

Case Report
Zoonotic Disease



Confirmed cases of severe fever with thrombocytopenia syndrome in companion cats with a history of tick exposure in the Republic of Korea

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ABSTRACT






Severe fever with thrombocytopenia syndrome (SFTS) is a zoonotic disease, and its clinical information and prevalence are important. This study was conducted on 22 feline patients from the Republic of Korea (ROK), suspected to suffer from a tick-borne disease. Four cats were positive for SFTS, and genotypes B-1, B-3, D, and F were identified. Clinical symptoms, such as anorexia, jaundice, thrombocytopenia, leukopenia, and hyperbilirubinemia, were detected. This is the first report of SFTS virus genotypes B-1, D, and F from cats in the ROK. Moreover, our results suggest that jaundice may be an indicator of SFTS in cats.

Keywords: Severe fever with thrombocytopenia syndrome; SFTSV genotype; jaundice; hyperbilirubinemia; creatine kinase; feline SFTS patients; zoonosis

INTRODUCTION

Severe fever with thrombocytopenia syndrome (SFTS) is an infectious, tick-borne disease (TBD) caused by the SFTS virus (SFTSV). Previous studies have reported that SFTSV is a causative agent of an emerging disease, mainly in China, Japan, and the Republic of Korea (ROK), and it is now prevalent in East Asian countries [1-3]. Incidentally, SFTSV-infected dogs and cats present human-like clinical symptoms, such as anorexia, leukopenia, and thrombocytopenia [4-7]. The interest in animal-to-human disease transmission has increased following the first report of direct SFTSV transmission from cats to humans in Japan [7-9]. In the ROK, although SFTSV infection has been confirmed in domesticated house and feral cats, the number of case reports remains limited [10,11]. Since SFTS is a zoonotic disease, it is important to report any clinical circumstances in veterinary fields, and search epidemiological situation in the region of occurrence for better understanding of public health risks.

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Conflict of Interest

The authors declare no conflicts of interest.

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In this study, we reported four cases, including one fatal case, in which SFTSV infection was confirmed in feline patients suspected of suffering from TBD in the ROK. Peripheral blood was used to detect the SFTSV antigen and examine the viral genotypes. Additionally, we performed a serological follow-up for the patients who tested positive for the SFTSV antigen for approximately one month.

CASE PRESENTATION

We examined 22 feline patients with a history of tick exposure, fever, anorexia, dyspnea, thrombocytopenia, leukopenia, liver enzyme elevation, and anemia for TBD-causing pathogens, such as *Anaplasma phagocytophilum*, *A. bovis*, *Ehrlichia chaffensis*, *E. canis*, *Borrelia* spp., *Babesia gibsoni*, and SFTSV, using reverse transcription (RT)-polymerase chain reaction (PCR) and nested PCR analysis at 16 animal hospitals in the ROK. As the amount of serum sample was insufficient, extraction of DNA and RNA for PCR testing was performed first, followed by antibody testing. Peripheral blood samples were collected with consent of the cat owners, and four of the 22 cats were single-positive for SFTSV. The regions where these cats live were identified as Seoul (cat 1), Gyeonggi (cat 2), Cheongju, Chungcheongbuk-do (cat 3), and Cheonan, Chungcheongnam-do (cat 4) in the ROK. Although the cats were domestic cats, they were often allowed to go outside, especially cats 3 and 4, according to their owners.

In the SFTSV-positive patients, anorexia was the most common clinical symptom, however, fever, depression, and jaundice were also reported (**Table 1**, **Fig. 1**). All SFTSV-positive cats exhibited thrombocytopenia (cat 1: 136,000 platelets/ μ L; cat 2: 0 platelets/ μ L; cat 3: 5,000 platelets/ μ L; and cat 4: 59,000 platelets/ μ L; reference range: 156,400–626,400 platelets/ μ L). Moreover, the patients displayed hematological abnormalities, including leukopenia (white blood cell [WBC] count: cat 2: 470 cells/ μ L; cat 3: 4,520 cells/ μ L; and cat 4: 4,100 cells/ μ L; reference range: 6,300–19,600 cells/ μ L), hyperbilirubinemia (total bilirubin: cat 2: 2.1 mg/dL; cat 3: 6.7 mg/dL; and cat 4: 5.3 mg/dL, reference range: 0.1–0.4 mg/dL), elevated feline serum amyloid A (fSAA; cat 3: 500.0 μ g/mL and cat 4: 198.6 μ g/mL, reference range: 0–0.5 μ g/mL), elevated aspartate aminotransferase (AST; cat 2: 222 U/L; and cat 4: 168 U/L, reference range: 18–51 U/L), elevated alanine transaminase (ALT; cat 4: 142 U/L, reference range: 22–84 U/L), and elevated creatine kinase (CK; cat 4: 579 U/L, reference range 87–309 U/L) (**Table 2**).

