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Case Study

Atypical Hyaline Vascular-Type Castleman's Disease With Thrombocytopenia, Anasarca, Fever, and Systemic Lymphadenopathy

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Recently, atypical Castleman's disease (CD) was reported in Japan. This disease is considered as TAFRO syndrome or non-idiopathic plasmacytic lymphadenopathy (IPL), a constellation of clinical symptoms, namely, thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly without hyper-γ-globulinemia. Histopathologically, this disease is similar to hyaline vascular (HV)-type CD. Here, we present a 43-year-old Japanese woman meeting the clinical criteria of TAFRO syndrome who was successfully treated with combined corticosteroid therapy. She showed a rapidly progressive course of thrombocytopenia, systemic lymphadenopathy, fever, anasarca, and increase in acute inflammatory proteins without hyper-γ-globulinemia. Lymph node biopsy was performed and revealed HV-type CD without human herpes virus 8 infection, which was clinicopathologically compatible with non-IPL. The association of these atypical features with well-known multicentric Castleman's disease (MCD), namely, HV-type histology with systemic lymphadenopathy, marked thrombocytopenia even with a high level of interleukin-6, and increased acute inflammatory proteins without hyper-γ-globulinemia, suggests that TAFRO syndrome as presented in our case is a novel entity, which may have been diagnosed as MCD in the past. To define this novel entity more clearly and to demonstrate its etiology, further nationwide surveys of this syndrome and MCD are needed. 〔*J Clin Exp Hematopathol 53(1) : 87-93, 2013*〕

Keywords: Castleman's disease, TAFRO syndrome, idiopathic plasmacytic lymphadenopathy, interleukin-6

INTRODUCTION

Castleman's disease (CD) is a rare atypical lymphoproliferative disorder,[1] and the diagnosis is based on the presence of histopathological features. The affected lymph nodes are histopathologically classified as hyaline-vascular (HV) type, plasma-cell (PC) type, or a mixed-type variant of the two.[2] Frizzera reviewed the eponym of CD clinicopathologically, and reported 3 types of variant. Localized CD of the HV type presents as an asymptomatic and slow-growing mass. Localized CD of the PC type features systemic manifestations of inflammation and B-cell hyperreactivity. The third group is multicentric Castleman's disease (MCD), characterized by systemic lymphadenopathy, frequent multi-organ involvement, and more aggressive behavior. Histopathologically, MCD appears as the PC type or the mixed type, and also has systemic manifestations of inflammation such as fever, sweating, fatigue, and laboratory findings of anemia, thrombocytosis, hyper-γ-globulinemia, hypoalbuminemia, and increased C-reactive protein (CRP). These symptoms are closely related to high interleukin (IL)-6 levels, suggesting a cytokine disease.[3,4]

Recent studies indicated that MCD is composed of several disease entities, including idiopathic MCD and secondary MCD, such as POEMS syndrome (polyneuropathy, anasarca, organomegaly, endocrinopathy, M proteins, and skin lesions), autoimmune disease-associated lymphadenopathy,[5] and non-Hodgkin's lymphoma. Furthermore, Souler *et al*.[6] reported the infection of human herpesvirus (HHV)-8 not only in human immunodeficiency virus-1 (HIV-1)-positive MCD patients, but also in HIV-1-negative ones. Although in Western countries infection of HHV-8 has been found in at least 40-50% of HIV-negative cases of MCD,[7,8] Suda *et al*. reported that HHV-8 infection appears to be unrelated to the etiology of MCD in Japan.[9]

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Recently, Kojima *et al*. revealed that Japanese MCD cases are classified into two variants based on the clinicopathological findings : idiopathic plasmacytic lymphadenopathy with polyclonal hyperimmunoglobulinemia (IPL) type and non-IPL type. IPL is considered identical to MCD in Western countries. Histologically, non-IPL was characterized by HV type despite these patients having systemic lymphadenopathy. The non-IPL type tended to have a high rate of pleural effusion and/ or ascites, thrombocytopenia, and autoimmune diseases. Kojima concluded that a portion of non-IPL cases might involve autoimmune disease-associated lymphoproliferative disorders.[10]

On the other hand, Takai *et al*. reported three patients who shared a constellation of clinical symptoms, namely, thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly (tentatively given the clinical term TAFRO syndrome). Interestingly, one of these three underwent a lymph node biopsy and histologically exhibited HV-type CD. These patients tended to respond to immunosuppressive therapy. Takai suggested that this novel clinical entity belongs to the systemic inflammatory disorders, with a background of immunological abnormality.[11]

TAFRO syndrome and non-IPI seem to describe similar novel clinical entities ; these diseases are suggestive of systemic inflammatory disorders with a background of immunological abnormality. They may have been diagnosed as MCD in the past.

