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Case Report

Human-to-human transmission of severe fever with thrombocytopenia syndrome virus through potential ocular exposure to infectious blood

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ABSTRACT

Severe fever with thrombocytopenia syndrome (SFTS), an emerging infectious disease with high mortality, was first reported in 2009 in China and subsequently endemic to South Korea, Japan, Vietnam, and Myanmar. This disease is transmitted predominantly by tick bites and potentially human-to-human. Personal protective equipments (PPEs) have been recommended to prevent SFTS human-to-human transmission, whereas the specific use of PPEs and the effect on viral transmission have rarely been reported. This report identified a family cluster of six patients with SFTS virus (SFTSV) infection. All five secondary patients had been wearing gloves and masks when exposed to the blood of the index patient, but none of them wore goggles or face shields for eye protection. Ocular route was suggested as a highly possible mode for SFTSV transmission through epidemiological, serological, and phylogenetic analysis. Eye protection should be stressed for clinicians when exposed to blood or bloody secretions.

Severe fever with thrombocytopenia syndrome (SFTS), caused by a novel tick-borne bunyavirus (SFTS virus [SFTSV]) in the genus *Banyangvirus*, is an emerging hemorrhagic fever, characterized by a tendency to progress to severe infection with hemorrhagic signs, neurological symptoms, and multiple organ failure or death, with a fatality rate of 12-50% (Yu *et al.*, 2011; Li *et al.*, 2018). SFTS has been endemic to more than five Asian countries (Yu *et al.*, 2011; Kim *et al.*, 2018; Takahashi *et al.*, 2014; Tran *et al.*, 2019; Win *et al.*, 2020). SFTS is primarily transmitted from ticks to humans (Zhuang *et al.*, 2018) and is also potentially transmitted human-to-human through direct contact with patients' blood (Gai *et al.*, 2012; Tang *et al.*, 2013; Gong *et al.*, 2015; Jung *et al.*, 2019). Personal protective equipment (PPE) has been recommended for healthcare workers and family members when handling blood or bloody secretions of patients with SFTS. However, the appropriate measures that can effectively reduce viral transmission have yet to be standardized. Here, we report a family cluster of six patients with SFTS in China due to inadequate PPEs taken during the period of blood exposure.

METHODS

From March 31 to April 5, 2022, five patients from one family with an acute febrile illness sought treatment at People's Liberation Army 990 Hospital, Xinyang City, Henan Province, for suspected SFTS (Li *et al.*, 2018), with all reporting a recent contact with a family member who had laboratory-confirmed SFTSV infection who died on March 21 (index patient). Medical record was reviewed to collect data about clinical manifestations and laboratory test results. Face-to-face interviews were performed for the patients and five other family members who had direct contact with the index patient. Viral ribonucleic acid (RNA) was isolated from serum samples and subjected to quantitative reverse transcription-polymerase chain reaction (qRT-PCR), targeting SFTSV S-segment (Zhuang *et al.*, 2018). SFTSV-specific immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies were examined using an enzyme-linked immunoassay. Virus isolation was performed by inoculating serum samples into Vero cells and confirmed by qRT-PCR and immunological focus assays. Nested RT-PCR assays were performed to obtain full-length genome sequence of SFTSV.