Table 1. Characteristics and clinical symptoms of the four cats infected with SFTSV

Characteristic feature	Case number of cats			
	1	2	3	4
Breed	Siamese	Persian	KSH	KSH
Age	6 yr	2 yr	2 yr	1 yr 4 mon
Sex	MC	M	MC	MC
Body weight (kg)	6.3	3.5	5.4	4.0
Clinical symptom				
History of tick exposure	O	X	O	O
Fever	X	X	O	O
Depression	X	X	O	O
Anorexia	X	O	O	O
Vomiting	X	X	X	X
Diarrhea	X	X	X	X
Jaundice	X	X	O	O
Anemia	X	X	X	X
Prognosis	Recovered	Recovered	Recovered	Died

SFTSV, severe fever with thrombocytopenia syndrome virus;

KSH, Korean short hair; MC, castrated male; M, male; O, symptoms present; X, symptoms absent.

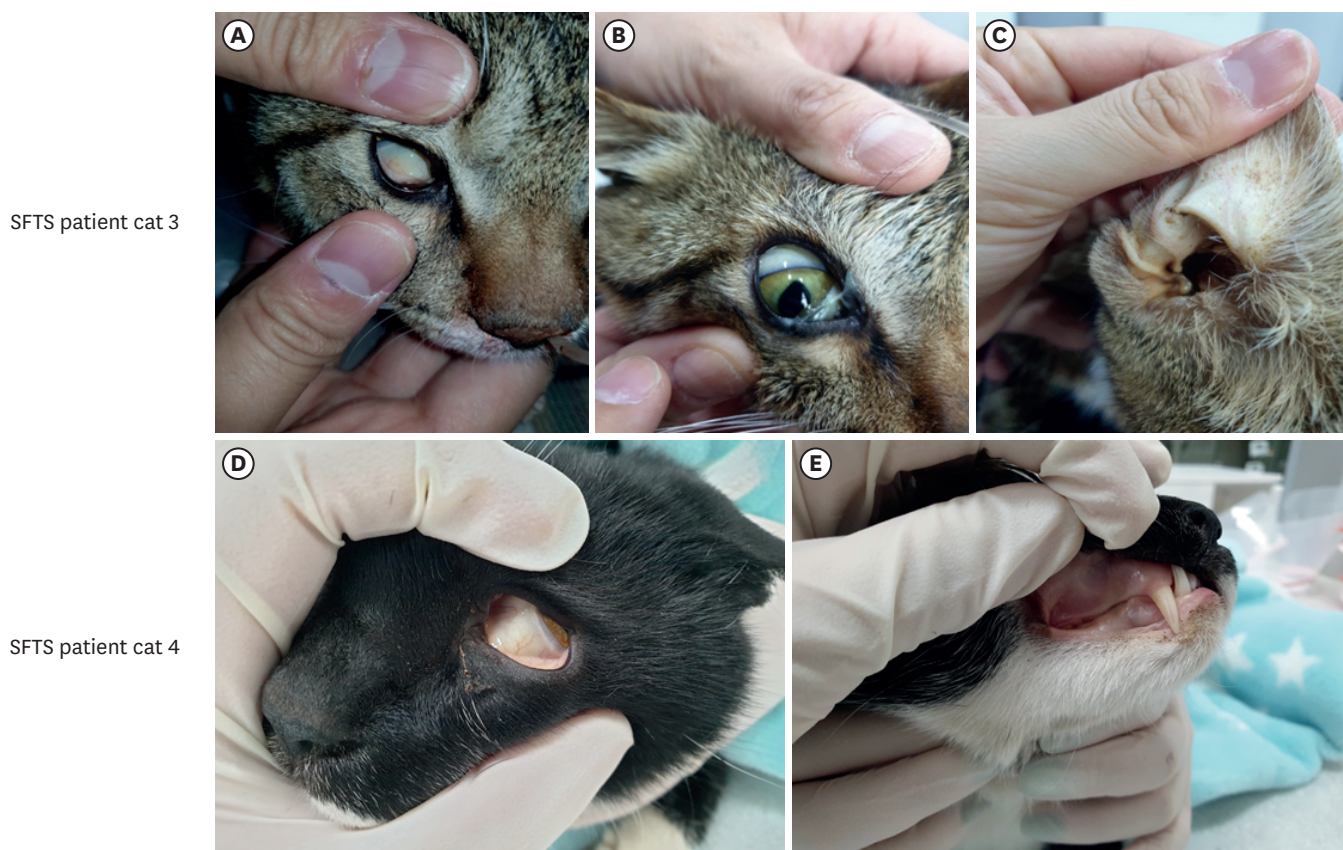


Fig. 1. Photographs of the cats suffering from SFTS. (A, B) Marked jaundice in the sclera of cat 3. (C) Marked jaundice in the ears of cat 3. (D) Marked jaundice in the sclera of cat 4. (E) Marked jaundice in the gingiva of cat 4. SFTS, severe fever with thrombocytopenia syndrome.

