Advance Publication by J-STAGE

Japanese Journal of Infectious Diseases

A Patient with Severe Fever with Thrombocytopenia Syndrome (SFTS) Infected from a Sick Dog with SFTS Virus Infection

Hiroaki Oshima, Hironobu Okumura, Ken Maeda, Keita Ishijima, Tomoki Yoshikawa, Takeshi Kurosu, Shuetsu Fukushi, Masayuki Shimojima, and Masayuki Saijo

Received: November 22, 2021. Accepted: February 16, 2022.

Published online: February 28, 2022.

DOI:10.7883/yoken.JJID.2021.796

Advance Publication articles have been accepted by JJID but have not been copyedited or formatted for publication.

**A Patient with Severe Fever with Thrombocytopenia Syndrome (SFTS) Infected
from a Sick Dog with SFTS Virus Infection**

Running title: Case of canine-associated SFTS

Hiroaki Oshima^{1#}, Hironobu Okumura^{2#}, Ken Maeda^{3#}, Keita Ishijima³, Tomoki Yoshikawa⁴, Takeshi Kurosu⁴, Shuetsu Fukushi⁴, Masayuki Shimojima⁴, Masayuki Saijo^{4*}

¹ Oshima Animal Hospital, 39-4 Yamahata, Okuno, Aizumi-cho, Itano, Tokushima 771-1201, Japan

² Clinic Okumura, 70-7 Nagaekuchi, Okuno, Aizumi-cho, Itano, Tokushima 771-1201, Japan

³ Laboratory of Veterinary Microbiology, Joint Faculty of Veterinary Medicine, Yamaguchi University; present address Department of Veterinary Science, National Institute of Infectious Diseases, 1-23-1 Toyama, Shinjuku-ku, Tokyo 162-8640, Japan

⁴ Department of Virology 1, National Institute of Infectious Diseases, 4-7-1 Gakuen, Musashimurayama City, Tokyo 208-0011, Japan

*** Corresponding author:** Masayuki Saijo, MD, PhD, Department of Virology 1, National Institute of Infectious Diseases, 1-23-1 Toyama, Shinjuku-ku, Tokyo 162-8640, Japan. E-mail: msaijo@nih.go.jp

(Present address: Medical Affairs Department, Health and Welfare Bureau, Sapporo City,
Building West 19, Odori West 19, Chuo-ku, Sapporo, Hokkaido 060-0042, Japan. E-mail:
masayuki.saijo@doc.city.sapporo.jp)

#: HOs, HOk, and KM contributed to this study equally.

Key words: severe fever with thrombocytopenia syndrome, SFTS, SFTS virus,
domesticated dogs, dog-to-human infection

ABSTRACT: Severe fever with thrombocytopenia syndrome (SFTS) caused by Dabie bandavirus (formerly SFTS virus, SFTSV), which belongs to the *Bandavirus* genus (formerly *Phlebovirus* genus) of the *Phenuiviridae* family (formerly *Bunyaviridae* family) is a tick-borne novel bunyavirus infection with high case fatality. A 4-year-old dog sickened with symptoms of lethargy and anorexia was diagnosed as having SFTSV infection virologically in western Japan in June 2017. The dog's owner, a man in his 40s, had taken care of the sick dog and became sick 10 days after disease onset in the dog, showing symptoms such as fever, arthralgia, headache, and nausea and vomiting. Total blood cell counts revealed leukocytopenia and thrombocytopenia. He was treated on an outpatient basis. He had no scars suggesting that he had been bitten by tick and was diagnosed as having SFTS by detection of IgM and neutralizing antibodies to SFTSV. The patient was infected with SFTSV directly from the SFTSV-infected dog. Humans can be at risk of SFTSV infections through direct contact with sick dogs infected with SFTSV.

Severe fever with thrombocytopenia syndrome (SFTS) caused by Dabie bandavirus (formerly SFTS virus, SFTSV), which belongs to the *Bandavirus* genus of the *Phenuiviridae* family was first reported as a novel bunyavirus infection in China (1). SFTS is also endemic to Japan (2) and the Republic of Korea (3). Patients usually suffer from SFTS when infected with SFTSV via the bite of the ticks *Haemaphysalis longicornis* and *Amblyomma testudinarium*.

