Nosocomial Transmission of Severe Fever With Thrombocytopenia Syndrome in Korea

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Of the 27 healthcare workers (HCWs) who had contact with a fatally ill patient with severe thrombocytopenia syndrome in Korea (SFTS), 4 who were involved in cardiopulmonary resuscitation complained of fever and were diagnosed with SFTS via seroconversion. Exposure to respiratory secretions, blood, or gowns soiled by body fluids was significantly associated with infection of HCWs.

Keywords. SFTS; nosocomial transmission; healthcare worker.

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease, first reported in China [1] and recently reported in Korea and Japan [2, 3]. The causative agent is a novel bunyavirus, designated SFTS virus (SFTSV) [1]. Although SFTS is thought to be transmitted by ticks such as *Haemaphysalis longicornis* [4], the exact mode of transmission remains unclear. Previous studies have identified several clusters of SFTSV infections in family members that appear to have been transmitted by human contact [4–9]. However, only 2 studies mention possible transmission from index patients to healthcare workers (HCWs) [4, 6], and data on the details of nosocomial transmission of SFTSV are limited in terms of attack rates and risk factors for transmission to HCWs. We report the results of an investigation of apparent cases of nosocomial transmission of SFTSV to HCWs.

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SUBJECTS AND METHODS

Epidemiologic Investigation

The cluster involving suspected nosocomial transmission occurred in a tertiary care hospital in Seoul, South Korea. On 15 September 2014, a doctor working in the emergency department was admitted with fever to the infectious disease ward. During history taking, his contact on 4 September 2014 with the index patient with suspected fatal scrub typhus was noted. On 18 September 2014, we received a report from the Korea Centers for Disease Control and Prevention that the index patient was positive for reverse transcription polymerase chain reaction (RT-PCR) for SFTSV. At that point, we suspected possible nosocomial transmission from the index patient. An epidemiological investigation of all HCWs who had been in contact with the index patient was immediately initiated. A standardized questionnaire was used to collect demographic information, symptoms, details of exposure to the index patient, and history of outdoor activity. We collected paired sera from all the HCWs between 19 and 25 September (about 3 weeks after exposure to the index patient) and 13–17 October (about 6 weeks after exposure to the index patient).

Laboratory Testing

An immunofluorescence assay (IFA) was used to detect anti-SFTSV immunoglobulin G (IgG), and RT-PCR was performed to detect SFTSV RNA. RNA was extracted from the serum using a viral RNA extraction kit (iNtRON Biotechnology, Gyeonggi, South Korea) according to the manufacturer's instructions. To detect SFTSV RNA, the one-step RT-PCR was performed using a DiaStar 2X OneStep RT-PCR Pre-Mix kit (SolGent, Daejeon, South Korea) with the primers MF3 (5′-GATGAGATGGTC-CATGCTGATTCT-3′) and MR2 (5′-CTCATGGGGTG-GAATGTCCTCAC-3′) under the following condition: 30 minutes at 50°C for reverse transcription and 15 minutes at 95°C for denaturation as initial step, followed by 35 cycles of 20 seconds at 95°C, 40 seconds at 58°C, and 30 seconds at 72°C, and a final extension step of 5 minutes of 72°C. Virus was isolated by incubating sera into 2 wells of Vero E6 cells. For IFA, Vero E6 cells infected with SFTSV were incubated at 37°C in a 5% CO_2 incubator. Cells were harvested, inoculated,

Table 1. Clinical, Laboratory, and Serological Findings for the Index Patient and 4 Healthcare Workers With Severe Fever With Thrombocytopenia Syndrome

		Nurses		Doctors	
Characteristic	Index	1	2	1	2
From contact to symptom onset	NA	5 d	12 d	7 d	9 d
Clinical findings					
Fever	Yes	Yes	Yes	Yes	Yes
Myalgia	Yes	Yes	Yes	Yes	Yes
Malaise	Yes	Yes	Yes	Yes	Yes
Bleeding	Yes	No	No	No	No
Rash	Yes	No	No	No	No
Personal protective device use					
Mask	NA	Yes	Yes	Yes	Yes
Glove	NA	No	No	Yes	Yes
Facial shield or goggle	NA	No	No	No	No
White blood cell count ($\times 10^9$/mL)	10 000	2900	2600	6000	2100
Platelet count ($\times 10^9$/mL)	52	151	123	221	101
IFA (IgG)					
Acute	<1:32	1:512	<1:32	1:64	<1:32
Convalescence	NA	1:1024	1:512	1:1024	1:512
RT-PCR	(+)	(–)	(–)	(–)	(–)
Viral culture	(+)	ND	ND	ND	ND

Abbreviations: (+), positive results; (–), negative results; IFA, immunofluorescence assay; IgG, immunoglobulin G; NA, not applicable; ND, not done; RT-PCR, reverse transcription polymerase chain reaction.

and fixed with acetone on Teflon-coated well slides. IFA was carried out using the patient's serum as the primary antibody and fluorescein-labeled antihuman IgG secondary antibodies (Thermo Fisher Scientific). A monoclonal anti-SFTSV N antibody (manufactured in our laboratory) was used as the positive control.