This report describes a case of HV-type CD with marked endothelial proliferation that meets the criteria of non-IPL, and approximately corresponds to TAFRO syndrome clinically.

CASE REPORT

Endometriosis was identified in a 43-year-old Japanese woman at an annual medical checkup in July 2012. She had a previous history of ulcerative colitis and had had colonic resection 5 years previously. Although she was scheduled to undergo an operation for endometriosis, preoperative tests showed a decreased platelet count of $4.6 \times 10^4/\mu L$, high alkaline phosphatase (ALP) at 673 IU/L, and high CRP at 11.5 mg/dL.

She was referred to our hospital for further examination about 2 months after the annual medical checkup. Although she had no symptoms at the initial visit, she rapidly developed high-grade fever and deterioration of respiratory status during the next few days, with no apparent trigger. She was admitted and put on a ventilator only 4 days after her first visit to our hospital.

On physical examination, her left small axillary lymph nodes were palpable with mild tenderness. Computed tomography examination revealed systemic mild lymphadenopathy, mild hepatosplenomegaly, and large amounts of bilateral pleural fluid.

The laboratory data were as follows : white blood count, 8,770/μL (normal range, 8,500-3,500/μL), without atypical lymphoid cells ; hemoglobin, 12.6 g/dL (11.5-15.0 g/dL) ; platelet count, $13.5 \times 10^4/\mu L$ ($15.0\text{-}35.0 \times 10^4/\mu L$) ; alanine aminotransferase, 15 IU/L ; ALP, 1,357 IU/L (110-360 IU/L) ; total bilirubin, 1.0 mg/dL ; creatinine, 0.86 mg/dL ; lactate dehydrogenase (LDH), 174 IU/L (120-240 IU/L) ; CRP, 20.1 mg/dL (< 0.30 mg/dL) ; total protein, 6.1 g/dL (6.5-8.0 g/dL) ; albumin, 2.3 g/dL (3.9-4.9 g/dL) ; prothrombin time, 15.0 sec (international normalized ratio 1.42) ; activated partial thromboplastin time, 38.5 sec (control 25-36 sec) ; fibrinogen, 1,400 mg/dL (157-390 mg/dL) ; ferritin, 386 ng/mL (6.2-138 ng/mL) ; fibrin/fibrinogen degradation products, 18.1 μg/mL (0-4.9 μg/mL) ; serum immunoglobulin (Ig) G, 965 mg/dL (880-1,818 mg/dL) ; IgM, 117 mg/dL (31-252 mg/dL) ; IgA, 231 mg/dL (110-421 mg/dL) ; CH 50, 51 U/mL ; soluble IL-2 receptor, 2,932 U/mL (122-496 mg/dL) ; serum IL-6, 45.6 pg/mL (< 4 pg/mL) ; pleural fluid IL-6, 1,860 pg/mL ; plasma vascular endothelial growth factor (VEGF), 665 pg/mL (< 115 pg/mL) ; and pleural fluid VEGF, 155 pg/mL. M-protein was not noted in serum protein fractionation (Table 1). Autoantibodies, including antinuclear antibody, anti-ds-DNA, anti-Sm, anti-RNP, anticardiolipin antibody, cytoplasmic antineutrophil cytoplasmic antibody, and myeloperoxidase-antineutrophil cytoplasmic antibody, were all negative.

Her symptoms were initially suspected of being caused by severe bacterial infection with disseminated intravascular coagulation. She was administered some antibiotics, anticoagulant agents, and clotting factors. In addition, despite receiving polymyxin B-immobilized fiber column direct hemoperfusion and cytokine adsorption, her general condition and the clinical and laboratory parameters deteriorated.

