Int J Hematol (2016) 103:686–692
DOI 10.1007/s12185-016-1979-1

ORIGINAL ARTICLE

Proposed diagnostic criteria, disease severity classification and treatment strategy for TAFRO syndrome, 2015 version

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Received: 28 January 2016 / Revised: 4 March 2016 / Accepted: 6 March 2016 / Published online: 18 March 2016

Abstract TAFRO syndrome is a systemic inflammatory disorder characterized by thrombocytopenia, anasarca including pleural effusion and ascites, fever, renal insufficiency, and organomegaly including hepatosplenomegaly and lymphadenopathy. Its onset may be acute or subacute, but its etiology is undetermined. Although several clinical and pathological characteristics of TAFRO syndrome resemble those of multicentric Castleman disease (MCD), other specific features can differentiate between them. Some TAFRO syndrome patients have been successfully treated with glucocorticoids and/or immunosuppressants, including cyclosporin A, tocilizumab and rituximab,

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whereas others are refractory to treatment, and eventually succumb to the disease. Early and reliable diagnoses and early treatments with appropriate agents are essential to enhancing patient survival. The present article reports the 2015 updated diagnostic criteria, disease severity classification and treatment strategy for TAFRO syndrome, as formulated by Japanese research teams. These criteria and classification have been applied and retrospectively validated on clinicopathologic data of 28 patients with this and similar conditions (e.g. MCD with serositis and thrombocytopenia).

Keywords Thrombocytopenia · Anasarca · Glucocorticoid · Cyclosporin A · Tocilizumab

Introduction

TAFRO syndrome, first described in 2010, includes thrombocytopenia, anasarca (edema, pleural effusion and ascites), fever, reticulin myelofibrosis and organomegaly (hepatosplenomegaly and lymphadenopathy) [1]. Similar cases have since been reported [2–10]. Although some of the histopathological features of TAFRO syndrome are similar to those of mixed type of multicentric Castleman disease (MCD) [1], other clinical characteristics can distinguish between the two conditions. For example, polyclonal hypergammaglobulinemia, multiple lymphadenopathy, thrombocytosis, and a chronic clinical course are characteristics of MCD; whereas normal immunoglobulin level, thrombocytopenia, relatively small lymphadenopathy, marked pleural effusion, ascites, and edema, and acute or subacute onset and clinical course are characteristics of TAFRO. The differential diagnosis of TAFRO syndrome also includes disorders with similar symptoms, such as lymphoma, autoimmune disease, and acid-fast bacillus infection.

Some patients with TAFRO syndrome die of disease [1, 4, 6], whereas others may be saved by early aggressive treatment. Thus, determining the diagnostic criteria and treatment strategies for TAFRO syndrome may benefit these patients. Several meetings have evaluated the diagnosis and treatment of TAFRO syndrome [3]. However, its epidemiology, etiology, diagnosis and treatment have not been defined. Multicenter retrospective study in Japan, based on an on-line patient registry (UMIN000011809, https://www.facebook.com/CastlemanTAFRO), has therefore been initiated.

In addition the Ministry of Health, Labour and Welfare of Japan has organized and funded, through Health and Labour Sciences Research Grants for Research on Rare and Intractable Diseases, a nation-wide research team on TAFRO syndrome (H27-Nanchi, etc. (Nan)-General-008).

To promote the research on TAFRO syndrome, the research team on TAFRO syndrome first defined its preliminary diagnostic criteria and disease severity classification. Then we verified these criteria and classification using clinicopathologic data on 28 patients, who were reported in research meetings, with this condition and similar symptoms (e.g. MCD with serositis and thrombocytopenia), retrospectively.

Methods

Twenty-seven members of the TAFRO research group, including hematologists, rheumatologists, pulmonologists, pathologists, radiologist and basic researchers, attended a meeting on October 31,2015, to discuss the diagnostic criteria, disease severity classification and treatment strategies for TAFRO syndrome based on data from patients they have treated, those reported [1–12] to have this disease, and patients registered in the retrospective study. Subsequent on-line meetings have led to serious, active and enthusiastic discussion.