Table 2. Body temperature, hematological parameters, and SFTS tests from cat patients

Parameters	Reference ranges	Case number of cats			
		1	2	3	4
Body temperature (°C)	37.7–39.2	N	N	40.5	40.3
Complete blood count					
WBCs (10 ³ /μL)	6.3–19.6	15.42	0.47	4.52	4.1
Lymphocytes (10 ³ /μL)	2–7.2	5.5	0.15	2.46	0.37
RBCs (10 ⁶ /μL)	6–10.1	9.26	4.94	9.34	7.86
HCT (%)	27.7–46.8	41.8	38.5	38.5	31.5
Platelets (10 ³ /μL)	156.4–626.4	136	0	5	59
Serum chemistry					
AST (U/L)	18–51	NI	222	NI	168
ALT (U/L)	22–84	NI	44	76	142
ALP (U/L)	38–165	NI	9	1	75
Bilirubin (mg/dL)	0.1–0.4	NI	2.1	6.7	5.3
CK (U/L)	87–309	NI	NI	NI	579
fSAA (μg/mL)	0–5	NI	NI	500.0	198.6
SFTS tests					
Nested-PCR		Positive	Positive	Positive	Positive
Genotypes		D	F	B-3	B-1
Real-time PCR (Copy No. 10 ⁴ /mL)		NA	NA	46	0.16
IFA		≤ 1:64	NA	NA	≤ 1:128

SFTS, severe fever with thrombocytopenia syndrome; N, within normal range; WBC, white blood cell; RBC, red blood cell; HCT, hematocrit; AST, aspartate transaminase; NI, no information; ALT, alanine aminotransferase; ALP, alkaline phosphatase; CK, creatine kinase; fSAA, feline serum amyloid A; SFTS, severe fever with thrombocytopenia syndrome; PCR, polymerase chain reaction; IFA, indirect fluorescent assay; NA, not applicable.

To relieve clinical symptoms, cats 3 and 4 were provided with supportive care, including antibiotics, antiemetics, and an antacid. Cats 1 and 2 did not require these treatments as severe clinical symptoms were not presented. Ultimately, cats 1, 2, and 3 recovered and clinical symptoms were not reported after 5 months. Unfortunately, cat 4 died after 3 days due to worsening of the symptoms.

We detected the SFTSV antigen and the nucleotide sequences obtained in this study were aligned and compared with the reference sequences; the viral genotype was determined in a previous study [4]. A phylogenetic tree was constructed using the maximum likelihood method in the Molecular Evolutionary Genetics Analysis (MEGA) 7 software [12]. The results indicated that the S segment of cats 1, 2, 3, and 4 were of the genotypes D, F, B-3, and B-1, respectively (**Supplementary Fig. 1**). These generated nucleotide sequences have been deposited in GenBank under the accession numbers MW004848, MW004852, MW004853, and MZ171137, respectively.

Indirect immunofluorescent assay (IFA) was used to detect anti-SFTSV antibodies in the samples of cats 1 and 4; cats 2 and 3 were not tested due to a lack of serum. Briefly, the SFTSV-infected Vero E6 cells were resuspended at 5×10^3 cells/well in medium, and incubated in 5% CO₂ for 16 h. The slides were fixed with 100% acetone for 10 min at -20°C. After blocking with 5% goat serum for 2 h, diluted serum was spotted onto IFA antigen slides and incubated in 5% CO₂ for 1.5 h. After washing with phosphate-buffered saline, fluorescein isothiocyanate-conjugated anti-cat immunoglobulin G (IgG) was added to each well of the antigen slide and incubated in 5% CO₂ for 1 h [4]. The results of the IFA confirmed IgG antibody titers in the serum (at 1:64 dilution) of cat 1 on both day 0 and day 10. Since cat 4 died, only one sample, i.e., sample collected on the day of admission, could be assessed using the IFA; however, the IgG antibody titer was confirmed in the serum (at 1:128 dilution) (**Supplementary Fig. 2**).

The SFTS viral copy numbers from cat 3 (4.6×10^5 copies/mL) and cat 4 (1.6×10^3 copies/mL) were quantified using the PowerChek SFTSV real-time PCR kit (KogeneBiotech, Korea) according to the manufacturer's instructions (**Table 2**).