A 4-year-old male dog showed symptoms of decreased appetite, decreased activity, and fever in western Japan, in June 2017. The dog was taken to an animal clinic 3 days after disease onset. Total blood cell counts (TBC) revealed leukocytopenia (1,700/ μ L; normal range: 6,000-170,000 cells/ μ L) and thrombocytopenia (148,000/ μ L; normal range: 200,000-500,000 cells/ μ L). Serum chemistry analyses revealed increased levels of C-reactive protein and liver-associated enzymes (Table 1). The dog's body temperature returned to a normal range 6 days later from the disease onset, but right cervical lymph node enlarged. Bloody stool and diarrhea occurred at the same time. The dog was diagnosed as having SFTSV infection virologically by detection of SFTSV genome with reverse transcription polymerase chain reaction (RT-PCR) targeting partial S-segment genome of SFTSV and antibody response to SFTSV (4, 5).

The male owner aged in his 40s of the dog got sick 10 days after disease onset of the dog. He showed symptoms of fever, joint pains, headache, and loss of appetite in the early phase of the disease, followed by nausea, vomiting, and diarrhea. He was treated at a clinic with hydration and symptoms-based treatment. He became afebrile and got well on Day 7, with the day on which fever appeared considered as Day 0. His TBC on Day 5

revealed the presence of leukocytopenia and thrombocytopenia, as indicated by white blood cell (WBC) and platelet counts of 2,600 cells/ μ L (normal range: 4,000-9,000 cells/ μ L) and 146,000 cells (normal range: 150,000-450,000 cells/ μ L), respectively. His C-reactive protein was negative, and urine was negative for proteinuria and hematuria.

The blood taken from the sick dog after 3 days of the disease onset showed a positive reaction in the RT-PCR. Phylogenetic analysis conducted using the nucleotide sequence of the partial S-segment amplified from the dog, indicating that the SFTSV that caused the SFTSV disease in the dog belonged to Genotype J1 (Fig. 2) (6). Furthermore, a significant increase in the optical density values for SFTSV-IgG between the acute and convalescent phases. SFTSV-IgM antibody was also detected in the acute phase in the ELISA (Fig. 1B).

Because the domesticated dog raised by the man was diagnosed as having SFTSV infection, a serum sample collected from the patient two months after disease onset was retrospectively tested for IgG and IgM by indirect immunofluorescence assay (IIFA), and neutralization antibodies to SFTSV (5). IgM and IgG antibodies to SFTSV measured in the IIFA were 40 and > 640 , respectively (Fig. 1B). It was also positive in the neutralization antibody assay. The patient was, therefore, diagnosed serologically as having SFTS in a retrospective manner.

The dog might have been infected with SFTSV through a tick bite as the dog owners frequently took the dog for a walk. Because approximately half of patients with SFTS do not have tick-bite scars (7), the possibility that the present patient was infected with SFTSV through a tick bite could not be ignored. However, we consider that he was infected with SFTSV through close contact with the sick dog for the following reasons:

1) he did not have tick-bite scars, 2) he took care of the sick dog with his bare hands and without wearing any personal protective equipment, 3) the symptoms appeared within the incubation time from disease onset in the dog, 4) the symptoms were similar to those of previously reported patients with SFTS (1, 2), and 5) IgG, IgM, and neutralization antibodies to SFTSV were detected 2 months after disease onset in the patient.

The SFTSV antibody-positive rate among populations consisting of elderly persons 50 years of age and older in the endemic area in Ehime prefecture was approximately 0.5% (8). A similar SFTSV antibody-positive rate was reported from Kagoshima prefecture, western Japan (9). These evidences support the speculation that he became IgM and IgG SFTSV-antibody positive by the infection through tick-bites is exceptionally rare event. He had an evidence that he directly touched the dog in an acute phase. It is acceptable that he was infected with SFTSV through the close contact with the sick dog.

