



Case report

A person-to-person transmission cluster of severe fever with thrombocytopenia syndrome characterized by mixed viral infections with familial and nosocomial clustering

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ABSTRACT

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging tick-borne infectious disease with sporadic occurrence and high mortality. Herein, we report an example of the in-hospital transmission of SFTS virus (SFTSV) infections with familial and nosocomial clustering in Zhejiang Province, eastern China, from March to April 2023. The epidemiological investigation and genomic analysis revealed that at least eight suspected cases of SFTS occurred in this cluster, including one death and one asymptomatic case. Our report reemphasizes the risk of familial and nosocomial SFTSV infections in healthcare settings and the urgent need for the long-term systematic surveillance of SFTSV evolution in humans and animals in the eastern coastal regions of China.

1. Introduction

Severe fever with thrombocytopenia syndrome (SFTS) virus (SFTSV) is a tick-borne virus of the genus *Phlebovirus* in the family *Bunyaviridae*, which was first identified in 2009 in Hubei and Henan provinces in China [1]. Since then, cases of SFTS caused by SFTSV have been reported in several Asian countries, including China, South Korea, and Japan [2–4], and occasionally in other regions [5]. SFTS usually occurs sporadically, and the main routes of transmission are the bites of infected ticks and contact with infected animals [4]. SFTS has become a serious public health threat because of its high mortality and person-to-person transmission.

In recent years, there has been increasing concern about the potential for familial and nosocomial transmission of SFTSV. Several studies have reported clusters of SFTS cases among patients and healthcare workers in China and South Korea [6–8]. Herein, we report an in-hospital transmission of SFTSV infection with familial and nosocomial clustering in eastern China. Epidemiological investigation revealed that at least eight suspected cases of SFTS occurred in this cluster, with one death and one asymptomatic case. These cases highlight the importance of infection control procedures to prevent transmission of SFTSV among healthcare workers and patients' family members in healthcare settings.

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2. Case descriptions

The index patient was an 82-year-old woman from Xinchang County, Zhejiang Province, an SFTS-endemic area in China. On or around March 20, 2023, she went to neighboring tea plantations twice to pick tea leaves. On March 24, she was admitted to a local hospital because of high fever and diarrhea. Laboratory tests identified leukopenia and thrombocytopenia. She was administered intravenous infusions for symptomatic treatment over the next 2 days. Because of gastric hemorrhage and her deteriorating condition, she underwent gastric surgery before being transferred to intensive care on March 30. She finally died of unknown causes after experiencing multiple organ failure on April 1 in the hospital.

After the death of the index patient, four secondary cases, who may have had blood contact with the patient through skin or mucosa, sequentially developed SFTS-like symptoms within 5–10 days. In addition, there was one person with a close contact history without symptoms (Fig. 1 and S1). They all went to Hangzhou, the capital of Zhejiang Province, for medical treatment on April 15. Patient 2 was the doctor who had operated on the index patient and had been exposed to the patient’s acute-phase serum during medical treatment. Patients 3–6, family members of the index patient, had stayed in the hospital to care for her during her hospitalization and may have come into direct contact with the blood flowing from the patient’s mouth and nose during tracheal extubation after her death. Although all the familial cases wore gloves, the index patient’s blood still splattered onto their skin. As the asymptomatic case only helped others to clean the body, she had the least amount of contaminated blood splattered on her.

The familial clustering of cases in this outbreak and the fact that most patients developed typical clinical symptoms, including fever, diarrhea, thrombocytopenia, and leukopenia, raised a high suspicion of SFTS. Through an epidemiological investigation and laboratory testing, we provisionally identified five close contacts of the index patient with SFTSV infection on April 18: four of her family members and the doctor who treated her (Table 1). After supportive care, the patients were gradually discharged after April 21. Subsequent epidemiological investigations identified two other healthcare workers infected with SFTSV in this cluster in Xinchang County. However, as these two cases were admitted to the local hospital and managed locally, data on their detailed clinical manifestations and samples were not available.

On April 18, RNA extracted from serum samples of five secondary cases was then subjected to whole-genome sequencing using nanopore sequencing on the GridION platform, and the bacterial and viral pathogen spectra of potential co-infections were detected using metagenomic next-generation sequencing on a HiSeq 2000 (Table 1). Three full-length genomes of SFTSV from Patients 3, 4, and 5 and partial sequences from Patients 2 and 6 were obtained (GenBank Accession Nos. OQ938866–OQ938881). All of the sequences