To verify these criteria and classification, 28 cases with TAFRO syndrome and similar conditions reported in previous meetings were analyzed. Thrombocytopenia was defined as <100,000 platelets/mm^3; anasarca as either pleural effusion or ascites on CT-scan; fever/inflammation as body (axillar) temperature >37.5 °C and/or elevated CRP level >2 mg/dl; reticulin myelofibrosis as a pathological diagnosis using gitter staining; organomegaly as hepatomegaly, splenomegaly or lymphadenopathy on CT-scans; anemia as hemoglobin <10.0 g/dl; and renal insufficiency as serum creatinine >1.2 mg/dl in males or >1.0 mg/dl in females.

The study protocol was approved by the review board of Kanazawa Medical University and each collaborating institute.

Results

Preliminary diagnostic criteria and disease severity classification

The intensive discussions of a meeting held on Oct. 31, 2015 and several online meetings resulted in the 2015 version of the diagnostic criteria (Table 1) and disease severity classification (Table 2). Furthermore, we made recommendation of treatment strategy based on our clinical experiences (Table 3).

Clinical features of reported cases and application of the diagnostic criteria

The 28 patients (12 male, 16 female) with TAFRO syndrome and similar conditions ranged in age from 21 to

Table 1 The 2015 diagnostic criteria for TAFRO syndrome, as determined by All Japan TAFRO Syndrome Research Group in the Research Program for Intractable Disease by Ministry of Health, Labor and Welfare (MHLW) Japan

Disease description
TAFRO syndrome is a systemic inflammatory disorder manifesting as fever; anasarca including pleural effusion and ascites; thrombocytopenia; renal insufficiency; anemia; and organomegaly including hepatosplenomegaly and lymphadenopathy. It has an acute or sub-acute onset of unknown etiology. The syndrome first reported by Takai et al. in 2010, includes Thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly; other patients with similar symptoms have been reported. Although several clinical and pathological findings of TAFRO syndrome resemble those of Castleman's disease, presence of other specific features that differentiate TAFRO syndrome and Castleman's disease are now being discussed. Several patients have been successfully treated with glucocorticoids, immunosuppressants including cyclosporin A, tocilizumab or rituximab, whereas others were refractory to treatment and took a fatal clinical course. Reliable early diagnosis and appropriate rapid treatment are therefore essential for favorable outcomes
Diagnostic criteria of TAFRO syndrome
A diagnosis of TAFRO syndrome requires all of the three major categories and at least two of four minor categories
As it is very important to exclude malignancies, including lymphoma, lymph node biopsy, if applicable, is strongly recommended
A. Major categories
(1) Anasarca, including pleural effusion, ascites and general edema
(2) Thrombocytopenia; defined as a pre-treatment platelet count $\leq$100,000/μl
(3) Systemic inflammation, defined as fever of unknown etiology above 37.5 °C and/or serum C-reactive protein concentration $\geq$2 mg/dl
B. Minor categories
(1) Castleman's disease-like features on lymph node biopsy
(2) Reticulin myelofibrosis and/or increased number of megakaryocytes in bone marrow
(3) Mild organomegaly, including hepatomegaly, splenomegaly and lymphadenopathy
(4) Progressive renal insufficiency
C. Diseases to be excluded
(1) Malignancies, including lymphoma, myeloma, mesothelioma, et cetera
(2) Autoimmune disorders, including systemic lupus erythematosus (SLE), ANCA-associated vasculitis, et cetera
(3) Infectious disorders, including acid fast bacterial infection, rickettsial disease, lyme disease, severe fever with thrombocytopenia syndrome (SFTS), et cetera
(4) POEMS syndrome
(5) IgG4-related disease
(6) Hepatic cirrhosis
(7) Thrombotic thrombocytopenic purpura (TTP)/hemolytic uremic syndrome (HUS)
D. Points to consider
Marked polyclonal hypergammopathy is rare in TAFRO patients, with serum IgG concentrations remaining below 3000 mg/dl
Obvious monoclonal protein should not be present
Few patients show elevated serum LDH
Most patients show elevated level of serum ALP
Hepatosplenomegaly in this disease is usually mild and only confirmed by CT-scan, whereas presence of huge hepatosplenomegaly may indicate lymphoma and other diseases
Lymphadenopathy in this disease is usually smaller than 1.5 cm in diameter, whereas huge lymphadenopathy may indicate lymphoma and other diseases
Exclusion criteria for Castleman's disease and immune thrombocytopenia (ITP) have not been determined, so these diseases may not be excluded at present

78 with a median of 52 and a mean of 52.5 years old. The incidence of each of the parameters of TAFRO findings are shown in Table 4.

