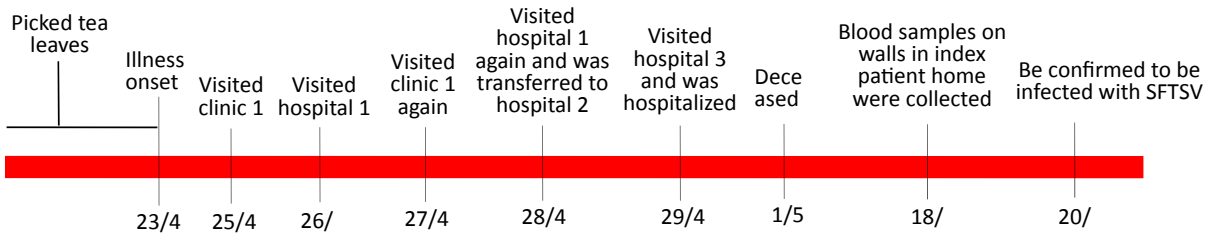

FIG. 4. Timelines of potential exposure and medical consultations of index patient.

TABLE 2. Exposure modes of secondary patients with severe fever with thrombocytopenia syndrome virus infection

Patient no.	Taking care of index patient in hospital	Carrying corpse into car	Carrying corpse from car to home	Washing and wiping corpse	Dressing corpse	Carrying corpse to coffin	Keeping vigil beside coffin	Staying in mourning hall but no contact with corpse
1	√	√	√			√	√	
2							√	√
3				√	√			
4				√	√			
5					√			
6			√			√		
7			√			√		
8								√
9					√			
10								√
12	√	√		√	√		√	

the virus load of dead patients was very high in blood, and people might be infected with SFTSV through contact with the blood of dead patients. According to the intervals of the dates of the onset of illness of secondary patients from the funeral of the index patient, we conclude that the infection of secondary patients was related to the index patient. However, secondary patients might have been infected with SFTSV via different transmission modes. We believe that patients 1, 3, 4, 5, 6, 7, 9 and 12 were infected with SFTSV through direct contact with the blood of the index patient. Although we cannot rule out the notion that they were infected through tick bites, we think that such a probability is very low as a result of the timing of their illness. Firstly, the nine secondary patients had an obvious exposure history of contact with blood of the index patient. Secondly, blood samples on the walls in house of the index patient tested positive for SFTSV. Thirdly, all of the patients did not have an obvious history of tick bites. Finally, all nine patients developed the disease 10 to 15 days after exposure.

The index patient died of massive hemorrhage in a car while being transported home, and her clothes were soaked with blood on 1 May. Of note, all three people who attended washing and wiping the corpse, and all five people who dressed the index patient were infected with SFTSV, and another three secondary patients had direct contact with the blood of the index patient when they moved the corpse from the car into her house. All these exposure occurred on 1 May, indicating that SFTSV-infected blood may remain infectious even after death.

Patient 2 did not have a history of direct contact with the blood of the index patient. However, he lived with the index patient, had a history of contact with the clothes of the index patient, which were soaked with the blood of the index patient, and he stayed for hours in the mourning hall. Therefore, he might have been infected with SFTSV through contact with contaminated clothes, aerosol transmission or tick bites. The probability of infection through contact with the clothes of the index patient was the highest.

Patients 8 and 10 did not have history of contact with the blood or contaminated clothes of the index patient. They may have acquired the infection through one of three possible transmission routes, including aerosol transmission, contact with utensils which were contaminated with blood or secretion of the index patient and tick bites. We thought the probability of aerosol transmission was the highest. Firstly, both of them had a history of staying in the mourning hall for hours. Secondly, they did not have a history of direct contact with the blood of the index patient. Thirdly, the corpse of the index patient was placed in a small space, thus facilitating aerosol transmission. Fourthly, the timing of their illness was compatible with exposure to the corpse of the index patient. Fifthly, they lived in different towns and they were unlikely to have been bitten by ticks all at the same time. Moreover, aerosol transmission of other viruses in the *Bunyaviridae* family has been reported. For example, *Andes* virus, a hantavirus causing hantavirus pulmonary syndrome in South America, had documented aerosol transmission under certain circumstances [14,15]. Aerosol transmission of hantavirus was also confirmed in the laboratory, and rodents could be infected by virus aerosol generated by infected *Apodemisagrarius* and artificial virus aerosol [16–19]. SFTSV was detectable in blood, throat, urine and faecal specimens of SFTS patients, and these excreta as well as the blood of patients might generate virus aerosol [11]. As a result, family members or physicians might be infected with SFTSV through aerosol transmission.

Patient 11 was a geomantic omen and had no history of contact with the index patient. He was most probably infected with SFTSV through a tick bite when he selected the grave site for the index patient. We found ticks around the cemetery the index patient was buried in, which supports our postulate.

There were several limitations to our study. Firstly, we could not isolate virus or obtain a viral sequence from the index patient because the corpse had been buried when the outbreak was identified. Therefore, we could not conduct sequencing for virus isolate analysis between the index patient and the

secondary patients. Secondly, we did not know the prevalence of SFTSV in ticks around the home of the index patient. We cannot completely rule out the notion that the majority of secondary patients, especially patients 8 and 10, were infected through tick bites, although we believe this to be unlikely.

To the our knowledge, this is the first report of probable aerosol transmission of SFTSV. Our findings suggest that SFTSV could be transmitted from person to person by direct contact and/or aerosol transmission, and it is of importance to consider aerosol transmission as a possible transmission route. Aerosol precautions should be considered and standard for doctors, nurses and family members when they take care of patients with SFTSV. Furthermore, laboratory experiments should be performed to study aerosol transmission in SFTSV.

Transparency Declaration

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