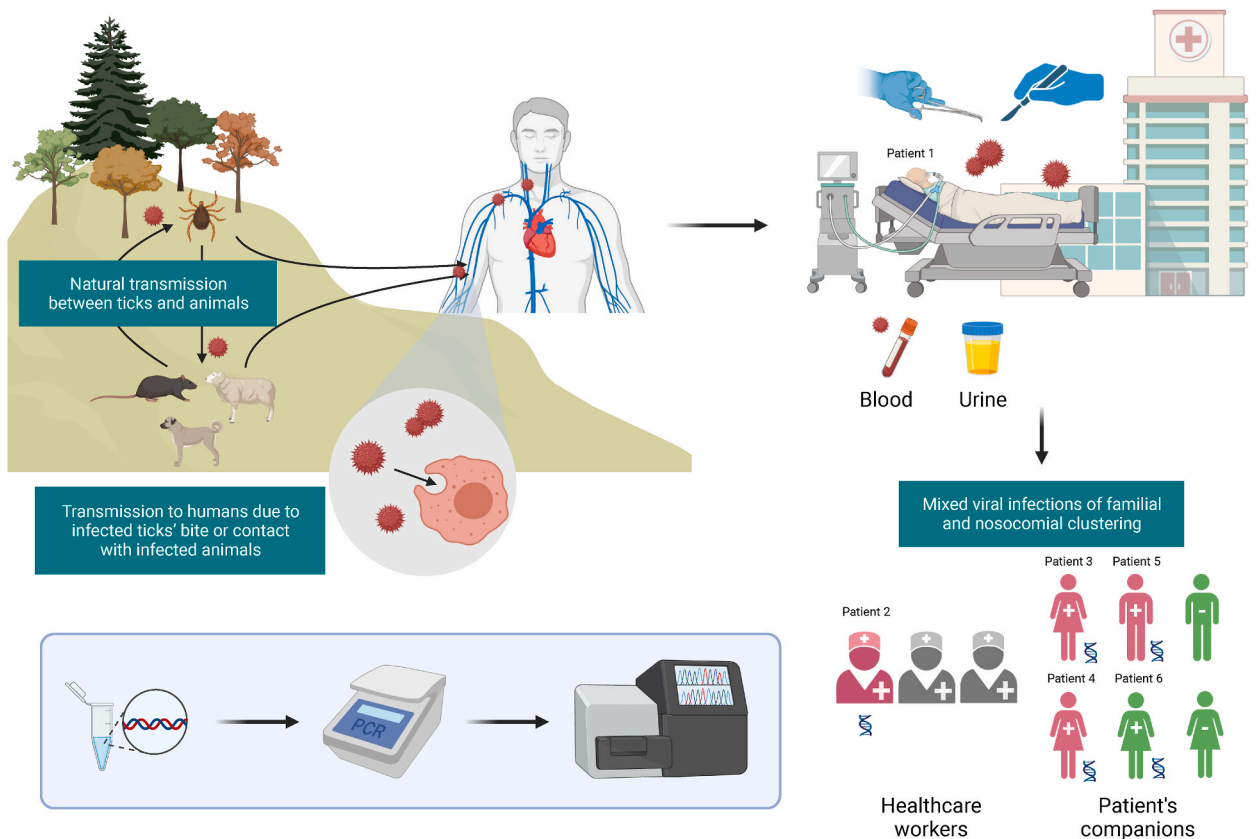


Fig. 1. Hypothetical route of person-to-person transmission cluster of SFTS characterized by mixed viral infections with familial and nosocomial clustering in this study. SFTS, severe fever with thrombocytopenia syndrome. Created with [BioRender.com](https://www.biorender.com).

Table 1

Clinical manifestations of the five secondary SFTS patients in this study. SFTS, severe fever with thrombocytopenia syndrome.

	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
General data					
Gender	Male	Female	Female	Male	Female
Age (years)	38	58	55	59	37
Date of onset	Apr 6, 2023	Apr 10, 2023	Apr 10, 2023	Apr 11, 2023	/
Outcome	Discharged	Discharged	Discharged	Discharged	Asymptomatic
Symptoms					
Maximal temperature (°C)	38.9	39.3	39.3	39.2	No fever
Nausea and vomiting	No	Yes	Yes	No	No
Diarrhea	Yes	Yes	Yes	Yes	No
Headache	Yes	No	No	Yes	No
Muscle pain	No	No	Yes	Yes	No
Abdominal pain	Yes	No	No	No	No
Bleeding	No	No	No	No	No
Coma	Yes	No	No	No	No
Convulsion	Yes	No	No	No	No
Laboratory finding					
Platelets (10 ⁹ /L)	48	53	104	55	/
White blood cell count (10 ⁹ /L)	2.21	1.42	2.72	1.39	/
Real-time RT-PCR (Ct) ^a	34.81	18.29	27.13	27.23	38.10
Genome sequencing					
Genome coverage (%) ^b	21.19	99.97	99.98	99.98	24.37
Average depth	34,368	6300	5422	7377	40,180

^a Samples were tested using real-time RT-PCR for SFTS virus.^b The lengths of L, M and S segments (GenBank Accession Nos. KY789434, KY789437, and KY789440) were 6368, 3378, and 1746 bp, respectively.

