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BRIEF REPORT

Occupational Risk of Severe Fever With Thrombocytopenia Syndrome in Healthcare Workers

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We identified a healthcare-associated infection of severe fever with thrombocytopenia syndrome (SFTS) virus (SFTSV), transmitted through direct blood contact with an index case. Following further epidemiological and clinical investigations, we identified SFTSV seropositivity in 2 healthcare workers and 2 family members, who were positive for anti-SFTSV immunoglobin G. It is important to prevent SFTSV transmission by early diagnosis of SFTS and universal precautions.

Keywords. disease transmission; infectious disease; nosocomial infection; *Phlebovirus*; SFTS.

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging and fatal hemorrhagic disease, which is mainly reported in East Asia [1, 2]. SFTS virus (SFTSV) is transmitted to humans via tick bites, and domestic animals are considered to be the potential reservoir hosts [3]. SFTS is largely observed among farmers involved in agricultural activities as well as forest workers, and the majority of cases are reported in people of 50 years of age or older [2, 3]. Although SFTS is tick-borne disease, some studies have reported that SFTSV can be transmitted from person to person [4–6]. As this transmission is mostly driven by close contact to the index case, SFTS has been reported in healthcare workers (HCWs) [7], and asymptomatic infections have been noted in family members with close contact [4, 5]. Herein, we report a secondary SFTS patient who was in close contact with an index case via ambulance, and who contracted SFTS via direct blood contact with a skin wound. We investigated the presence of SFTSV and anti-SFTSV immunoglobulin (Ig) M and IgG in family members and other HCWs who had no history of blood exposure or tick bites.

METHODS

Clinical Investigation

The index patient was transferred from a local clinic to our hospital in October 2018 and was observed in the medical intensive care unit. SFTS was diagnosed on the first hospital day at our hospital. Unfortunately, despite receiving fully supportive treatment, the patient died on the second hospital day. Subsequently, we identified a secondary case of SFTS in the index patient's daughter, who had been in close contact with him without standard protection. Following this, we investigated other related HCWs and their family members to detect any additional secondary patients. We collected data on epidemiology, clinical features, transmission mode, and clinical outcome (Figure 1). Written informed consent to participate in the study was obtained from the patient, family members, and HCWs.

Epidemiological Investigation

The secondary patient contracted SFTS as a healthcare-associated infection from the index patient on Jeju Island in 2018. On October 26, 2018, we conducted an epidemiological investigation and began active surveillance on 5 family members and 4 HCWs who had been in contact with the index patient. We also interviewed family members and HCWs who had provided medical services to the index patient. Additionally, we obtained serum samples obtained from the family members and HCWs, and analyzed thses using reverse transcription polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA) to detect SFTSV and antibodies of SFTSV, respectively.

Molecular Diagnosis and Phylogenetic Analysis of SFTSV

RNA was extracted from stored patient serum using a QIAamp Viral RNA Mini Kit (QIAGEN, Hilden, Germany). RT-PCR was performed to amplify the partial small (S) and medium (M) segment of the viral RNA from the stored serum and confirmed SFTSV infection [8]. RT-PCR products (1480 bp) were sequenced using the BigDye Terminator Cycle Sequencing kit (Perkin Elmer Applied Biosystems, Warrington, UK). Phylogenetic analysis of the partial S segment sequences (1480 bp) was performed with MEGA6, and phylogenetic trees were constructed using the maximum likelihood method, which confirmed SFTSV infection [9].

Antibody Detection in Sera

ELISA was performed as previously described [4]. The cutoff value was set as the average value detected in control sera (sera

Received 19 February 2019; editorial decision 30 April 2019; accepted 1 May 2019.

