

Membranoproliferative glomerulonephritis-like findings for TAFRO syndrome, associated with an anterior mediastinal tumor

A case report

Yoshitaka Furuto, MD^{a,*}, Hirotsugu Hashimoto, MD, PhD^b, Hajime Horiuti, MD, PhD^b, Yuko Shibuya, MD, PhD^a

Abstract

Rationale: TAFRO syndrome is a systemic inflammatory disease proposed recently from Japan. The cause of TAFRO syndrome is unclear. Moreover, the disease characteristics and kidney pathology are yet unknown well and there are few cases. Herein, we report a patient with TAFRO syndrome and present the features of the renal histopathology.

Patient Concerns: A 55-year-old woman presented to our hospital with the main complaint of subacute dyspnoea.

Diagnosis: Physical findings included a low-grade fever and generalised oedema. A blood test showed anaemia, coagulation abnormalities, hypoproteinaemia, impaired renal function, proteinuria, and elevated alkaline phosphatase (ALP), C-reactive protein (CRP), interleukin-6 (IL-6). Chest and abdominal computed tomography showed an anterior mediastinal mass and multiple enlarged lymph nodes.

Interventions: Nephrotic syndrome secondary to a malignant mediastinal tumour was suspected; therefore, the patient underwent resection of the anterior mediastinal mass. Histopathological examination of the resected specimen showed lymphocytic proliferation without signs of malignancy. These findings were compatible with hyaline vascular type Castleman disease (CD), and with the associated multiple lymph nodes enlargement, the patient was initially diagnosed with multicentric CD.

Outcomes: After resection of the whole tumour, all the clinical symptoms improved. However, after resection 6 months passed, the patient developed thrombocytopenia, anaemia, renal dysfunction, further enlargement of the residual lymph nodes, hepatosplenomegaly, and mild myelofibrosis. A diagnosis of TAFRO syndrome (TS) was eventually made. All symptoms improved with initial intravenous pulse steroid therapy followed by oral steroids. Histopathological examination of the renal biopsy samples showed findings resembling membranoproliferative glomerulonephritis (MPGN).

Lessons: In TS, all characteristic signs may not exist from the beginning. The association between TS and CD is not clear. When we compared our findings with previously published cases of TS and CD, we found that the renal pathology findings resembled MPGN in many cases of TS, while only a few cases showed amyloidosis. Recent results suggest that TS may be an independent disease from CD, and given the frequency of renal pathology findings, it may also have a different aetiology. To the best of our knowledge, this case report is rare to demonstrate the renal pathology in a patient with conventional TAFRO syndrome.

Abbreviations: ALP = alkaline phosphatase, CD = Castleman disease, Cr = creatinine, CRP = C-reactive protein, CyA = cyclosporin, EBV = Epstein-Barr virus, HHV-8 = human herpes virus-8, HIV = human immunodeficiency virus, HV = Hyaline vascular, IL-6 = interleukin-6, IPL = idiopathic plasmacytic lymphadenopathy, MCD = multicentric Castleman disease, MPGN = membranoproliferative glomerulonephritis, Pa-IgG = platelet associated immunoglobulin G, PaIgG = platelet-associated IgG, PC = plasma cell, PET = positron emission tomography, PSL = prednisolone, SAA = serum amyloid A, sIL-2R = soluble IL-2 receptor, TS = TAFRO syndrome, UCD = unicentric Castleman disease.

Keywords: Castleman disease, membranoproliferative glomerulonephritis-like findings, TAFRO syndrome

Editor: N/A.

Funding: The authors did not receive any funding for this study.

The authors have no conflicts of interest to disclose.

^a Department of Hypertension and Nephrology, ^b Department of Diagnostic Pathology, NTT Medical Centre Tokyo, Higasi-Gotanda, Shinagawa-ku, Tokyo, Japan.

* Correspondence: Yoshitaka Furuto, Department of Hypertension and Nephrology, NTT Medical Centre Tokyo, NTT Medical Centre Tokyo, 5-9-22, Higasi-Gotanda, Shinagawa-ku, Tokyo, 141-8625, Japan (e-mail: furuto19761006@yahoo.co.jp).

Copyright © 2018 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Medicine (2018) 97:24(e11057)

Received: 13 March 2018 / Accepted: 18 May 2018

<http://dx.doi.org/10.1097/MD.00000000000011057>

1. Introduction

TAFRO syndrome (TS) is a systemic inflammatory disease of unknown aetiology, and published reports suggest that it might be related to Castleman disease (CD).^[1]

In 2010, Takai et al^[2] reported 3 patients with megakaryocytosis, severe thrombocytopenia, mild myelofibrosis, high fever, pleural effusion, abdominal ascites, hepatosplenomegaly, and lymph node enlargement; and proposed the name TAFRO syndrome (TS), using the first letters of the symptoms that make up the characteristic clinical picture: thrombocytopenia, anasarca, reticulin fibrosis, renal dysfunction, and organomegaly.

