Med. Sci. Innov. 72(1-2):13-20, 2025

Severe Fever with Thrombocytopenia Syndrome Initially Diagnosed as Diffuse Large B-cell lymphoma

Taishi Ando,[1,3] *Kohei Nakano,*[2,3] *Shunsuke Hayashi,*[3] *Kohji Yamashita,*[3] *Katsuhiro Hatao,*[3] *Yoshimi Yamashita,*[4] *Yuichiro Hirata,*[5] *Sohtaro Mine,*[5] *Harutaka Katano,*[5] *Tadaki Suzuki*[5,6] *and Toru Takahashi*[2]

[1] Endocrinology, Metabolism, Hematological Sciences and Therapeutics, Yamaguchi University Hospital, 1-1-1 Minami-Kogushi, Ube, Yamaguchi 755-8505, Japan
[2] Department of Hematology, Yamaguchi Prefectural Grand Medical Center, 10077 Osaki, Hofu, Yamaguchi 747-8511, Japan
[3] Department of Hematology, Japan Community Health care Organization Tokuyama Central Hospital, 1-1 Koda, Shunan, Yamaguchi 745-8522, Japan
[4] Department of Pathology, Japan Community Health care Organization Tokuyama Central Hospital, 1-1 Koda, Shunan, Yamaguchi 745-8522, Japan
[5] Department of Infectious Disease Pathology, National Institute of Infectious Diseases, Japan Institute for Health Security, 1-23-1 Toyama, Shinjuku, Tokyo 162-8640, Japan
[6] Department of Infectious Disease Pathobiology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan
(Received October 22, 2024, accepted January 9, 2025)
Correspondence to Taishi Ando, MD, E-mail: tando.bfmt@gmail.com

Abstract A 70-year-old woman presented with acute fever, impaired consciousness, leukopenia, thrombocytopenia, and right inguinal lymphadenopathy. A lymph node biopsy was diagnosed as diffuse large B-cell lymphoma (DLBCL). However, her symptoms were consistent with severe fever with thrombocytopenia syndrome (SFTS), and RT-PCR for SFTS virus (SFTSV) RNA was positive. The patient's condition and lymphadenopathy gradually improved with supportive measures and short-term steroid treatment and no lymphadenopathy recurrence was observed. Lymph node pathological examination revealed SFTSV-infected cells, leading to the final diagnosis of necrotizing lymphadenitis associated with SFTS. Careful consideration is required to differentiate necrotizing lymphadenitis associated with SFTS from that associated with DLBCL.

Key words: diffuse large B-cell lymphoma, severe fever with thrombocytopenia syndrome, necrotizing lymphadenitis

Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is a severe infectious systemic inflammatory reaction syndrome (viral hemorrhagic fever) caused by the SFTS virus (SFTSV, the taxonomy name is Bandavirus dabieense). The mortality rate associated with SFTS is approximately 27%.[1] SFTSV is transmitted to humans through the bite of an SFTSV-carrying tick, or an SFTSV-infected cat or dog. The lymph nodes surrounding the bite site, which is the portal of viral entry, may swell, and pathological findings may

https://doi.org/10.60462/29973

show necrotizing lymphadenitis.[2] Because the histopathological findings of necrotizing lymphadenitis sometimes resemble those of malignant lymphoma,[3] there is a risk of misdiagnosis in differentiating the two diseases in clinical practice.

Here, we report a case of SFTS that was initially diagnosed as diffuse large B-cell lymphoma (DLBCL) via lymph node biopsy.

Patients

The patient was a 70-year-old woman presented with fever and impaired consciousness, who was transported to our hospital in September 2022. Blood tests revealed leukopenia (930/μL) and thrombocytopenia (93,000/μL), and the patient was hospitalized for further examination and treatment. Medical history revealed dyslipidemia and dizziness. The patient lived in the countryside and she was in contact with wild boars, monkeys, dogs, and cats.

The level of consciousness score according to the Japan Coma Scale (JCS) was 3 and the Glasgow Coma Scale (GCS) was E4V5M6. The temperature was 38.9℃. The blood pressure was 123/73 mmHg. The pulse rate was 95 beats/min and the respiratory rate was 18 breaths/min. Percutaneous oxygen saturation was 95% (room air). Chest examination revealed no abnormalities. The abdomen was flat and soft, with no hepatomegaly or splenomegaly.