Biopsy of a left axillary lymph node was performed to make a definitive diagnosis. The lymph node was histologically compatible with HV-type CD. It exhibited interfollicular expansion and atrophic germinal centers penetrated by blood vessels. The interfollicular zone was characterized by the proliferation of highly dense endothelial venules and there were only a small number of mature plasma cells. Immunohistochemical studies showed that the follicular dendritic cell networks were expanded or disrupted. Plasma cells in the interfollicular area were IL-6-positive and the HHV-8 was negative. The *in situ* hybridization of κ and λ light chains showed no apparent light chain restriction (Fig. 1). Bone marrow aspiration revealed a hyperplastic marrow with megakaryocytic hyperplasia. These findings were compatible with non-IPL.

Furthermore, the patient met the clinical criteria of TAFRO syndrome, such as thrombocytopenia, anasarca, renal dysfunction, no polyclonal hyper-γ-globulinemia, elevated level of ALP but not of LDH, and elevated levels of IL-6 and

Table 1. Laboratory data on admission

Complete blood cell count		Blood chemistry		Serum protein fractionation	
White blood cell	8,770/μL	Total protein	6.1 g/dL	M-peak was not detected.	
Basophil	0.4%	Albumin	2.3 g/dL	Viral antibody	
Eosinophil	0.6%	Total bilirubin	1.08 mg/dL	HIV-1,2	-
Neutrophil	76.6%	Direct bilirubin	0.56 mg/dL	HHV-8	-
Lymphocyte	12.3%	AST	15 IU/L	Urine	
Monocyte	10.1%	ALT	15 IU/L	pH	5.5
Red blood cell	421 × 10^4/μL	ALP	1,357 IU/L	Protein	±
Hemoglobin	12.6 g/dL	Choline esterase	78 IU/L	Suger	-
Hematocrit	33.8%	LDH	174 IU/L	Occult blood	-
Platelet	13.5 × 10^4/μL	γ-GTP	166 IU/L	Pleural effusion	
Coagulation test		Blood urea nitrogen	15.1 mg/dL	Total protein	2.8 g/dL
PT	15 sec	Creatinin	0.86 mg/dL	LDH	119 IU/L
PT-INR	1.42	C-reactive protein	20.1 mg/dL	Cell count	173/μL
APTT	38.5 sec	IgG	965 mg/dL	Mononuclear cell	85%
Fibrinogen	1,400 mg/mL	IgA	231 mg/dL	Multinuclear cell	15%
FDP	18.1 μg/mL	IgM	117 mg/dL		
D-dimer	48 μg/mL	CH50	51 U/mL		
Antithrombin III	50%	sIL-2R	2,932 U/mL		

PT, prothrombin time ; PT-INR, prothrombin time-international normalized ratio ; APTT, activated partial thromboplastin ; FDP, fibrin/fibrinogen degradation products ; AST, aspartate aminotransferase ; ALT, alanine aminotransferase ; LDH, lactate dehydrogenase ; γ-GTP, γ-glutamyl transpeptidase ; sIL-2R, soluble IL-2 receptor (normal value 122-496 mg/dL) ; HIV-1,2, human immunodeficiency virus-1,2 ; HHV-8, human herpesvirus-8