from the five secondary cases were almost identical (>99.99 % similarity), providing genetic evidence for the epidemiological findings of possible transmission of SFTSV from the index patient to the secondary patients. To determine the evolutionary relationship, the representative genome designated as SF23-6 from Patient 3 was compared with that of other SFTSV sequences downloaded from the GenBank database and with recent epidemic strains isolated from Zhejiang Province. Phylogenetic trees generated using MEGA X [9] revealed that the SFTSV SF23-6 belonged to genotype A (Fig. S2). The L, M, and S nucleotide sequences of these viruses clustered with the reported SFTSV isolates ZJ2014-02, NB38/CHN/2013, and KAICH collected from human serum in Taizhou, Ningbo (two cities surrounding Xinchang) and Korea, respectively, and isolate Ydog34 collected from *Canis lupus familiaris* in Japan, with high nucleotide identities ranging from 99.37 % to 99.76 %. Bayesian evolutionary analysis of the temporal dynamics using BEAST v2.7.3 [10] indicated that these isolates from eastern China, Korea, and Japan had the time of origin of the most recent common ancestor at 1992, 1987, and 1989 for the L, M, and S segments, respectively (Fig. S3). Their ancestral geographic states were estimated to be in Zhejiang Province, China (posterior probability = 1), suggesting a possible introduction of genotype A from eastern China to Korea and Japan in the latter part of the 20th century. No reassortment or recombination event was found using SIMPLOT v3.5 and RDP v4.101 [11,12]. Three amino acid substitutions potentially associated with SFTS lethality were identified, each occurring in the proteins of Gn (I491V), Gc (T960S), and NS (I223T) (Table S1).

3. Discussion

SFTSV is a tick-borne virus that causes SFTS and has a high mortality rate in humans, with reported rates ranging from 12 % to 30 % [1,13]. Although transmission is primarily by tick bite, the virus can also be transmitted through contact with the blood or body fluids of infected individuals, including those who are asymptomatic. Herein, we report person-to-person transmission of SFTSV in a cluster of eight SFTS patients in eastern China. Although the index patient was not laboratory-confirmed for SFTSV infection because of misdiagnosis and lack of a serum sample, epidemiological data and genomic evidence support person-to-person transmission through contact with contaminated blood.

The timely clinical diagnosis of SFTSV is crucial to prevent disease transmission. However, sporadic cases, nonspecific symptoms, and differential diagnosis with other infectious diseases make the diagnosis of SFTS difficult [14]. In this study, the index patient died of an unknown cause, whereas Patients 2, 3, and 5 were misdiagnosed as encephalitis or gastroenteritis at the early stage. The study emphasizes the importance of early detection and isolation of infected individuals to prevent further transmission.

Of the five secondary cases listed in Table 1, Patient 2 (the doctor) had the earliest onset and developed the most severe symptoms, including fever, loss of consciousness, and convulsions 11 days after the index patient's death, which may be related to exposure to a high viral load during the treatment process. The other four cases that were exposed to the index patient's blood after her death had mild clinical manifestations, suggesting a decreased but still infectious viral load in SFTSV-contaminated blood even after the patient's death. The asymptomatic cases in this cluster had confirmed blood exposure, in contrast to other reported asymptomatic cases without blood exposure [6]. Infection dose and immunological differences may explain the variation in clinical symptoms. Based on this study and other previous reports [6,7,15,16], most cluster outbreaks of SFTS were associated with nosocomial infections, family clusters, and funeral ceremonies. This highlights the need for standard precautions to prevent direct contact and blood-borne transmission, not only

during treatment, but also during the handling of the body, such as cleaning and dressing.

Based on these SFTSV cases, disease control measures need to be strengthened to prevent cluster transmission of the virus. 1) Infected patients should be isolated in single rooms with negative pressure ventilation. Limit the number of healthcare workers and visitors in contact with patients. 2) Direct contact with patients' bodily fluids should be avoided. Wearing gloves alone is not sufficient to prevent transmission of SFTSV. It is vital to wear waterproof protective clothing, face shields, and masks properly to prevent transmission through liquid splashes and aerosols. 3) Health education should be strengthened by disseminating knowledge on SFTSV prevention and control measures to healthcare workers, and awareness of disease prevention should be increased among community members. 4) Routine surveillance in humans and animals should be conducted to better understand and monitor the evolution of SFTSV.

4. Conclusions

Our report reemphasizes the risk of familial and nosocomial SFTSV infections in healthcare settings and the urgent need for the long-term systematic surveillance of SFTSV evolution in humans and animals in the eastern coastal regions of China.

Ethics declarations

This study was reviewed and approved by the Ethical Committee of Hangzhou Center for Disease Control and Prevention, with the approval number: [2022-HS12]. All participants/patients (or their proxies/legal guardians) provided informed consent to participate in the study and to the publication of their anonymised case details and images prior to the investigations.

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Data availability statement

Data are available from the corresponding author.

CRediT authorship contribution statement

Yanping Wen: Writing – review & editing, Writing – original draft, Validation, Software, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Yezen Fang:** Writing – review & editing, Resources, Investigation, Formal analysis, Data curation, Conceptualization. **Feifei Cao:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis. **Guozhong Zhang:** Writing – review & editing, Validation, Resources, Methodology. **Shi Cheng:** Writing – review & editing, Visualization, Resources, Methodology. **Yue Yu:** Writing – review & editing, Supervision, Software. **Renjie Huang:** Writing – review & editing, Investigation. **Zhimin Ni:** Writing – review & editing, Investigation. **Jun Li:** Writing – review & editing, Writing – original draft, Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.heliyon.2024.e24502>.

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