A small erythema was noted in the right lumbar region, while the right inguinal lymph nodes were mildly swollen. Although neck stiffness was present, jolt accentuation and Kernig's sign were negative. The laboratory test results are listed in Table 1. Blood tests showed leukopenia and thrombocytopenia as well as elevated levels of liver enzymes, LDH, CK, soluble interleukin-2 receptor (sIL-2R), and ferritin. Urinary tests revealed the

Table 1 Laboratory data on admission.

Complete blood cell count		Biochemistry	
WBC	930/μL	AST	187 IU/L
Mye	+	ALT	49 IU/L
Met	1.0%	LDH	767 IU/L
Stb	27.0%	γGTP	33 IU/L
Seg	40.0%	T-Bil	0.41 mg/dL
Baso	1.0%	BUN	20.7 mg/dL
Lym	30.0%	Cre	0.75 mg/dL
Mono	1.0%	Glu	131 mg/dL
Aty.Ly	+	CK	369 IU/L
RBC	473 × 10^4/μL	CRP	0.75 mg/dL
Hb	13.3 g/dL	β2MG	3.8 mg/L
Ht	39.4%	sIL-2R	1,678 IU/mL
Plt	9.3 × 10^4/μL	Ferritin	24,333 ng/mL
Coagulation		**Urinalysis**	
PT	99%	Protein	3+
APTT	41.8 sec	Blood	2+
D-dimer	24.6 μg/mL	Nitrite	-
Fib	304 mg/dL	Leukocyte	-

presence of urinary proteins and occult blood. Cerebrospinal fluid examination revealed no abnormal cells. Examination of the bone marrow revealed slight hypoplasia and a slight decrease in the number of megakaryocytes; however, no atypical cells were observed. Nevertheless, activated macrophages with phagocytosis of erythroblasts and platelets were noticed. Computed tomography (CT; Fig. 1) revealed multiple enlarged lymph nodes in the right inguinal, right external iliac, and left internal deep cervical regions, with the largest lesion measuring 20 mm in diameter in the right inguinal region.

Clinical Course

Based on the results of the blood and bone marrow examinations, the patient was diagnosed with hemophagocytic syndrome. This condition was suspected be a lymphoma-associated hemophagocytic syndrome (LAHS), and a right inguinal lymph node biopsy was performed on the second day of admission. However, on the same day, the patient's consciousness and respiratory failure progressed, and she required intensive care, including artificial respiration. Therefore, she was to the intensive care unit. Since the patient was in close contact with wild boars, monkeys, dogs, and cats at home, and presented with an acute infectious disease accompanied by elevated LDH and CK levels and hemophagocytic syndrome, SFTS was suspected. A detailed examination was performed revealing the presence of SFTSV gene detected by RT-PCR testing in the peripheral blood, thus, establishing the diagnosis of SFTS.

In addition to supportive measures provided in the intensive care unit, steroid pulse therapy (methylprednisolone 1,000mg/day for 3 days) was administered to treat the hemophagocytic syndrome; consequently, the patient's overall condition gradually improved.

A lymph node biopsy showed that the normal structure of the lymph node tissue was altered, while diffuse proliferation of large atypical lymphocytes was observed