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DOI: 10.1093/ofid/ofz210

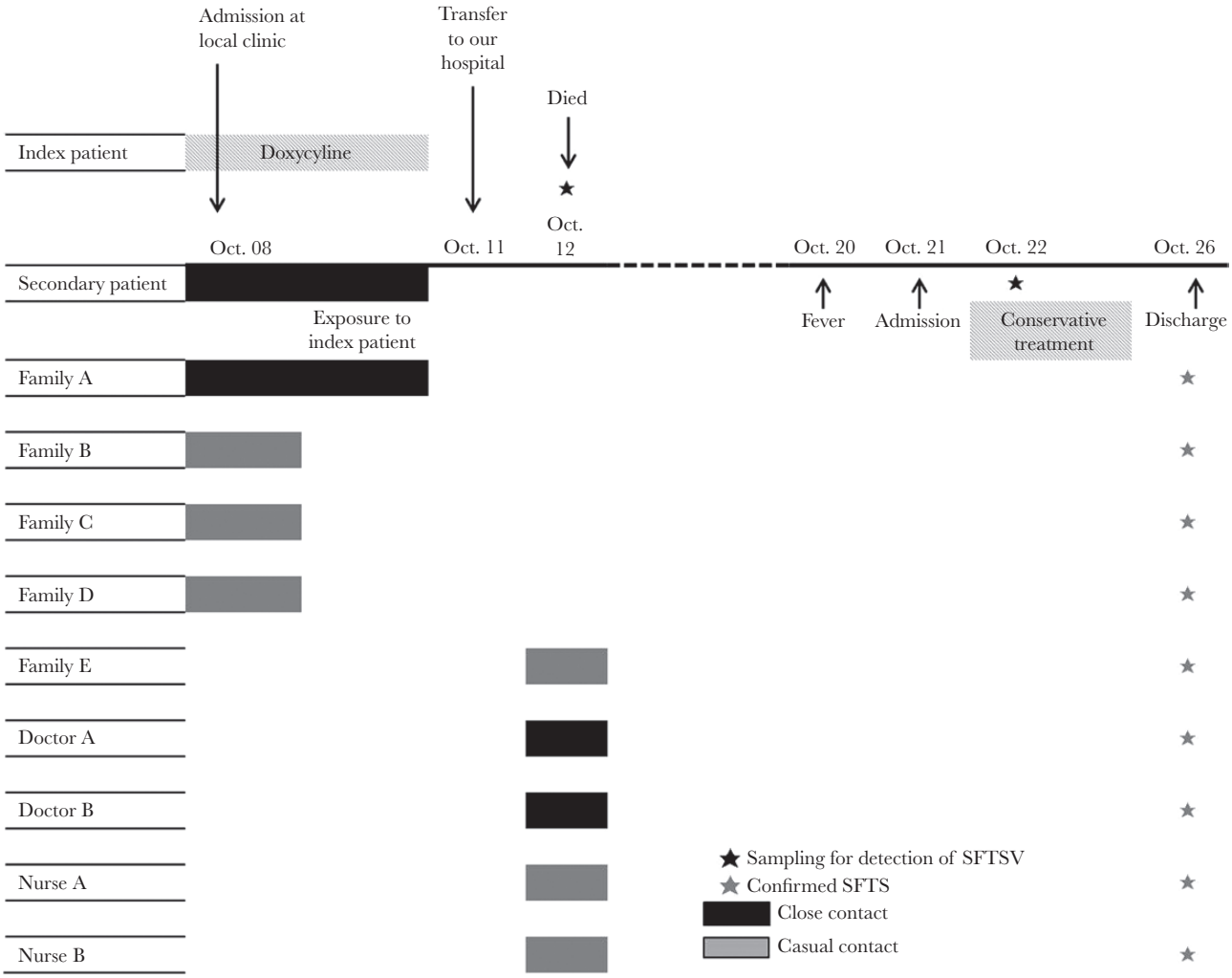

Figure 1. Time Table of the Family Cluster, Healthcare Workers, and Key Events That Occurred During the Index Patient's Illness. Patient A indicates index patient; family member A, index patient's wife; family member B,index patient's third daughter; family member C, index patient's son-in law; family member D, index patient's son; family member E, index patient's first daughter; IgG, immunoglobulin G; IgM, immunoglobulin M; Oct, October; RT-PCR, reverse transcription polymerase chain reaction; SFTS, severe fever with thrombocytopenia syndrome; SFTSV, severe fever with thrombocytopenia syndrome virus.

from healthy donors) plus three times the standard deviation (SD; cutoff value = mean + 3 × SD). A sample was considered positive if it yielded an OD_{405nm} value that was higher than the cutoff value.