According to the diagnostic criteria for TAFRO syndrome (Table 1), 18 of 28 patients (8 male, 10 female, median age 54, mean of 54.7 years old) in this series were diagnosed as TAFRO syndrome. By disease severity classification (Table 2) patients one (5.5 %), 11 (61.1 %), 4 (22.2 %) and 2 (11.1 %) were categorized into grades 1, 2, 3 and 4, respectively.

All patients in this study were negative for HHV8 (DNA and/or antibody), HIV and Epstein Barr virus (EBV). Some patients presented with anasarca (pleural effusion and ascites), thrombocytopenia and normo- to microcytic anemia on hemograms, renal dysfunction, ALP elevation, low level of LDH, relatively mild polyclonal

Table 2 The 2015 disease severity classification for TAFRO syndrome

Total points are calculated by adding the points of present symptoms	
(1) Anasarca: three points maximum	
One point for pleural effusion on imaging	
One point for ascites on imaging	
One point for pitting edema on physical examination	
(2) Thrombocytopenia: three points maximum	
One point for lowest platelet counts <100,000/μl	
Two points for lowest platelet counts <50,000/μl	
Three points for lowest platelet counts <10,000/μl	
(3) Fever and/or inflammation: three points maximum	
One point for fever ≥37.5 °C but <38.0 °C or for CRP ≥2 mg/dl but <10 mg/dl	
Two points for fever ≥38.0 °C but <39.0 °C or for CRP ≥10 mg/dl but <20 mg/dl	
Three points for fever ≥39.0 °C or for CRP ≥20 mg/dl	
(4) Renal insufficiency: three points maximum	
One point for GFR <60 ml/min/1.73 m^2	
Two point for GFR <30 ml/min/1.73 m^2	
Three points for GFR <15 ml/min/1.73 m^2 or need for hemodialysis	
Relationship between score and disease severity	
0–2 points	Insufficient for diagnosis
3–4 points	Mild (grade 1)
5–6 points	Moderate (grade 2)
7–8 points	Slightly severe (grade 3)
9–10 points	Severe (grade 4)
11–12 points	Very severe (grade 5)

hypergammopathy, some immunological abnormalities (but few specific autoantibodies), or elevation of IL-6 and/or vascular endothelial growth factor (VEGF). Other clinical findings included myelofibrosis, increased levels of megakaryocytes in bone marrow, and small or unclear lymphadenopathy (<1.5 cm in diameter) with weak accumulation of ^{18}F-fluorodeoxy glucose (^{18}FDG) on ^{18}FDG-positron emission tomography (PET). Autoantibodies were sometimes detected, but patients did not fulfill the diagnostic criteria for autoimmune diseases, such as systemic lupus erythematosus (SLE). Lymph node histology in most patients was of mixed type, with few patients having hyaline-vascular type MCD histology. Most patients demonstrated dry tap on bone marrow aspiration, and bone marrow biopsy confirmed reticulin myelofibrosis and increased megakaryocytes in these patients.

Although glucocorticoids, immunosuppressive therapy, and tocilizumab were effective in some patients with this condition, others showed clinical deterioration despite treatment (2 of the 18 patients died in this series).

Discussion

Relations between TAFRO syndrome and MCD

MCD in western countries has been thought to be associated with HIV and/or HHV-8 infection. HHV-8 infection has been found to induce the expression of viral IL-6 (vIL-6), resulting in the development of hyper IL-6 syndrome [13, 14]. This results in the production of VEGF, causing