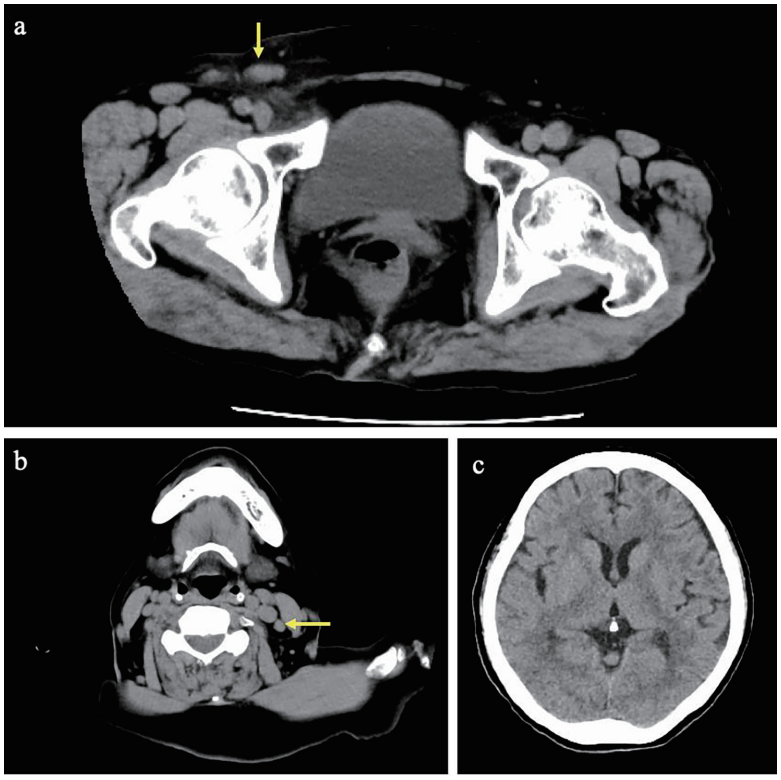

Fig. 1 Images of computed tomography (CT) on admission.
CT scan showing swelling of the right inguinal lymph node (arrow) and left cervical lymph node (a, b), and no intracranial abnormalities (c).

in the center of the blood vessels against a background of necrotic tissue. The atypical lymphocytes were CD3 negative, UCHL-1 negative, CD20 positive, CD79a positive, CD10 negative, BCL-2 positive, BCL-6 negative, MUM1 positive, and EBER-negative, and the histological diagnosis was DLBCL (non-GCB type) (Figs. 2 and 3). However, these cells showed no restriction in the expression of immunoglobulin light chains by flow cytometry, while no rearrangement of immunoglobulin heavy chains was observed by Southern blotting. The pathological diagnosis was malignant lymphoma; however, a repeat CT scan on the 18th day of hospitalization showed that the enlarged lymph nodes had shrunk, while the blood test results had also clearly improved. Since worsening of lymphoma was eliminated, it was decided to carefully observe the patient without administering chemotherapy.

The steroids were gradually tapered and discontinued on the 33rd day of hospitalization. The patient's overall condition and level of consciousness improved completely. There was no recurrence of lymphadenopathy, and the patient was discharged on the 52nd day of hospitalization.

Because the course of lymph node shrinkage without chemotherapy is not typical

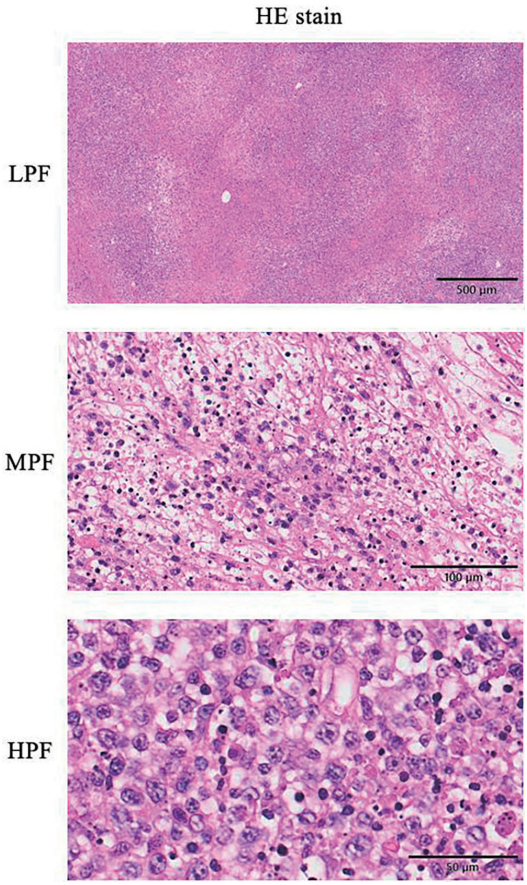

Fig. 2 Right inguinal lymph node biopsy specimen stained with hematoxylin and eosin.
Atypical lymphocytes with large hyperchromatic nuclei, while one to several distinct nucleoli proliferate diffusely and are accompanied by significant apoptosis, degeneration, and necrosis.

HE stain ; hematoxylin and eosin stain
HPF ; high power field
LPF ; low power field
MPF ; middle power field