RESULTS

Case Description

The index patient was a 68-year-old man, who was admitted to a local clinic with fever of unknown origin. He was suspected of having scrub typhus and was treated with doxycycline for 3 days. However, his altered mental status and multiple organ dysfunctions worsened, and he was transferred to our hospital via ambulance with a nurse (who was also his second daughter) without standard protection. During this process, his intravenous line fell out and the patient began bleeding from the site. The nurse immediately covered the bleeding site using her bare hand, which had a small entry wound on the right 3rd finger. The index patient was diagnosed with SFTS in our hospital and died of multi-organ failure the next day. The secondary patient was the index patient's daughter, a healthy 36-year-old woman, who worked as a paid nurse at a local clinic. She presented with fever, chills, and myalgia 10 days after experiencing contact with the index patient's blood. There were no signs of tick bite lesions or skin rashes on her whole body. The following vital signs were recorded on physical examination: body temperature, 39.4°C; blood pressure, 120/80 mmHg; pulse rate, 95 beats/minute; and respiratory rate, 20 breaths/minute. An initial complete blood count revealed leukopenia (2000/mm^3) and thrombocytopenia (136 000/mm^3). Aspartate aminotransferase and alanine aminotransferase levels were in the normal range. Additionally, creatinine phosphokinase and lactate dehydrogenase levels

were also in the normal range. She was diagnosed with SFTS using RT-PCR on the first hospital day (Supplementary figure 1A); phylogenetic tree analysis showed that SFTSV S and M segments with 100% similarity were detected in both the index and the secondary patient (Supplementary figure 1B). She was discharged on the sixth hospital day.

Epidemiological Investigation of Subjects Who Were in Close Contact With the Index Patient

Serum samples from a total of 11 subjects (2 SFTS patient, 5 family members, and 4 HCWs) were tested for SFTSV using RT-PCR, and tested anti-SFTSV IgM and IgG using ELISA. SFTSV was not detected in the serum of any HCWs and family members. Anti-SFTSV IgM antibody was not detected in any of the subjects except the secondary patient (Table1). Two family members (family member A and D) and 2 HCWs (doctor A and B) tested positive for anti-SFTSV IgG antibody (Figure 1). After 2 months, the secondary patient was tested again for anti-SFTSV IgM/IgG in her blood and exhibited seroconversion to anti-SFTSV IgG (Table 1). During the study period, no additional family members or HCWs were confirmed as having SFTS. Family member A had been living in the index patient's house for a long time; while family member B, C, and D had maintained only casual contact with the index patient at the local clinic without exposure to body fluids. Among these, family member A and D both tested positive for anti-SFTSV IgG. They showed no infectious symptoms after contact with the index patient. Family member D, who frequently visited the index patient's farm, reported that he had never experienced a tick bite. Four HCWs had been in direct contact with the index patient in our hospital. Doctor A and B were exposed to the index patient when they inserted a central venous catheter on the first hospital day, which resulted in bleeding; in addition, they performed a spinal tap without using masks. They also did not show a infectious symptoms during the 2 months of post-exposure.

DISCUSSION

We oberved that SFTSV could be transmitted to a HCW through direct blood contact with an index SFTS patient. Additional secondary patients were identified using molecular methods to identify the presence of SFTSV-specific antibodies, even though they did not have any direct contact with the index patient's blood. Secondary infection probably could have been prevented if the nurse (secondary patient) had used gloves. Furthermore, the index patient was initially misdiagnosed with tsutsugamushi disease, as the region is endemic for *Orientia tsutsugamushi* and the patient was admitted during the outbreak season. It may be that the HCWs ignored usual contact precautions for this reason. In addition, 4 subjects (2 family members and 2 HCWs) tested positive for anti-SFTSV IgG. As our region has a SFTSV seroprevalence rate of 2.4% (unpublished data), the 2 family members could have been exposed previously to SFTSV in the community. However, it is unlikely that the 2 HCWs were exposed to ticks or vertebrate reservoirs as they were both young and did not participate in outdoor activities. It is more likely that they were previously exposed to other SFTS patients at the hospital. Our results highlight the importance of standard precautions against SFTSV in both HCWs and in family members of cases, especially in endemic areas.