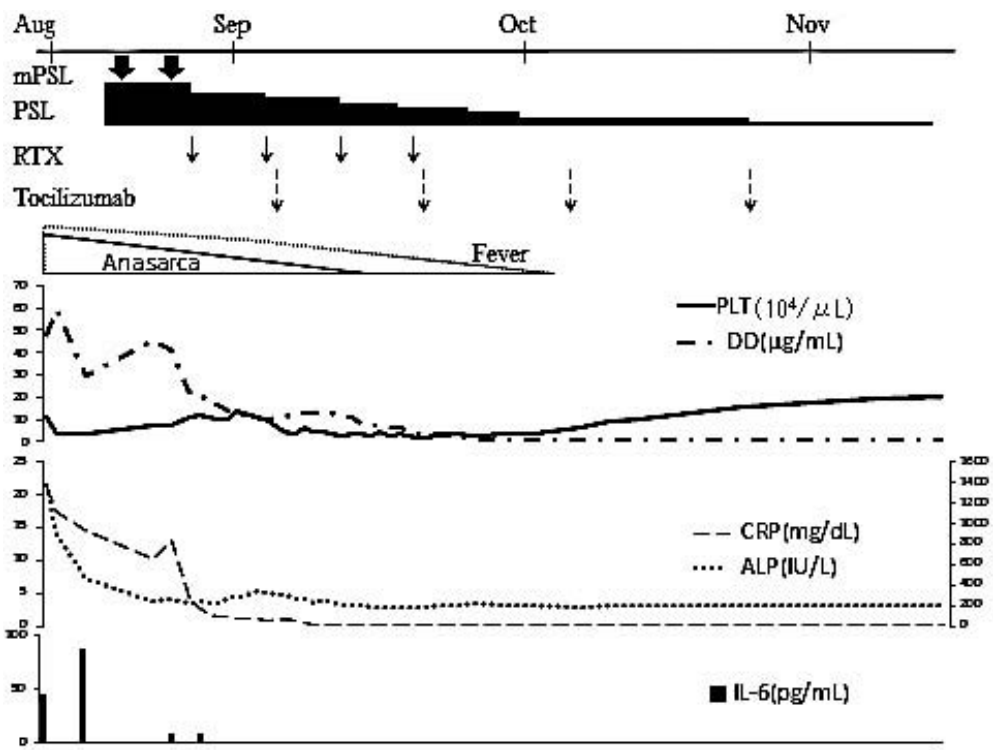

Fig. 1. Clinical course of the patient. PSL (prednisolone) could be gradually tapered from 80 mg/day to 15 mg/day. mPSL, methylprednisolone (500 mg/body 3 days) ; RTX, rituximab (375 mg/m^2) ; PLT, platelet ; DD, D-dimer ; CRP, C-reactive protein ; ALP, alkaline phosphatase ; IL-6, interleukin-6 ; tocilizumab, 6 mg/kg

VEGF. There was no evidence of malignant lymphoma or known autoimmune disease.

She was intravenously administered corticosteroid (methylprednisolone, 500 mg/day, 3 consecutive days) 2 times, followed by oral corticosteroid as well as 375 mg/m^2 rituximab, an anti-CD20 monoclonal antibody, every week for 4 weeks, and 8 mg/kg tocilizumab, an anti-IL-6 receptor antibody, every 3 weeks.

Laboratory data and clinical findings, including thrombocytopenia, an increase in acute inflammatory proteins, anasarca, and organomegaly, responded to these treatments. She was taken off ventilatory support at 1 month and was discharged from the hospital at about 2 months (Fig. 2).

DISCUSSION

Since MCD is suggested to be composed of several disease entities, we need to diagnose it in a comprehensive manner using clinical findings, laboratory data, and histopathological findings. It is postulated that the mechanism of lymphoproliferation in MCD is mediated by IL-6.[12] Furthermore, HHV-8 encodes a viral homologue of IL-6, which stimulates the known human IL-6-induced signaling pathway.[6,13,14] In our patient, the results of a viral serological test for HIV and polymerase chain reaction analysis for the HHV-8 sequence in peripheral blood were both negative ; moreover, immunohistochemical staining for HHV-8 in lymph node was also negative. Compared with that in Western countries, the association of MCD with HIV and HHV-8 occurs at a lower frequency in Japan.[9] It thus appears that there is some other unclear pathogenesis of MCD in Japan.

Here, we present an atypical CD patient who met the criteria of TAFRO syndrome and non-IPL, which both have some common and some different characteristics from MCD. Our patient showed high levels of IL-6 and VEGF and, as a result, had systemic manifestations of inflammation and an increase in acute inflammatory proteins. These findings match those of MCD. On the other hand, typical MCD often shows polyclonal hyperimmunoglobulinemia and thrombocy-