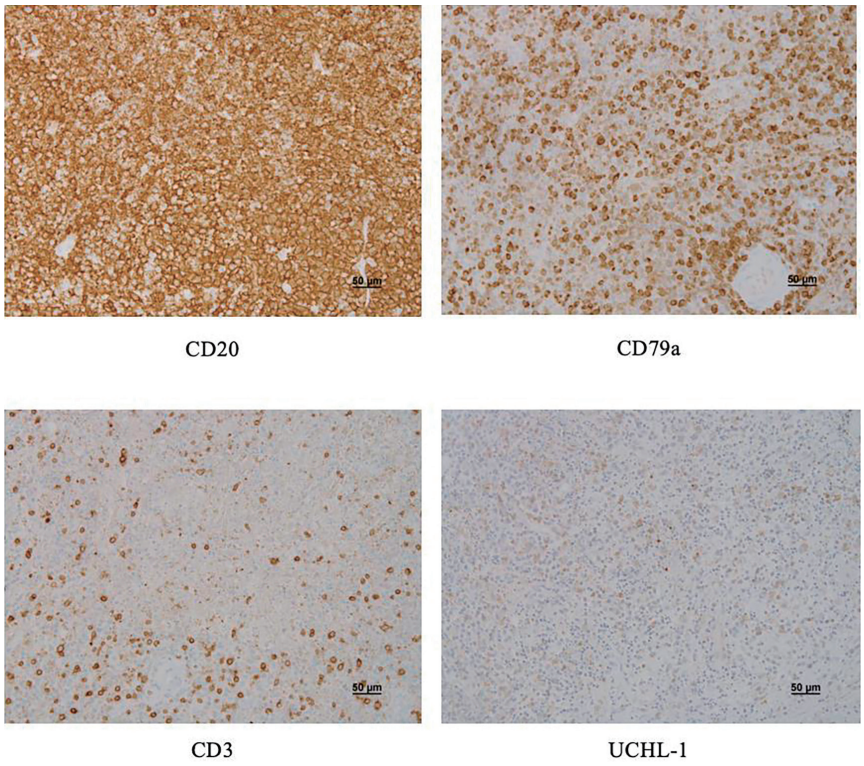

Fig. 3 Right inguinal lymph node biopsy specimen with immunohistochemical staining.
Atypical lymphocytes were CD3 negative, CD20 (L26) positive, CD45RO (UCHL-1) negative, and CD79a positive.

of DLBCL, we re-examined the lymph node biopsy specimen. In the lymph node tissue, many blast-like lymphocytes were observed in its necrotic part containing a large amount of nuclear dust, which is a typical finding of necrotizing lymphadenitis in SFTS.[2] Immunostaining with the anti-SFTS virus NP antibody showed that numerous large blast-like lymphocytes were positive for the SFTSV antigen (NP) (Fig. 4). Furthermore, when nucleic acid was extracted from paraffin sections of lymph node tissue and quantitative PCR was performed,[4,5] a high copy number (3.23×10^7 copies/μL) of SFTSV-RNA was detected. Therefore, the pathological findings were revised, and the final diagnosis was established as necrotizing lymphadenitis associated with SFTS rather than DLBCL.

Discussion

Approximately 35% of SFTS cases are accompanied by lymphadenopathy, and the pathological findings include image of hemophagocytosis by histiocytes, indicating hemophagocytic syndrome, and necrotizing lymphadenitis.[6]

Generally, lymph nodes in necrotizing lymphadenitis measure less than 2 cm in diameter, while there is no adhesion to the surrounding area. From a pathological point of view, no neutrophils or eosinophils were observed in the lesions, and the majority of constituent cells were large blastoid lymphocytes and histiocytes. In most cases, necrosis was prominent at the center of the lesion. The large lymphocytes are usually T cells, while very few B or NK cells are detected. In the early stages of the disease, tissue images in which large lymphocytes are predominant can be mistakenly diagnosed as diffuse lymphoma.[7] Moreover, and in some cases of necrotizing lymphadenitis without necrotic foci, the histological boundary between the lesion and healthy tissue can be clear, making misdiagnosis of malignant lymphoma more likely.[8] Additionally, in necrotizing lymphadenitis caused by SFTS, B lymphocytes, which account for the majority of virus-infected cells, become enlarged and resemble with blast cells