As there is a type of CD known as multicentric Castleman disease (MCD) that often presents with generalized symptoms, TS frequently needs to be differentiated from MCD, and currently, investigation is underway to determine the characteristics of this disease. We encountered a patient with TS who

presented with an anterior mediastinal tumor, associated by multiple lymph nodes enlargement, fever, anemia, proteinuria, and renal dysfunction.

Only a small number of reports have been published about the renal pathology in patients with TS. The renal pathology in many of these reports was membranoproliferative glomerulonephritis (MPGN), which is consistent with our case. On the other hand, amyloidosis, which is often seen in patients with MCD, was not a finding in these reports. Therefore, we postulate that renal pathology findings may assist in the diagnosis of TS.

2. Case presentation

A 55-year-old woman presented to our hospital with the main complaint of dyspnoea in December 2014. Mediastinal imaging showed pleural effusion and an anterior mediastinal mass. A CT-guided biopsy was performed, but showed no significant findings. The patient then developed proteinuria, secondary exacerbation of pleural effusion and generalized oedema. In January 2015, the patient was hospitalized in our department with dyspnoea.

As this is a case study, ethics approval was not required. The patient received an explanation of the procedures and possible risks of this study and gave written informed consent along the policy of our ethical committee.

The past medical history was significant for hypertension and a renal stone. The patient smoked 20 cigarettes/day for

approximately 35 years, but did not drink alcohol. Family history was unremarkable and she had no known drug allergies.

The patient's height was 151.4 cm, body weight was 81.6 kg, blood pressure was 164/82 mm Hg, heart rate was regular at 92/min, body temperature was 37.1°C, and oxygen saturation was 97% with oxygen administered via nasal cannula at a rate of 1 L/min.

She was conscious and lucid. Palpebral conjunctiva showed pallor. Neck palpation revealed a number of enlarged lymph nodes measuring 1 cm in diameter, which were painless with elastic consistency. No murmurs were auscultated on cardiac examination. Chest auscultation revealed bilaterally diminished breathing sounds in the lower lung fields. The abdomen was soft but distended, and not tender to palpation. Bowel sounds were enhanced. Shifting dullness was elicited.

Marked oedema was noted in both lower limbs. There was no joint pain, dermal, or neurological findings.

2.1. Clinical course during the first hospitalisation

Urinalysis showed proteinuria (Table 1), and the blood tests revealed anemia, abnormal coagulation, hypoproteinemia, mild renal dysfunction, elevated alkaline phosphatase (ALP), elevated inflammatory markers, and elevated cardiac enzymes. The patient did not have hypergammaglobulinemia or hypocomplementemia, and the tumor marker soluble IL-2 receptor (sIL-2R) was elevated. The patient tested negative for various autoantibodies, human

Table 1

Laboratory data on the first admission.

Urinalysis		Biochemistry		Tumour marker	
Protein	3+	TP	5.8 g/dL	CEA	1.0 ng/mL
Occult blood	±	Alb	2.3 g/dL	CYFRA-21	1.1 ng/mL
Glucose	(-)	UA	7.6 mg/dL	ProGRP	33.0 pg/mL
RBC	5–9/HPF	BUN	23.5 mg/dL	sIL-2R	1128 U/mL
Protein content	2264 mg/gCr	Cr	0.89 mg/dL		
Bence jones protein	(-)	eGFR	52 mL/min/1.73 m ²	Immunologic test	986 mg/dL
		TB	0.4 mg/dL		188 mg/dL
		AST	34 IU/L	IgG	125 mg/dL
Complete blood cell count		ALT	16 IU/L	IgA	16 mg/dL
White blood cell	7700/μl	ALP	568 IU/L	IgM	145 mg/dL
Neutrophil	69.6%	γ-GT	99 IU/L	IgG4	29 mg/dL
Lymphocyte	18.4%	ChE	167 IU/L	C3	39 U/mL
Monocyte	8.8%	LDH	226 IU/L	C4	1: 40
Eosinophil	1%	CK	43 IU/L	CH50	(-)
Red blood cell	326×10 ⁴ /μl	Na	140 mEq/L	Antinuclear antibody	(-)
Hemoglobin	8.6 g/dL	K	4.2 mEq/L	Anti-dsDNA-Ab	(-)
Hematocrit	27%	Cl	108 mEq/L	Anti-CCP-Ab	(-)
Platelet		Ca	8.5 mg/dL	Anti-MPO-ANCA	
		IP	4.0 mg/dL	Anti-PR3-ANCA	(-)
Coagulation test		Glu	119 mg/dL		(-)
PT	84%	TC	129 mg/dL	Virologic test	(-)
PT-INR	1.08	LDLC	82 mg/dL	HIV-Ab	13 pg/mL
APTT	28.1 sec	TG	155 mg/dL	EBV-DNA	
FDP	20.8 μg/ml	CRP	6.3 mg/dL	HHV-8-DNA	
Fibrinogen	44.3 mg/mL	HbA1c	6.1%	Cytokine	
D-dimer	6.1 μg/ml	TSH	1.488 μIU/mL	IL-6	
		FT4	1.32 ng/dL		
		Ferritin	377 ng/mL		
		β2MG	5.2 mg/L		
		HANP	94.8 pg/mL		
		BNP	137.8 pg/mL		
		KL-6	140 U/mL		