Statistical Analysis

Categorical variables were compared using the χ^2 test or Fisher exact test, as appropriate. All tests of significance were 2-tailed and a P value of <.05 was considered to indicate statistical significance. Calculations were performed using the SPSS for Windows software package, version 21 (SPSS Inc, Chicago, Illinois).

RESULTS

Index Patient

The index patient was a 68-year-old woman who lived in a rural area 50 km from Seoul and frequently worked in a kitchen garden. She was admitted to hospital with altered mental status on 4 September 2014. Physical exam revealed an eschar on her arm. Laboratory testing performed on admission revealed leukopenia (white blood cell count, 10.0×10^9/L) and thrombocytopenia (platelet count, 52×10^9/L). Scrub typhus, which is endemic in South Korea, was suspected initially and doxycycline was administrated. Seizure with respiratory arrest occurred 9 hours after admission, and cardiopulmonary resuscitation (CPR) was performed. Despite this, the patient died 12 hours after admission. The final diagnosis was available on 18 September 2014: RT-PCR for SFTSV was positive and the viral titer was 3.7×10^8 copies/mL. Culture was positive for SFTSV, but IgG against SFTSV was <1:32 (Table 1).

Nosocomial Cases of SFTS and Contact Investigation

A total of 27 HCWs contacted the index patient in the emergency department and isolation ward. Of these, 7 were actively involved in CPR of the index patient, of whom 4 complained of fever (Table 1). The median time from contact to symptom onset was 8 days (range, 5–12 days). At the time of the epidemiologic investigation, only 1 of the HCWs, a doctor, had fever. PCR using sera from these 4 HCWs about 3 weeks after the exposure gave negative results. IFA using paired sera obtained from all the HCWs at about 3 weeks and again about 6 weeks after the exposure revealed seroconversion in 3 of the symptomatic HCWs and a 2-fold increase in titer in the remaining symptomatic HCW (Table 1). One HCW without any symptoms had IgG titers of 1:256 both 3 and 6 weeks after the exposure. He had no recent history of outdoor activity. The remaining 22 HCWs all exhibited IgG titers of <1:32 approximately 3 weeks and 6 weeks after the exposure. There was no evidence by serology of subclinical infection. The overall attack rate was 15% (95% confidence interval [CI], 4%–34%), but in the subgroup of 7 HCWs who were actively involved in CPR, the attack rate was 57% (95% CI, 18%–90%). HCWs who were exposed to respiratory secretions (3 of 7 HCWs) and blood (4 of 13 HCWs) demonstrated more symptomatic infection than those who were not exposed to respiratory secretions (1 of 20 HCWs; $P = .02$) or blood (0 of 14 HCWs; $P = .04$). In addition, HCWs who had gowns soiled with body fluid (3 of 5 HCWs) exhibited more symptomatic infection than those who did not (1 of 22 HCWs; $P = .01$). None of the HCWs used a face shield or goggles as personal protective equipment (PPE). Only 9 HCWs wore a surgical mask, 5 wore gloves, and 3 wore a surgical mask and gloves. Four of 11 HCWs who had used PPE (ie, surgical mask, gloves) had symptomatic infection vs 0 of 16 HCWs who had not used PPE ($P = .02$). Four of 9 HCWs who wore surgical mask had symptomatic infection vs 0 of 17 HCWs who did not ($P = .007$), and 2 of 5 HCWs who wore gloves had symptomatic infection vs 2 of 22 HCWs who did not ($P = .14$).

DISCUSSION

The previous studies mentioned possible transmission from the index patient to HCWs [4, 6]. Our report, together with

previous studies, indicates that SFTSV should be listed among possible nosocomially transmissible pathogens. Indeed, the HCWs who contacted the index patient did not wear appropriate PPE (as they would have been unlikely to do in a developed country) because the initial presumptive diagnosis was scrub typhus, in which no human-to-human transmission has been reported. We found that wearing PPE such as mask or gloves was associated with an increased risk of transmission. Possible explanations could be that the PPE was a proxy for the risk procedures in this study; on the other hand, inappropriate use of PPE (ie, only 3 HCWs wore both surgical mask and gloves and there was no facial shield or goggle usage) might not protect against transmission of SFTSV. The strict adherence to routine blood and body fluid precautions is necessary when HCWs are in contact with any patient, especially with anyone with suspected viral hemorrhagic fever or a tick-borne rickettsial disease.

There was no evidence of subclinical infection in any of the HCWs who were in contact with the index patient. Data on subclinical infection with SFTSV are limited. One study reported 1 symptomatic and 1 asymptomatic infection with SFTSV among 6 family members who were contacts of a fatally ill patient with SFTS [9]. Further studies are needed on this issue.

Our study has several limitations. First, infection in 1 of the symptomatic HCWs was not confirmed by IFA because there was only a 2-fold increase in antibody titer between the paired samples. However, those symptoms developed 5 days after contact with the index patient. The first serum was taken 2 weeks after symptom onset, and the IFA titer was high (1:512). We therefore assume that we were unable to document a 4-fold rise in titer because we failed to get an acute-stage serum sample. Second, because all HCWs breached the universal precautions, we could not evaluate what type of breaches of standard precautions were associated with SFTS transmission.

In conclusion, we have demonstrated transmission of SFTSV from a fatally ill patient to HCWs, possibly by blood or respiratory secretions. Standard strict precautions are needed with suspected patients with SFTS.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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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