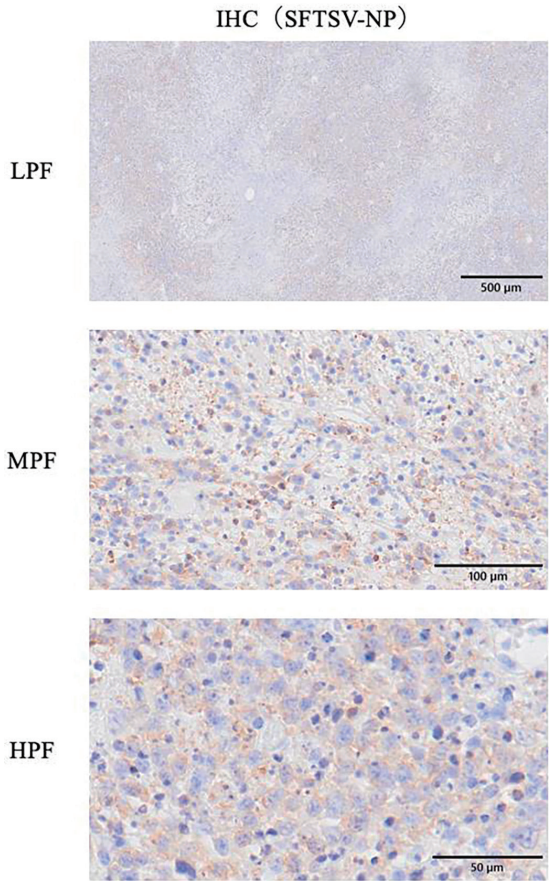

Fig. 4 Right inguinal lymph node biopsy specimen with immunohistochemical staining. Blastoid lymphocytes are positive for SFTSV antigen.

IHC；immunohistochemistry
HPF；high power field
LPF；low power field
MPF；middle power field

with a diffuse pattern of growth in the lymph nodes,[9] thus, mimicking DLBCL.

From the point of view of clinical symptoms, necrotizing lymphadenitis and malignant lymphoma share many common features, such as fever, lymphadenopathy, and hemophagocytic syndrome. Some reports have shown that scoring the following criteria are useful for distinguishing between the two conditions (body temperature ≥ 37.8℃, maximum lymph node diameter ≤ 3.2 cm, and β2-microglobulin ≥ 1.8 mg/L (sensitivity and specificity both 100%),[10] nevertheless, a comprehensive diagnosis combining physical examination findings, clinical course, and immunohistochemical staining results is required.

In this case, SFTSV RNA was detected in blood and lymph node samples, establishing the diagnosis of SFTS, and the clinical course was consistent. Although a histological diagnosis of DLBCL was initially made based on the lymph node biopsy, flow cytometry and immunoglobulin rearrangement tests on the biopsy material did not reveal any findings suggesting clonal B-cell proliferation. Moreover, to our knowledge, there are no reported cases of DLBCL that had been cured with steroid administration alone. Based on these findings, the possibility of the coexistence of DLBCL is unlikely. When the lymph node tissue was retrospectively examined by the initial pathologist based on the patient's clinical course, the diagnosis was revised to

necrotizing lymphadenitis.

SFTS is a tick-borne infectious disease, but infections from companion animals, such as cats and dogs[11] and human-to-human transmission have also been reported.[12] In this patient's case, SFTS was suspected based on the living environment and contact history with pets; therefore, obtaining a medical history is extremely important.

The pathological findings of necrotizing lymphadenitis in SFTS closely resemble those of DLBCL, while distinction of the two conditions is challenging. Therefore, for an accurate diagnosis, it is important to obtain a detailed medical history when SFTS is suspected.