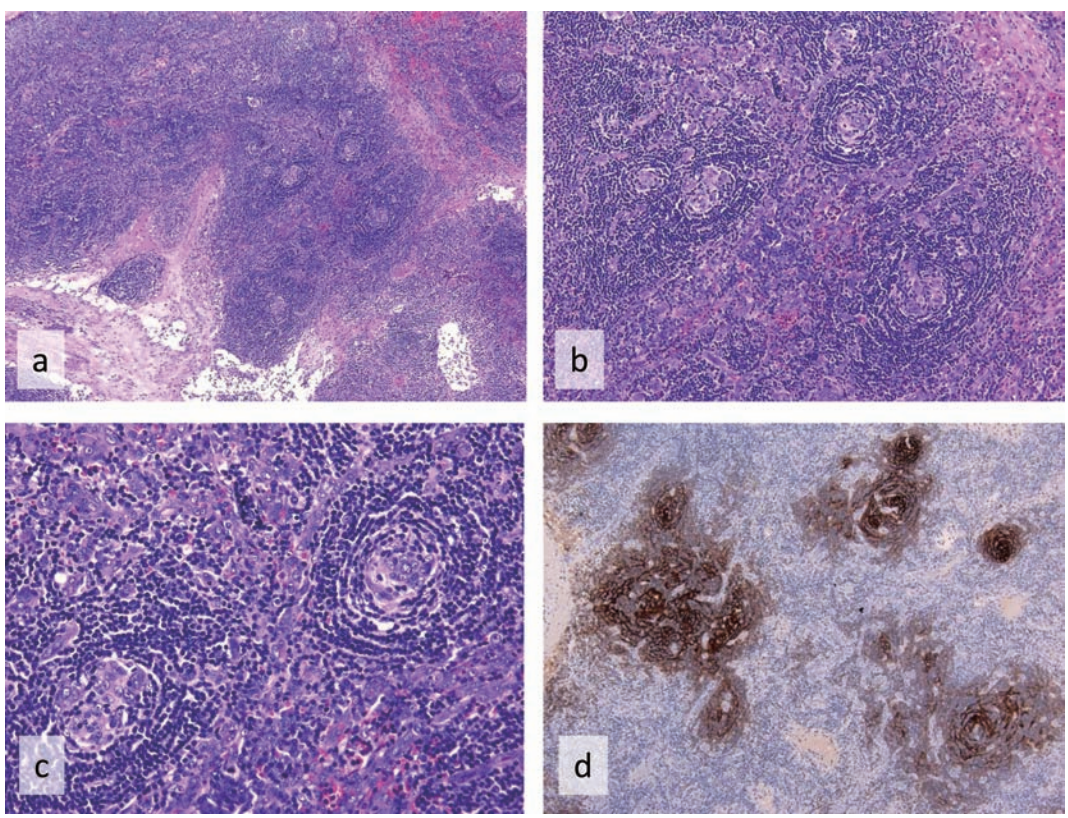

Fig. 2. Histological and immunohistochemical findings. (***2a***) The biopsy specimen was from a small lymph node and showed atrophic germinal centers and intact sinuses. H&E stain. (***2b***) Interfollicular zone was expanded and atrophic germinal centers were penetrated by highly dense endothelial venules. H&E stain. (***2c***) The interfollicular zone was characterized by the proliferation of highly dense endothelial venules and there were only a small number of mature plasma cells. H&E stain. (***2d***) CD21 immunostain showed an expanded or disrupted pattern of follicular dendritic cell networks. CD21 immunostaining.

tosis. Our patient showed marked thrombocytopenia and no hyperimmunoglobulinemia, which differ from MCD but meet the criteria for TAFRO syndrome.[2,4,10,11] IL-6 is also associated with the maturation of megakaryocytes and promotes platelet production.[15,16] In our case, bone marrow aspiration showed megakaryocytic hyperplasia with no abnormal morphology. However, as in the patients reported as having TAFRO syndrome, our case showed marked thrombocytopenia in peripheral blood. The thrombocytopenia was probably caused by an increase of peripheral thrombocyte consumption. In our case, the thrombocytopenia had been initially considered to have been caused by disseminated intravascular coagulation ; however, after recovery from abnormal coagulation, the platelet count had been under $3.0 \times 10^4/\mu L$ without platelet transfusion. Platelet-associated IgG was as high as 98.0 ng/10^7 cells. The thrombocytopenia was overcome by anti-inflammatory therapy with corticosteroid, rituximab, and tocilizumab. These findings suggest that the thrombocytopenia may have been attributable etiologically to some kind of immune-mediated mechanism. Furthermore, they may suggest that the elevation of IL-6 is not the main problem in TAFRO syndrome ; not only elevated IL-6 but also another unknown causal factor may be involved in the etiology of this syndrome. This is also compatible with the finding in our case that the concentration of IL-6 was restored only by using corticosteroid therapy without tocilizumab at a comparatively early phase of the disease.