To identify secondary patients, we used RT-PCR and ELISA to detect anti-SFTSV IgM in serum. Although SFTSV isolation and viral RNA detection are the gold standards for diagnosis [1], we additionally tested for anti-SFTSV IgM using ELISA, because the index patient's family members and related HCWs had been exposed for 2 weeks and did not show any SFTS-related symptoms. As anti-SFTSV IgM can be detected at a median of 9 days and persists until 6 months after disease onset [10], we were able to use this method to confirm that there were no additional secondary patients. We hypothesized that the secondary patient was infected following exposure of her skin wound to the index patient's blood. Based on the duration

Table 1. Results of the Tests for Anti-SFTSV Antibodies and of RT-PCR for SFTSV in SFTS Patient, Family Members, and Healthcare Workers

	1st sampling result			Result for follow up after 2 months	
Subjects	RT-PCR	IgM	IgG	IgM	IgG
Index patient	**P**	**N (0.41)**	**N (0.65)**	**N/A**	**N/A**
Secondary patient	**P**	**P (1.81)**	**N (0.86)**	**N (0.80)**	**P (6.71)**
Family A	**N**	**N (0.68)**	**P (1.57)**	**N/A**	**N/A**
Family B	**N**	**N (1.00)**	**N (0.89)**	**N/A**	**N/A**
Family C	**N**	**N (0.46)**	**N (0.53)**	**N/A**	**N/A**
Family D	**N**	**N (1.47)**	**P (1.22)**	**N/A**	**N/A**
Family E	**N**	**N (0.58)**	**N (0.62)**	**N/A**	**N/A**
Doctor A	**N**	**N (0.72)**	**P (2.00)**	**N/A**	**N/A**
Doctor B	**N**	**N (0.83)**	**P (1.27)**	**N/A**	**N/A**
Nurse A	**N**	**N (0.56)**	**N (0.76)**	**N/A**	**N/A**
Nurse B	**N**	**N (0.59)**	**N (0.83)**	**N/A**	**N/A**

Abbreviations: IgG, immunoglobulin G; IgM, immunoglobulin M; N/A, not applicable ; N, negative; P, positive; RT-PCR, reverse transcription polymerase chain reaction; SFTS, severe fever with thrombocytopenia syndrome; SFTSV, severe fever with thrombocytopenia syndrome virus.

between exposure and testing in the 2 doctors, we presumed that 2 HCWs had contracted healthcare-associated infections from the other SFTS patient other than this index patient, because SFTSV IgG antibody could be detected at a median of 6 weeks [10].

According to previous reports, person-to-person transmission of SFTSV to HCWs can occur through contact with blood or respiratory secretions [7] and through aerosol transmission during resuscitation in HCWs [11]. Transmission is reported through direct contact, aerosol transmission [12], and through frequent personal contact [4, 5] in household members of primary patients. A previous study has suggested that person-to-person transmission might occur via direct contact with blood or bloody discharge [13]. In addition, SFTSV has been detected in blood, tracheal aspirate, gastric aspirate, and urine [14]. Therefore, precautions regarding direct contact and droplet transmission should be considered in both family members and HCWs [15]. Fortunately, most secondary patients show mild clinical presentations and good prognoses compared with the primary patient, suggesting that the transmission route makes a difference in SFTS progression [6].

Our study described a secondary SFTS patient who contracted the infection through direct contact with the index patient and reported seropositive HCWs in whom the transmission modes were unknown. As our region has the highest incidence of SFTS in South Korea and as most patients have visited our hospital [3], HCWs are always at risk for SFTS exposure until diagnosis of the patient is confirmed. As such, we recommend universal precautions at all times while dealing with patients with fever.

This study had several limitations. First, the evidence of SFTS transmission from the index patient to the 2 HCWs and 2 family members is weak. Second, we have likely underestimated the proportion of transmission, because it has been shown that IgM and IgG are detectable in 60% and 20% of SFTS patients by 2 weeks post-onet, respectively [10]. Third, it is difficult to draw a firm conclusion on the source of SFTS in the 2 HCWs, as they may have had contact with other SFTS patients unknowingly. Finally, there are other viable transmission routes, such as mucosa contact, droplet, and aerosol, which cannot be excluded completely.

To our knowledge, this is the first report of SFTSV transmitted via skin wounds in a HCW. In conclusion, HCWs and family members of cases should follow universal precautions while taking care of SFTS patients.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

The study was approved by the institutional review board (IRB) at the Jeju National University Hospital (IRB file no. 2018-11-002).

Financial support. This work was supported by a research grant from Jeju National University Hospital in 2018.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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