Table 3 The 2015 treatment strategy for TAFRO syndrome

(1) High-dose glucocorticoid: prednisolone 1 mg/kg/day for 2 weeks, followed by tapering; OR Methyl-prednisolone pulse therapy with 500–1000 mg/day for 3 days if an emergency
(2) CyclosporinA (CsA): may be added for patients refractory or dependent on glucocorticoids. The starting dose of oral CsA is 3–5 mg/kg/day, divided into two doses per day. The target trough level (C0) of serum CsA is 150–250 ng/ml. However, measurement of serum concentration at 2 h after taking medicine (C2) is recommended. Patients with C2 level of CsA <600 ng/ml, suggesting an insufficient serum concentration, should be switched from after-meal to before-meal administration. If serum creatinine level increase >150 %, CsA dose should be decreased 50–75 %
(3) Tocilizumab (anti-IL-6 receptor antibody): for patients with TAFRO syndrome complicated by Castleman's disease
(4) Rituximab (anti-CD20 antibody)
(5) Thrombopoietin receptor agonists romiplostim and eltrombopag: for patients with persistent thrombocytopenia
Glucocorticoids are the first line treatment for patients with TAFRO syndrome, with CsA recommended as the second line treatment for patients refractory to glucocorticoids
If CsA is contraindicated, as in patients with renal insufficiency, tocilizumab or rituximab is recommended
Plasma exchange, cyclophosphamide, combination chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone), thalidomide and lenalidomide, have been successful in the treatment of selected patients
Splenectomy and high-dose gamma-globulin have not been shown effective
This treatment strategies are not based on evidences but on our experiences

Table 4 Clinical and laboratory findings in all 28 patients investigated in this study, including the 18 patients with TAFRO syndrome

		All ($n = 28$)	(%)	TAFRO ($n = 18$)	(%)
Age	Median	52 years/old		54 years/old	
	Mean	52.5 years/old		54.7 years/old	
Sex	Male	12/28	42.9	8/18	44.4
	Female	16/28	57.1	10/18	55.6
Thrombocytopenia	PLT <100,000/μl	21/28	75.0	18/18	100
Anasarca		27/28	96.4	18/18	100
Fever		19/28	67.9	11/18	61.1
Elevated CRP	CRP >2 mg/dl	22/28	78.6	15/18	83.3
Reticulin-myelofibrosis		10/14	71.4	9/12	75.0
Renal insufficiency		14/28	50.0	10/18	55.6
Organomegaly		22/28	78.6	16/18	88.9
Lymphadenopathy		26/28	92.9	17/18	94.4
Anemia	Hb <10.0 g/dl	15/28	53.6	9/18	50.0
Leukocytosis	WBC >10,000/μl	10/28	35.7	7/18	38.9
relatively low IgG level	IgG <2000 mg/dl	17/26	65.4	11/16	68.9
Elevated ALP	ALP >500 U/l	12/23	56.5	9/14	64.3
Decreased LDH	LDH <200 U/l	13/25	52.0	4/16	25.0
Elevated IL-6	IL-6 >10 pg/ml	13/22	59.1	8/12	66.7
Elevated VEGF	VEGF >100 pg/ml	9/13	69.2	5/8	62.5
Elevated sIL2R	sIL2R >1000 U/ml	17/21	81.0	12/13	92.3
Various autoantibodies		13/28	46.4	11/18	61.1
MCD pathology in LND		21/28	75.0	12/13	92.3
Treatment	Glucocorticoid	26/28	92.9	18/18	100
	CyclosporinA	3/28	10.7	2/18	11.1
	Tocilizumab	5/28	17.9	2/18	11.1
	Interferon	1/28	3.6	0/18	0
	Azathiopurin	1/28	3.6	1/18	5.6
	CHOP + etoposide	1/28	3.6	1/18	5.6
D/A	Dead	4/28	14.3	2/18	11.1

IL6 interleukin-6, *VEGF* vascular endothelial growth factor, *sIL2R* soluble interleukin-2 receptor, *MCD* multicentric Castleman's disease, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisolone, *D/A* dead or alive

angiogenesis; B cell differentiation, causing plasma cell expansion and polyclonal hypergammaglobulinemia; megakaryocyte differentiation in bone marrow causing thrombocytosis; and the production by the liver of acute inflammatory proteins, such as C-reactive protein (CRP), fibrinogen, and serum amyloid A (SAA). Hyper IL-6-syndrome can also induce hepcidin production in the liver, inhibiting iron absorption in the gastrointestinal tract and reducing iron recycling in the reticuloendothelial systems, thus causing microcytic anemia. Most Japanese patients with MCD are negative for HIV and HHV-8 infection [15] and display a chronic disease course. Moreover, MCD in Japan does not appear to progress to Kaposi's sarcoma or B-cell lymphoma [16]. Recently, Fajgenbaum et al. summarized MCD cases in western countries, where more than half of them were also HHV-8 negative [17]. They classified such HHV-8 negative MCD cases as idiopathic MCD (iMCD). Therefore, most Japanese MCD patients are classified into iMCD.