Kobayashi et al conducted an epidemiologic study on SFTS in Japan during 2013–2017 (7). The study reported that 48% of 64 patients had a close contact with companion animals within 2 weeks of disease onset. Three patients were confirmed to have had direct contact with body fluids of their ill companion animals, and 2 of them had direct contact with the saliva of an ill cat or a pet dog each. The patient with SFTS in this study was the SFTS patient, who had been reported as a patient with SFTS who had a close contact with a sick dog in the Kobayashi's epidemiologic study (7). Although there have not been the reports describing SFTSV shedding in saliva in dogs infected with SFTSV, there are the reports describing that saliva contained SFTSV in cats infected with SFTSV (10, 11). It is very likely that the saliva of dogs and cats with SFTSV infection contain infectious

SFTSV because they might show hemorrhagic symptoms (12).

The present study indicates that dog owners and veterinary doctors and nurses, who have a higher chance to contact sick animals, should take this risk into account and should strictly practice infection control measures in SFTS-endemic areas when animals become sick for no known reason. Development of therapies based on antiviral agents and preventive measures, including vaccine development, against SFTS are required. The efficacy of favipiravir has been reported in the treatment of patients with SFTS (13-15). If people bitten by sick animals, which are diagnosed as or are suspected of having SFTSV infections, they should be treated with favipiravir as soon as possible. Physicians in SFTS-endemic areas should include SFTS in the differential diagnoses for patients who become ill after taking care of sick dogs with unknown origins.

Acknowledgement We would like to thank Ms. Momoko Ogata and Ms. Mina Ogawa for their technical and clerical assistance. Written informed consent for this study was obtained from the patient and his wife. We declare that the study was conducted in accordance with the World Medical Assembly Declaration of Helsinki. This study was financially supported by the Japan Agency for Medical Research and Development (No. 19fk0108081j, 20fk0108081j, and 21fk0108081j, 18fk0108069h, 21fk0108615). The case has already been described partially in an article "Case reports of infection with SFTS virus from pets and causing SFTS" published in the IASR (Vol. 40 p117-118:2019) in Japanese.

Conflicts of interest The authors have no conflicts of interests.

Accepted Manuscript

REFERENCES

1. Yu XJ, Liang MF, Zhang SY, et al. Fever with thrombocytopenia associated with a novel bunyavirus in China. *N Engl J Med*. 2011;364(16):1523-32.
2. Takahashi T, Maeda K, Suzuki T, et al. The first identification and retrospective study of Severe Fever with Thrombocytopenia Syndrome in Japan. *J Infect Dis*. 2014;209(6):816-27.
3. Kim KH, Yi J, Kim G, et al. Severe fever with thrombocytopenia syndrome, South Korea, 2012. *Emerg Infect Dis*. 2013;19(11):1892-4.
4. Yoshikawa T, Fukushi S, Tani H, et al. Sensitive and specific PCR systems for detection of both Chinese and Japanese severe fever with thrombocytopenia syndrome virus strains and prediction of patient survival based on viral load. *J Clin Microbiol*. 2014;52(9):3325-33.
5. Fukuma A, Fukushi S, Yoshikawa T, et al. Severe fever with thrombocytopenia syndrome virus antigen detection using monoclonal antibodies to the nucleocapsid protein. *PLoS Negl Trop Dis*. 2016;10(4):e0004595.
6. Yoshikawa T, Shimojima M, Fukushi S, et al. Phylogenetic and geographic relationships of severe fever with thrombocytopenia syndrome virus in China, South Korea, and Japan. *J Infect Dis*. 2015;212(6):889-98.
7. Kobayashi Y, Kato H, Yamagishi T, et al. Severe fever with thrombocytopenia syndrome, Japan, 2013-2017. *Emerg Infect Dis*. 2020;26(4):692-9.
8. Kimura T, Fukuma A, Shimojima M, et al. Seroprevalence of severe fever with thrombocytopenia syndrome (SFTS) virus antibodies in humans and animals in Ehime prefecture, Japan, an endemic region of SFTS. *J Infect Chemother*. 2018;24(10):802-6.
9. Gokuden M, Fukushi S, Saijo M, et al. Low Seroprevalence of severe fever with thrombocytopenia syndrome virus antibodies in individuals living in an endemic area in Japan. *Jpn J Infect Dis*. 2018;71(3):225-8.
10. Park ES, Fujita O, Kimura M, et al. Diagnostic system for the detection of severe fever with thrombocytopenia syndrome virus RNA from suspected infected animals. *PLoS One*. 2021;16(1):e0238671.
11. Park ES, Shimojima M, Nagata N, et al. Severe fever with thrombocytopenia syndrome phlebovirus causes lethal viral hemorrhagic fever in cats. *Sci Rep*. 2019;9(1):11990.