Moreover, there were unique findings in that a high level of ALP was observed in the early phase of the disease, without the appearance of fragmented red cells, elevated LDH, aspartate aminotransferase, or indirect bilirubin level. The proportions of ALP isozymes were as follows : ALP1 28% (normal range : 0%), ALP2 67% (36-74%), and ALP3 5% (25-59%). These findings suggest that hemolysis and thrombotic microangiopathy were unlikely to have occurred. With regard to bone marrow observation, Takai reported that TAFRO syndrome showed reticulin fibrosis,[11] but our case did not undergo bone marrow biopsy because of her bleeding tendency.

Histologically, this patient was characterized by an HV-type germinal center with marked proliferation of endothelial venules in the interfollicular zone. VEGF is known as a direct angiogenesis factor. Cohen *et al*. reported that IL-6 induced the expression of VEGF *in vitro* and suggested that IL-6 may induce angiogenesis indirectly by inducing VEGF expression.[17] Nishi *et al*. studied VEGF expression in sera and lymph nodes from PC-type and mixed-type CD patients, and reported the high VEGF level of the sera and the expression in plasma cells in the interfollicular region.[18] In our patient, not only the serum IL-6 level but also the plasma VEGF level was high. The proliferation of endothelial venules may thus have been influenced by VEGF.

In our patient, there was a dissociation between the levels of IL-6 in serum and pleural effusion. The serum IL-6 level was 45.6 pg/mL, but its level in pleural effusion was markedly higher at 1,860 pg/mL (Table 2). According to previous reports, a high level of IL-6 was found in the cerebrospinal fluid of patients with systemic lupus erythematosus with active central nervous system disease, even when the serum level was normal.[19] IL-6 was also found to be highly upregulated in RA joints or pericardial effusion.[20] These findings may suggest that the concentration of IL-6 reflects local acute inflammation. The presence of severe anasarca including ascites, pleural effusion, and cardiac effusion with a markedly high level of IL-6 in pleural effusion in our patient may suggest the occurrence of systemic inflammation of the serosa by an unknown mechanism.

It is interesting that the plasma VEGF level was 665 pg/mL and its level in pleural effusion was 155 pg/mL, which are almost the same. Since the serum levels of VEGF are affected by the unpredictable release of platelet-derived VEGF because of *ex vivo* platelet activation during the clotting process, it is well established that serum VEGF levels are 10-50 times higher than plasma VEGF levels in both healthy and diseased states.[21] It has been reported that IL-6 is produced by a variety of cells, including mesothelial cells,[22] dendritic cells, macrophages, fibroblasts, monocytes, and lymphocytes.[23] VEGF is also secreted from a variety of cells, including mesothelial cells,[24] macrophages, and plasma cells, as well as enlarged lymph nodes.[25,26] Further studies are needed to clarify the source of IL-6 and VEGF in effusion and the meaning of the divergence of their levels in the etiology of TAFRO syndrome.

The standard therapeutic strategy of MCD has yet to be established. There are various therapeutic strategies including corticosteroid, chemotherapy, rituximab, and tocilizumab.[2,11,27-30] Our patient required the administration of rituximab and tocilizumab along with corticosteroid. Takai suggested the efficacy of immunosuppressive therapy, such as corticosteroid and cyclosporine A, for TAFRO syndrome

Table 2. Concentrations of cytokines in serum, plasma and pleural effusion

Cytokine	Serum (pg/mL)	Plasma (pg/mL)	Pleural effusion (pg/mL)
Interleukin-6	45.6	ND	1,860
Vascular endothelial growth factor	ND	665	155

Interleukin-6 (serum normal value : < 4.0 pg/mL) ; Vascular endothelial growth factor (plasma normal value : < 115 pg/mL) ; ND, not done

Table 3. Commonality and difference between our case, TAFRO syndrome, and multicentric Castleman's disease (MCD)

Clinicopathological findings		MCD (PC-type)	TAFRO syndrome	Our case
Symptoms	Fever	+	++	++
	Anasarca	±	++	++
	Lymphoid adenopathy	+	±	+
	Hepatosplenomegaly	+	+	+
	Polyneuropathy	-	-	-
Laboratory date	Blood platelet count	Increased	Severely depleted	Severely depleted
	Immunoglobulin	Polycloal gammopathy	Normal	Normal
	Cytokine	Interleukin-6	Unclear	Interleukin-6 plasma and pleural effusion
Pathological findings	GC	Hyperplastic GC	Atrophic GC with hyaline vessels	Atrophic GC with hyaline vessels
	Interfollicular area	Plasma cells	Proliferation of small vessels	Proliferation of endothelial venules
	Bone marrow	Immunoblast, Plasma cell	Megakaryocytic hyperplasia	Megakaryocytic hyperplasia
Treatment		Corticosteroid	Corticosteroid	Corticosteroid
		Tocilizumab	CyclosporinA	Rituximab, Tocilizmab