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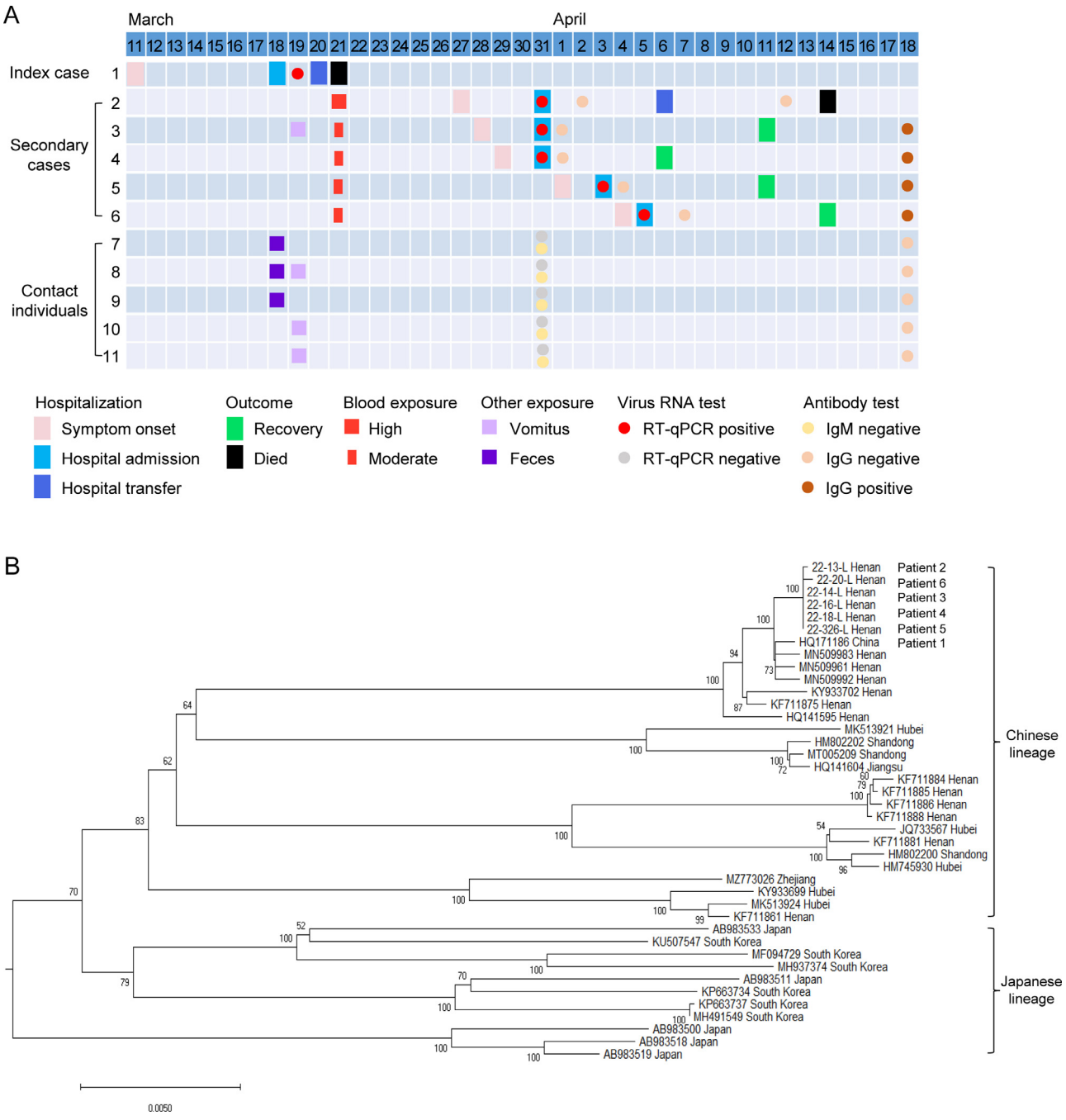

Figure 1. Epidemiologic curve, clinical course, and virus sequence analysis of the family cluster. Epidemiologic curves and key events during clinical course were shown (a). The specified number of each patient or contact individual was shown on the left side of the panel. Patients 2, 3, and 7-11 have taken care of the index patient. Phylogenetic tree (b) was conducted based on nucleotide sequences of SFTSV L-segment (6,368 bp) by using the Neighbor-joining method with p-distance model in the software MEGA X. Sequence from Heartland virus was used as the outgroup. The confidence of the phylogenetic tree was tested using 1000 bootstrap replications. Scale bar indicates number of substitutions per site. RT-qPCR, reverse-transcription quantitative polymerase-chain-reaction; SFTSV, Severe fever with thrombocytopenia syndrome virus.

Phylogenetic trees were conducted using MEGA X (detailed in the Supplementary Data).

RESULTS

The index patient, an 81-year-old man, was feeble, had fever, headache, anorexia, and nausea on March 11, and was admitted to a local hospital on March 18 and then diagnosed with SFTS (Figure 1a). The patient used to plant vegetables every day before symptom onset but reported no recent tick bite (Table S1). After admission, he had a high-level viremia and his condition deteriorated with development of cough, vomiting, diarrhea, and confusion and rapid progress to severe thrombocytopenia, disseminated intravascular coagulation (prothrombin time (PT) 15.9 seconds, activated partial thromboplastin time (APTT) 88.5 seconds, fibrinogen (FIB) 1.45 g/l), and multiple organ dysfunction (Figure S1). He was transferred to the intensive care unit on March 20; his disease aggravated and 1 day, later he was discharged from hospital and died at home that night.

Patients 2, 3, 6 (the sons of the index patient), 4, and 5 (the nephews of the index patient) had illness onset from March 27 to April 4 and were admitted to the hospital from March 31 to April

5, with laboratory-confirmed SFTSV infection (Figure 1a, Tables S1-S2). During hospitalization, patient 2 progressed to severe disease, complicated by diarrhea, convulsion, lethargy (Table S1), and persistent exacerbation of viremia, thrombocytopenia, and multiple organ dysfunction (Figure S1); he was then transferred and admitted to the intensive care unit in another local hospital and died on April 14. The other four patients recovered from the illness and had a negative qRT-PCR (Figure S1) after receiving supportive treatment for about 7-12 days. Seroconversion was observed in the four surviving patients but not in the patient who died (patient 2).