12. Saijo M. Pathophysiology of severe fever with thrombocytopenia syndrome and development of specific antiviral therapy. *J Infect Chemother* 2018;59(10):2255-9.
13. Yuan Y, Lu QB, Yao WS, et al. Clinical efficacy and safety evaluation of favipiravir in treating patients with severe fever with thrombocytopenia syndrome. *EBioMedicine*. 2021;72:103591.
14. Suemori K, Saijo M, Yamanaka A, et al. A multicenter non-randomized, uncontrolled single arm trial for evaluation of the efficacy and the safety of the treatment with favipiravir for patients with severe fever with thrombocytopenia syndrome. *PLoS Negl Trop Dis*. 2021;15(2):e0009103.
15. Li H, Jiang XM, Cui N, et al. Clinical effect and antiviral mechanism of T-705 in treating severe fever with thrombocytopenia syndrome. *Signal Transduct Target Ther*. 2021;6(1):145.

Figure legends

Fig. 1. A) Optical density (OD) values of serum samples collected from the dog virologically diagnosed as having SFTSV infection 3, 11, 26, and 45 days later from the disease onset in the IgG-ELISA and IgM-ELISA. Significant increases in the OD values were observed in the IgG-ELISA (bar shown in orange). IgM antibody to SFTSV was positive in IgM-ELISA (bar shown in gray). B) Indirect immunofluorescence assay (IIFA) signals of the human patient serum for IgG and IgM in the IIFA at the dilution levels of 1:640 and 1:20, respectively (upper panel). The serum tested for the IIFA was collected from the patient approximately 2 months after disease onset. The staining patterns of the negative control serum are shown (lower panel).

Fig. 2. Phylogenetic analysis indicated that the dog suffered from SFTSV infection caused by SFTSV Genotype J1. The phylogenetic analyses were conducted using the nucleotide sequence of the partial SFTSV genomes deposited in GenBank (GenBank accession numbers are shown in the figure as the form of strain name, followed by the accession number). The partial S-segment genome nucleotide sequence was deposited in the GenBank under the accession number of LC570802.

Table 1. Clinical manifestations and laboratory findings of the dog over the clinical course

Clinical manifestations/laboratory findings	Normal range	Day from the disease onset				
		3	8	11	26	45
Body temperature (°C)		40.7	38.8	38.7	Not measured	Not measured
Appetite		Decreased	Decreased	Normalized	Normalized	Normalized
Stool appearance		Not checked	Diarrhea	Bloody stool	Not checked	Not checked
WBC ($10^2/\mu\text{L}$)	60-170	17	95	86	92	105
RBC ($10^4/\mu\text{L}$)	550-850	840	792	698	759	832
PLT ($10^4/\mu\text{L}$)	20-50	14.8	14.4	14.4	42	21.3
Alanine transaminase (U/L)	17-78	120	108	170	134	71
Aspartate transaminase (U/L)	17-78	47	47	48	24	25
ALP (U/L)	47-254	370	955	1545	432	107
BUN (mg/dL)	9.2-29.2	5.9	26.5	21.1	18	20.6
CRE (mg/dL)	0.4-1.4	0.7	0.9	0.7	1.1	1

GLU (mg/dL)	75-128	100	119	103	98	105
ALB (g/dL)	2.6-4.0	3.4	3.7	3.1	3.5	3.6
LIP (U/L)	10-60	39	>1000	221	34	39
TP (mg/dL)	5.0-7.2	no data	no data	6.1	6.3	no data
Tbil (mg/dL)	0.1-0.5	no data	no data	0.3	0.2	no data
CRP (mg/dL)	≤ 0.7	>7.0	5.3	1.5	<0.3	0.3

WBC: white blood cells, RBC: red blood cells, PLT: platelets, ALT: alanine transaminase, AST: aspartate transaminase, ALP: alkaline phosphatase, BUN: blood urea nitrogen, CRE: creatinine, GLU: glucose, ALB: albumin, LIP: lipase, TP: total protein, Tbil: total bilirubin, CRP: C-reactive protein.

A)

B)

A)

B)

Enlarged view of the red frame to the left