-, none ; ± , often ; +, mild ; ++, marked ; GC, germinal center ; Tocilizum, anti-IL-6 receptor antibody ; Rituximab, anti-CD20 monoclonal antibody

(Table 3).[11]

TAFRO syndrome is a rare and newly recognized clinical entity that may have been included in MCD in the past. Time is sometimes required to make a definitive diagnosis of this syndrome and to start the treatment. However, some cases, such as the present one, have an aggressive clinical course and some of them demonstrate a rapid fatal outcome.[2,11] Therefore, we need better definition of this novel entity, criteria for diagnosis, and a therapeutic strategy.

In conclusion, we presented a case of atypical CD : histopathologically presented HV-type CD with endothelial proliferation and suspected systemic inflammatory disorder. Moreover, the patient's clinical findings and laboratory data met the reported criteria for the syndrome of TAFRO and non-IPL. For better definition of this novel entity, as well as to demonstrate the etiology of MCD more clearly in Japan, further nationwide surveys of this syndrome and MCD are needed.

Conflict of interest disclosure

The authors declare no competing financial interests.

REFERENCES

1 Castleman B, Iverson L, Menendez VP: Localized mediastinal lymphnode hyperplasia resembling thymoma. Cancer 9:822-830, 1956

2 Frizzera G, Peterson BA, Bayrd ED, Goldman A: A systemic lymphoproliferative disorder with morphologic features of Castleman's disease : clinical findings and clinicopathologic correlations in 15 patients. J Clin Oncol 3:1202-1216, 1985

3 Frizzera G: Castleman's disease and related disorders. Semin Diagn Pathol 5:346-364, 1988

4 Keller AR, Hochholzer L, Castleman B: Hyaline-vascular and plasma-cell types of giant lymph node hyperplasia of the mediastinum and other locations. Cancer 29:670-683, 1972

5 Kojima M, Nakamura S, Itoh H, Yoshida K, Asano S, *et al*.: Systemic lupus erythematosus (SLE) lymphadenopathy presenting with histopathologic features of Castleman' disease : a clinicopathologic study of five cases. Pathol Res Pract 193:565-571, 1997

6 Soulier J, Grollet L, Oksenhendler E, Cacoub P, Cazals-Hatem D, *et al*.: Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. Blood 86:1276-1280, 1995

7 Chadburn A, Cesarman E, Nador RG, Liu YF, Knowles DM: Kaposi's sarcoma-associated herpesvirus sequences in benign lymphoid proliferations not associated with human immunodeficiency virus. Cancer 80:788-797, 1997

8 Gessain A: Human herpesvirus 8 and associated diseases : Kaposi's sarcoma, body cavity based lymphoma and multicentric Castleman disease : clinical and molecular epidemiology. Bull Acad Natl Med 181:1023-1034, 1997 (in *French*)

9 Suda T, Katano H, Delsol G, Kakiuchi C, Nakamura T, *et al*.: HHV-8 infection status of AIDS-unrelated and AIDS-associated multicentric Castleman's disease. Pathol Int 51:671-679, 2001

10 Kojima M, Nakamura N, Tsukamoto N, Otuski Y, Shimizu K, *et al*.: Clinical implications of idiopathic multicentric Castleman disease among Japanese : A report of case. Int J Surg Pathol 16:391-398, 2008

11 Takai K, Nikkuni K, Shibuya H, Hashidate H: Thrombocytopenia with mild bone marrow fibrosis accompanied by fever, pleural effusion, ascites and hepatosplenomegaly. Rinsho Ketsueki 51:320-325, 2010 (*in Japanese*)

12 Yoshizaki K, Matsuda T, Nishimoto N, Kuritani T, Taeho L, *et al*.: Pathogenic significance of interleukin-6 (IL-6/BSF-2) in Castleman's disease. Blood 74:1360-1367, 1989