For the complete genetic sequencing of SFTSV, serum samples isolated from cats 3 and 4 were inoculated onto monolayers of Vero E6 cells for virus isolation. Cytopathic effects were visible within 5 days. The inoculated cells were subjected to an IFA and RT-PCR to detect the presence of SFTSV, and positive reactivity results were obtained. After the final identification of the SFTSV isolate, the nucleotide sequences analyses of the full segments of S, M, and L were completed using rapid amplification of cDNA ends (RACE) PCR. All generated nucleotide sequences for cats 3 and 4 have been deposited in GenBank under accession numbers OK423755, OL773688, OL773689, MZ342903, MZ352108, and MZ363633.

Ethics approval and consent to participate

This study was approved by the Seoul National University Institutional Animal Care and Use Committee (IACUC No. SNU-190617-6) and performed in strict accordance with the recommendations in the national guideline.

DISCUSSION

SFTSV presents an imminent threat to public health, particularly due to its ability of nosocomial transmission. Recent reports of the widespread occurrence of SFTS in Asia, as well as the inter-regional dispersal of competent vectors, indicate progression of the SFTS epidemic. Incidentally, the secretions of SFTSV-infected cats are indicative of high levels of viremia; therefore, secondary transmission of the virus through body fluids of infected cats is an important concept with respect to public health [13]. Recently, two veterinarians infected with SFTSV while handling a sick cat were reported in Japan [9]. Although SFTSV was not transmitted from the infected cats to humans in the present study, continuous surveillance is necessary to detect this pathogen in animals, particularly in human surroundings [7-9].

The SFTSV genotypes B (sub-genotypes B-1 and B-3), D, and F were identified in the present study. To date, B-3 and B-2 have been reported in the ROK, while only B-2 has been reported in Japan [14]. Interestingly, B-3 has been previously reported in humans (MK301482) and also in dogs (MN398158) and wild boars (MT502543) in the ROK. This study is the first to report B-1, D, and F in cats in the ROK. It is likely that this B-3 genotype has circulated in humans, tick, and wild animal populations in their natural environment, and therefore, animal viral sequence data could be useful for understanding the geographical distribution of these pathogens.

The symptoms of SFTS in humans include fever, loss of appetite, depression, thrombocytopenia, leukopenia, and elevated activities of liver enzymes [2]. Reports regarding feline-specific symptoms of SFTSV infection are limited, although hyperbilirubinemia and elevated fSAA have been reported previously [6,7]. In addition, liver damage in feline SFTS patients is caused by secondary pathological processes similar to that in human SFTS cases [13]. In the present report, the hematological parameters of infected cats were consistent with those previously described; jaundice with elevated activities of liver enzymes and fSAA were detected in two of the four cases (i.e., cats 3 and 4). Although additional studies are needed, we can infer that an increase in total bilirubin and fSAA levels, in combination with the general clinical symptoms of SFTS, maybe among clinical symptoms of SFTS in cats.

In a previous study in Japan, the CK level was increased in 10 of 24 SFTSV-infected cats and in 1 of 2 infected cheetahs [6,15]. In the current study, an increase in CK levels was confirmed in cat 4, which eventually died during the course of this study. Although the association of CK levels with the prognosis of SFTS requires further investigation, high CK levels may be a prognostic marker for evaluating SFTS infection in cats. Since animal to human transmission of SFTSV has been reported, veterinary hospitals, pet owners, veterinarians and veterinary staffs should be aware of potential risks, with particular emphasis on the importance of using personal protective equipment.

In conclusion, this case report indicates that jaundice, occurring due to elevated bilirubin levels, can be used as an important indicator symptom of SFTS in cats. Furthermore, this is the first report of the genetic subtypes B-1, D, and F in cats from the ROK; however, further study is required on the close phylogenetic relationship to determine an epidemiological association in the ROK. The fatal case of the SFTSV genotype identified in the four domestically infected cats was sub-genotype B-1, which may be closely related to the predominant domestic genotype B.

SUPPLEMENTARY MATERIALS

Supplementary Fig. 1

Phylogenetic tree and genotypes of SFTSV, based on analysis of partial sequences of small segments (346 bp) of SFTSV RNA. The sequences identified from SFTSV-positive companion cat samples of the current study are indicated in red-boldface. Maximum-likelihood analysis was used to construct the phylogenetic tree, based on the Kimura two-parameter model (1,000 bootstrap replicates).

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Supplementary Fig. 2

Results of the indirect IFA test for diagnosis of SFTS antibody from sera of companion cats. (A) Negative control; (B) 1:128 of dilution ratio in patient serum. Blue (4',6-diamidino-2-phenylindole), Green (green fluorescent protein). Scale bar = 75 μ m.

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