Acknowledgements

We express our sincere gratitude to Dr. Yuichi Yamada, Dr. Kei Takano, and Dr. Koichi Oshima of the Department of Pathology, Kurume University School of Medicine, for their assistance in reviewing the pathology findings.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Kobayashi Y, Kato H, Yamagishi T, Shimada T, Matsui T, Yoshikawa T, Kurosu T, Shimojima M, Morikawa S, Hasegawa H, Saijo M, Oishi K; SFTS Epidemiological Research Group Japan. Severe Fever with Thrombocytopenia Syndrome, Japan, 2013-2017. Emerg Infect Dis. 2020 Apr; 26(4): 692-699. doi: 10.3201/eid2604.191011.
2. Takahashi T, Maeda K, Suzuki T, Ishido A, Shigeoka T, Tominaga T, Kamei T, Honda M, Ninomiya D, Sakai T, Senba T, Kaneyuki S, Sakaguchi S, Satoh A, Hosokawa T, Kawabe Y, Kurihara S, Izumikawa K, Kohno S, Azuma T, Suemori K, Yasukawa M, Mizutani T, Omatsu T, Katayama Y, Miyahara M, Ijuin M, Doi K, Okuda M, Umeki K, Saito T, Fukushima K, Nakajima K, Yoshikawa T, Tani H, Fukushi S, Fukuma A, Ogata M, Shimojima M, Nakajima N, Nagata N, Katano H, Fukumoto H, Sato Y, Hasegawa H, Yamagishi T, Oishi K, Kurane I, Morikawa S, Saijo M. The First Identification and Retrospective Study of Severe Fever With Thrombocytopenia Syndrome in Japan. J Infect Dis. 2014 Mar; 209(6): 816-827. doi: 10.1093/infdis/jit603. Epub 2013 Nov 14.
3. Weiss LM, O'Malley D. Benign lymphadenopathies. Mod Pathol. 2013 Jan; 26 Suppl 1: S88-96. doi: 10.1038/modpathol.2012.176.
4. Yu XJ, Liang MF, Zhang SY, Liu Y, Li JD, Sun YL, Zhang L, Zhang QF, Popov VL, Li Chuan, Qu Jing, Li Q, Zhang YP, Hai R, Wu W, Wang Q, Zhan FX, Wang XJ, Kan B, Wang SW, Wan KL, Jing HQ, Lu JX, Yin WW, Zhou H, Guan XH, Liu JF, Bi ZQ, Liu GH, Ren J, Wang H, Zhao Z, Song JD, He JR, Wan T, Zhang JS, Fu XP, Sun LN, Dong XP, Feng ZJ, Yang WZ, Hong T, Zhang U, Walker DH, Wang Y, Li DX. Fever with thrombocytopenia associated with a novel bunyavirus in China. N Engl J Med. 2011 Apr 21; 364(16): 1523-1532. doi: 10.1056/NEJMoa1010095. Epub 2011 Mar 16.
5. Katano H, Kano M, Nakamura T, Kanno T, Asanuma H, Sata T. A novel real-time PCR system for simultaneous detection of human viruses in clinical samples from patients with uncertain diagnoses. J Med Virol. 2011 Feb; 83(2): 322-330. doi: 10.1002/jmv.21962.
6. Hiraki T, Yoshimitsu M, Suzuki T, Goto Y, Higashi M, Yokoyama S, Tabuchi T, Futatsuki T, Nakamura K, Hasegawa H, Saijo M, Kakihana Y, Arima N, Yonezawa S. Two autopsy cases of severe fever with thrombocytopenia syndrome (SFTS) in Japan: a pathognomonic histological feature and unique complication of SFTS. Pathol Int. 2014 Nov; 64(11): 569-575. doi: 10.1111/pin.12207. Epub 2014 Oct 20.
7. Seo Y, Prome SA, Kim L, Han JY, Kim JM, Choi SJ. Florid lambda - monotypic B - cell proliferation in fatal severe fever with thrombocytopenia syndrome virus infection - associated necrotizing lymphadenitis: a potential diagnostic pitfall.

Journal of Hematopathology. 2022 Oct; 15: 221-228. doi: https://doi.org/10.1007/s12308-022-00520-9.
8. Yoshino T, Mannami T, Ichimura K, Takenaka K, Nose S, Yamadori I, Akagi T. Two cases of histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto's disease) following diffuse large B-cell lymphoma. Hum Pathol. 2000 Oct; 31(10): 1328-1331. doi: 10.1053/hupa.2000.18504.
9. Suzuki T, Sato Y, Sano K, Arashiro T, Katano H, Nakajima N, Shimojima M, Kataoka M, Takahashi K, Wada Y, Morikawa S, Fukushi S, Yoshikawa T, Saijo M, Hasegawa H. Severe fever with thrombocytopenia syndrome virus targets B cells in lethal human infections. J Clin Invest. 2020 Feb 3; 130(2): 799-812. doi: 10.1172/JCI129171.
10. Omachi T, Atsumi N, Yamazoe T, Tamanouchi S, Matsuno R, Kitawaki T, Kaneko K. Differential Diagnosis of Histiocytic Necrotizing Lymphadenitis and Malignant Lymphoma with Simple Clinical Findings. Children (Basel). 2022 Feb 20; 9(2): 290. doi: 10.3390/children9020290.
11. Tsuru M, Suzuki T, Murakami T, Matsui K, Maeda Y, Yoshikawa T, Kurosu T, Shimojima M, Shimada T, Hasegawa H, Maeda K, Morikawa S, Saijo M. Pathological Characteristics of a Patient with Severe Fever with Thrombocytopenia Syndrome (SFTS) Infected with SFTS Virus through a Sick Cat's Bite. Viruses 2021 Jan 29; 13(2): 204. doi: 10.3390/v13020204.
12. Seo JW, Kim D, Yun N, Kim DM. Clinical Update of Severe Fever with Thrombocytopenia Syndrome. Viruses. 2021 Jul; 13(7): 1213. doi: 10.3390/v13071213.