Some of the characteristic findings in TAFRO syndrome, such as severe inflammation with hyper IL-6 and histopathological findings of lymph nodes, are similar to those in patients with iMCD. However, other characteristic findings such as thrombocytopenia, anasarca, renal insufficiency and reticulin myelofibrosis are not considered typical of iMCD. Few diseases are characterized by severe inflammation with thrombocytopenia and anasarca. In our cohort, most of patients had thrombocytopenia, and some of them had been diagnosed as having immune-thrombocytopenia (ITP), thrombotic thrombocytopenic purpura (TTP), anti-phospholipid antibody syndrome (APS), or disseminated intravascular coagulation (DIC).

Several questions remain regarding the mechanism and etiology of TAFRO syndrome. It is not clear whether

TAFRO syndrome is a disease entity distinct from iMCD, a subset of iMCD, or a part of it overlaps with iMCD. Moreover, it is not clear whether this syndrome is neoplastic, autoimmune, infectious, or some other type of disease entity.

Future prospects

The multicenter retrospective clinical study of patients with TAFRO syndrome is now recruiting participants. This study register patients with MCD, as well as with TAFRO syndrome. The clinical characteristics of these two groups will be compared. The study will include TAFRO syndrome patients successfully treated with glucocorticoid treatment alone [1, 4], or in combination with other immunosuppresants [1, 4], tocilizumab [3, 5, 10, 11] and rituximab [12], as well as patients who died of disease, without improvement, despite treatment. As TAFRO syndrome is currently diagnosed by combinations of clinical conditions, this syndrome may be heterogeneous. To assess heterogeneity and establish the disease concept, it is necessary to compare patients with relatively mild TAFRO syndrome and those with severe, even fatal, disease. These diagnostic criteria should be used to design prospective clinical studies. Collected patients data and clinical materials may help in determining the pathophysiology and etiology of TAFRO syndrome. We also made the treatment strategy based on our clinical experiences (Table 3), and will strengthen evidence from now on.

Results of this study will also be coordinated with the research group on Castleman disease, represented by Dr. Kazuyuki Yoshizaki. This group is also funded by Health and Labour Sciences Research Grants for Research on Rare and Intractable Diseases from the Ministry of Health, Labour and Welfare of Japan (H27-Nanchi, etc. (Nan)-General-002). Differences between TAFRO syndrome and MCD will be discussed.

As the formulation of these clinical guidelines are based on update data, these guidelines will be revised, if necessary, based on further clinical and pathophysiological evidence.

Acknowledgments We thank all participants in the All Japan, Ministry of Health, Labor, and Welfare (MHLW) TAFRO Syndrome Team and Castleman Disease Team including for their critical discussion.

Compliance with ethical standards

Supportive foundations Sources of support in the form of grants: This work was partially supported by the Research Program of Intractable Disease provided by the Ministry of Health, Labor, and Welfare (MHLW) of Japan (H27-Nanchi, etc.(Nan)-General-008), and by the Japanese Ministry of Education, Culture, Sports, Science and Technology (Grant No. 17591060 and 15K09510), the Kanazawa Medical University Research Foundation (Grant Nos. S2004-16 and S2007-5), Grant for Assist KAKEN from Kanazawa Medical University (Grant No. K2011-7), Grant for Project Research from High-Tech Research Center of Kanazawa Medical University (Grant No. H2011-11) and Grant for Alumni Research(A) from Kanazawa Medical University (AR2012-06).

Conflict of interest The authors declare there is no conflict of interest.