The five secondary patients resided in different villages (Figure S3), and none reported recent tick bite. They all reported having wiped and dressed the corpse of the index patient and having been exposed to the index patient's blood during the process while wearing masks and gloves but no eye protection (Figure S4). Particularly for patient 2, a massive amount of blood splashed onto his coat and soiled the gloves of the five patients while pulling the needle from the corpse. A total of 15 minutes after dressing the corpse, they left the mourning hall, sequentially took off and packed the gloves and coats; after disinfecting hands, they took off the masks at the last step.

Five family members had direct contact with the index patient's feces (patients 7-9) or vomit (patients 8, 10, and 11) while taking care of the index patient in the hospital (Figure 1a). None entered the mourning hall or had contact with the index patient's blood (Figure S4). Serum samples collected at 12 days after exposure to the feces or vomit were negative for SFTSV RNA or immunoglobulin M antibody, and serum samples collected after 30 days of exposure were also negative for SFTSV immunoglobulin G antibody.

SFTSV was successfully isolated from the index patient and the secondary patients 2 and 3. Phylogenetic analysis based on nearly complete SFTSV L- (6368 bp), M- (3378 bp), and S-segment (1744 bp) showed the sequences from the six patients were clustered into a separate branch belonging to Chinese lineage (Figure 1b, Figure S2, Table S3). Only 1-2 bp differences were determined in the L- and M-segment from two secondary patients (Table S4).

DISCUSSION

We reported a family cluster of SFTS human-to-human transmission. The index patient might have been infected with SFTSV through the bite of infected ticks because he had frequent field activity within 2 weeks before illness onset in such a hotspot endemic region (Li *et al.*, 2018). The five secondary patients were believed to be infected with SFTSV through simultaneous exposure to the blood of the index patient who had hyperviremia ($>10^8$ copies/ml) and the virus was successfully isolated. This can be evidenced by the identical SFTSV genome sequences from three of patients (patients 3-5) to that from the index patient. The nucleotide mutations in SFTSV sequences from patients 2 and 6 might result from the potential error rate derived from reverse-transcription process in the qRT-PCR. The tick-to-human transmission route is unlikely because none had a recent tick bite before symptom onset.

The intervals between exposure to blood and onset of illness ranged from 6-14 (median 8) days, which was comparable with previous case clusters that reported a median incubation of 10 days (Fang *et al.*, 2021). Differing from previously reported person-to-person transmission (Fang *et al.*, 2021), all the five secondary patients had been wearing gloves and masks when exposed to the blood; however, none of them wore goggles or face shields for eye protection. Therefore, ocular exposure to infectious blood might be a highly possible mode for SFTSV transmission. Indeed, SFTSV transmission through ocular membranes has recently been demonstrated in infection and lethal mouse models (Zhou *et al.*, 2022). Furthermore, the eyes acting as a source of infection transmission has been reported for other RNA viruses, such as Chikungunya virus and SARS-CoV-2 (Couderc *et al.*, 2012; Qu *et al.*, 2021).

Patient 2 developed the earliest disease with persistent hyperviremia ($>10^9$ copies/ml) and finally succumbed to the SFTSV infection, which might have been due to his greater exposure to the blood than the others through the direct splash of the blood onto him. The other five family members who had taken care of the index patient had been in close contact with the index patient's excretions in the absence of PPEs but were free of SFTSV infection, suggesting excretions, such as vomit and feces, from patients with SFTS without bleeding may confer lower transmission risks.

Few studies evaluated the efficacy of using PPEs in preventing SFTS human-to-human transmission. This study suggests that adequate PPEs should include protective clothing, gloves, masks, and goggles or face shields when caring for patients with SFTSV with hemorrhagic signs or handling a patient's needles or intubations. Among the PPEs, the eye protection is easily neglected and thus should be stressed for the clinicians who are frequently exposed to blood or bloody secretions.

Conflict of interest

The authors have no competing interests to declare.

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Ethical approval statement

The research protocol was approved by the human ethics committee of the institute, in accordance with the medical research regulations of China (AF/SC-08/02.114). All participants provided written informed consent to have their samples and information collected.

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Author contributions

W.L. and H.L. designed the study. H.L. and W.L. wrote the paper. Y. -X. W., X. Y., L. Y., Z. W., X. -J. F., and C. Y. recruited and followed up the subjects and collected the data. Y. -X. W., X. Y., and J. -C. L. performed laboratory tests. H. L. and Y. L. performed the data analysis. All authors contributed to review and revision and have seen and approved the final version of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.08.008.

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