13 Luppi M, Barozzi P, Maiorana A, Artusi T, Trovato R, *et al*.: Human herpesvirus-8 DNA sequences in human immunodeficiency virus-negative angioimmunoblastic lymphadenopathy and benign lymphadenopathy with giant germinal center hyperplasia

and increased vascularity. Blood 87:3903-3909, 1996

14 Aoki Y, Jaffe ES, Chang Y, Jones K, Teruya-Feldstein J, *et al*.: Angiogenesis and hematopoiesis induced by Kaposi's sarcoma-associated herpesvirus-encoded interleukin-6. Blood 93:4034-4043, 1999

15 Ishibashi T, Kimura H, Shikama Y, Uchida T, Kariyone S, *et al*.: Interleukin-6 is a potent thrombopoietic factor *in vivo* in mice. Blood 74:1241-1244, 1989

16 Tomer A: Human marrow megakaryocyte differentiation : multiparameter correlative analysis identifies von Willebrand factor as a sensitive and distinctive marker for early (2N and 4N) megakaryocytes. Blood 104:2722-2727, 2004

17 Cohen T, Nahari D, Cerem LW, Neufeld G, Levi BZ: Interleukin 6 induces the expression of vascular endothelial growth factor. J Biol Chem 271:736-741, 1996

18 Nishi J, Arimura K, Utsunomiya A, Yonezawa S, Kawakami K, *et al*.: Expression of vascular endothelial growth factor in sera and lymph nodes of the plasma cell type of Castleman's disease. Br J Haematol 104:482-485, 1999

19 Hirohata S, Miyamoto T: Elevated levels of interleukin-6 in cerebrospinal fluid from patients with systemic lupus erythematosus and central nervous system involvement. Arthritis Rheum 33:644-649, 1990

20 Shikama N, Terano T, Hirai A: A case of rheumatoid pericarditis with high concentrations of interleukin-6 in pericardial fluid. Heart 83:711-712, 2000

21 Webb NJ, Bottomley MJ, Watson CJ, Brenchley PE: Vascular endothelial growth factor (VEGF) is released from platelets during blood clotting : implications for measurement of circulating VEGF levels in clinical disease. Clin Sci (Lond) 94:395-404, 1998

22 Lanfrancone L, Boraschi D, Ghiara P, Falini B, Grignani F, *et al*.: Human peritoneal mesothelial cells produce many cytokines (granulocyte colony-stimulating factor [CSF], granulocyte-monocyte-CSF, macrophage-CSF, interleukin-1 [IL-1], and IL-6) and are activated and stimulated to grow by IL-1. Blood 80:2835-2842, 1992

23 Tanaka T, Kishimoto T: Targeting interleukin-6 : all the way to treat autoimmune and inflammatory diseases. Int J Biol Sci 8:1227-1236, 2012

24 Ilonidis G, Parapanisiou E, Anogeianaki A, Giavazis I, Theofilogiannakos EK, *et al*.: Interleukin-1-β (IL-1β), interleukin 6 (IL-6) and tumor necrosis factor (TNF) in plasma and pleural fluid of pneumonia, lung cancer and tuberculous pleuritis. J Biol Regul Homeost Agents 20:41-46, 2006

25 McLaren J, Prentice A, Charnock-Jones DS, Millican SA, Müller KH, *et al*.: Vascular endothelial growth factor is produced by peritoneal fluid macrophages in endometriosis and is regulated by ovarian steroids. J Clin Invest 98:482-489, 1996

26 Ito A, Hirota S, Mizuno H, Kawasaki Y, Takemura T, *et al*.: Expression of vascular permeability factor (VPF/VEGF) messenger RNA by plasma cells : possible involvement in the development of edema in chronic inflammation. Pathol Int 45:715-720, 1995

27 Bower M : How I treat HIV-associated multicentric Castleman disease. Blood 116 : 4415-4421, 2010

28 Ide M, Kawachi Y, Izumi Y, Kasagi K, Ogino T: Long-term remission in HIV-negative patients with multicentric Castleman's disease using rituximab. Eur J Haematol 76:119-123, 2006

29 Ocio EM, Sanchez-Guijo FM, Diez-Campelo M, Castilla C, Blanco OJ, *et al*.: Efficacy of rituximab in an aggressive form of multicentric Castleman disease associated with immune phenomena. Am J Hematol 78:302-305, 2005

30 Nishimoto N, Kanakura Y, Aozasa K, Johkoh T, Nakamura M, *et al*.: Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. Blood 106:2627-2632, 2005