References

1. Takai K, Nikkuni K, Shibuya H, Hashidate H. Thrombocytopenia with mild bone marrow fibrosis accompanied by fever, pleural effusion, ascites and hepatosplenomegaly. Rinsho Ketsueki. 2010;51:320–5 **(in Japanese)**.
2. Kojima M, Nakamura N, Tsukamoto N, Yokohama A, Itoh H, Kobayashi S, et al. Multicentric Castleman's disease representing effusion at initial clinical presentation: clinicopathological study of seven cases. Lupus. 2011;20:44–50.
3. Kawabata H, Takai K, Kojima M, Nakamura N, Aoki S, Nakamura S, et al. Castleman-Kojima disease (TAFRO syndrome): a novel systemic inflammatory disease characterized by a constellation of symptoms, namely, thrombocytopenia, ascites (anasarca), microcytic anemia, myelofibrosis, renal dysfunction, and organomegaly: a status report and summary of Fukushima (6 June, 2012) and Nagoya meetings (22 September, 2012). J Clin Exp Hematop. 2013;53:57–61.
4. Takai K, Nikkuni K, Momoi A, Nagai K, Igarashi N, Saeki T. Thrombocytopenia with reticulin fibrosis accompanied by fever, anasarca and hepatosplenomegaly: a clinical report of five cases. J Clin Exp Hematop. 2013;53:63–8.
5. Kawabata H, Kadowaki N, Nishikori M, Kitawaki T, Kondo T, Ishikawa T, et al. Clinical features and treatment of multicentric Castleman's disease: a retrospective study of 21 Japanese patients at a single institute. J Clin Exp Hematop. 2013;53:69–77.
6. Masaki Y, Nakajima A, Iwao H, Kurose N, Sato T, Nakamura T, et al. Japanese variant of multicentric Castleman's disease associated with serositis and thrombocytopenia—a report of two cases: is TAFRO syndrome (Castleman-Kojima disease) a distinct clinicopathological entity? J Clin Exp Hematop. 2013;53:79–85.
7. Iwaki N, Sato Y, Takata K, Kondo E, Ohno K, Takeuchi M, et al. Atypical hyaline vascular-type Castleman's disease with thrombocytopenia, anasarca, fever, and systemic lymphadenopathy. J Clin Exp Hematop. 2013;53:87–93.
8. Inoue M, Ankou M, Hua J, Iwaki Y, Hagihara M. Complete resolution of TAFRO syndrome (thrombocytopenia, anasarca, fever, reticulin fibrosis and organomegaly) after immunosuppressive therapies using corticosteroids and cyclosporin A: a case report. J Clin Exp Hematop. 2013;53:95–9.
9. Awano N, Inomata M, Sonoda Y, Kondoh K, Ono R, Moriya A, et al. A case of multicentric Castleman's disease of mixed-type, which showed constellation of symptoms, i.e., thrombocytopenia, anasarca, anemia, fever, myelofibrosis, and lymphadenopathy. J Clin Exp Hematop. 2013;53:101–5.
10. Kawabata H, Kotani S, Matsumura Y, Kondo T, Katsurada T, Haga H, et al. Successful treatment of a patient with multicentric Castleman's disease who presented with thrombocytopenia, ascites, renal failure and myelofibrosis using tocilizumab, an anti-interleukin-6 receptor antibody. Intern Med. 2013;52:1503–7.
11. Kubokawa I, Yachie A, Hayakawa A, Hirase S, Yamamoto N, Mori T, et al. The first report of adolescent TAFRO syndrome,

a unique clinicopathologic variant of multi centric Castleman's disease. BMC Pediatr. 2014;14:139.
12. Ozawa T, Kosugi S, Kito M, Onishi M, Kida T, Nakata S, et al. Efficacy of rituximab for TAFRO syndrome, a variant type of multicentric Castleman's disease. Rinsho Ketsueki. 2014;55(3):350–5 **(in Japanese)**.
13. Cesarman E, Knowles DM. The role of Kaposi's sarcoma-associated herpes virus (KSHV/HHV-8) in lymphoproliferative diseases. Semin Cancer Biol. 1999;9:165–74.
14. Dupin N, Diss TL, Kellam P, Tulliez M, Du MQ, Sicard D, et al. HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked HHV-8-positive plasmablastic lymphoma. Blood. 2000;95:1406–12.
15. Suda T, Katano H, Delsol G, Kakiuchi C, Nakamura T, Shiota M, et al. HHV-8 infection status of AIDS-unrelated and AIDS-associated multicentric Castleman's disease. Pathol Int. 2001;51:671–9.
16. Kojima M, Nakamura N, Tsukamoto N, Otuski Y, Shimizu K, Itoh H, et al. Clinical implications of idiopathic multicentric Castleman's disease among Japanese: a report of 28 cases. Int J Surg Pathol. 2008;16:391–8.
17. Fajgenbaum DC, van Rhee F, Nabel CS. HHV-8-negative, idiopathic multicentric Castleman disease: novel insights into biology, pathogenesis, and therapy. Blood. 2014;123:2924–33.