IL-6=interleukin-6(normal value ≤4 pg/mL), sIL-2R=soluble IL-2 receptor (normal value 122–496 U/mL), VEGF=vascular endothelial growth factor (normal value≤38.3 pg/mL).

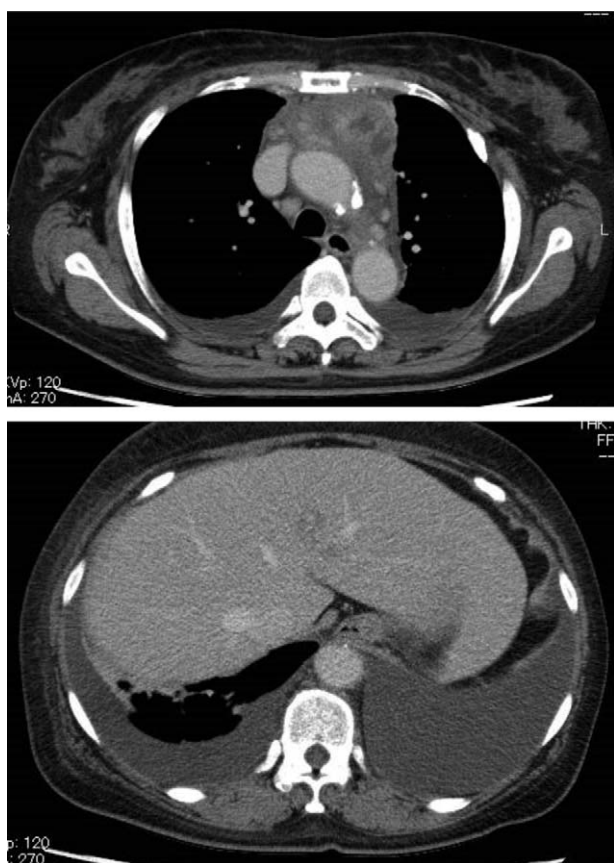


Figure 1. Computed tomography scan of the chest and abdomen.

immunodeficiency virus (HIV), human herpes virus-8 (HHV-8), and Epstein-Barr virus (EBV) infections, so there were no disease-specific findings. Interleukin-6 (IL-6) was mildly elevated. A CT scan of the chest and abdomen showed cardiomegaly, pleural effusion, abdominal ascites, severe subcutaneous oedema, a 65- × 25-mm mass with internal heterogeneity in the anterior mediastinum and multiple enlarged lymph nodes in the neck, both axillae, mediastinum, and groin (Fig. 1). An ^{18}F FDG-positron emission tomography (PET) scan showed multiple enlarged lymph nodes in both sides of the neck, in the supraclavicular fossa, axilla, mediastinum, and from the right common iliac to the external iliac artery (maximum diameter of approximately 20 mm, with multiple different sizes), with abnormal FDG uptake (Fig. 2). Initially, we suspected nephrotic syndrome secondary to a malignant mediastinal tumor, based on the findings of the anterior mediastinal tumor, multiple enlarged lymph nodes, and anemia. Renal biopsy was considered risky at that time; therefore, large doses of different diuretics (furosemide 500 mg, trichlormethiazide 8 mg, tolvaptan 15 mg, eplerenone 50 mg) were administered to control the pleural effusion. In late January 2015, resection of the anterior mediastinal tumor was performed. Gross examination of the resected anterior mediastinal tumor showed lesions with multinodular fibrosis (Fig. 3), and histological examination showed hyperplastic lymphoid follicles and lymphocytes concentrically arranged in the mantle layer. Vascular proliferation with hyalinization was seen in the germinal centre, which was consistent with the features of hyaline vascular (HV)-type CD (Fig. 4).

Based on the CT and PET scan findings, there were multiple enlarged cervical lymph nodes, which showed the same

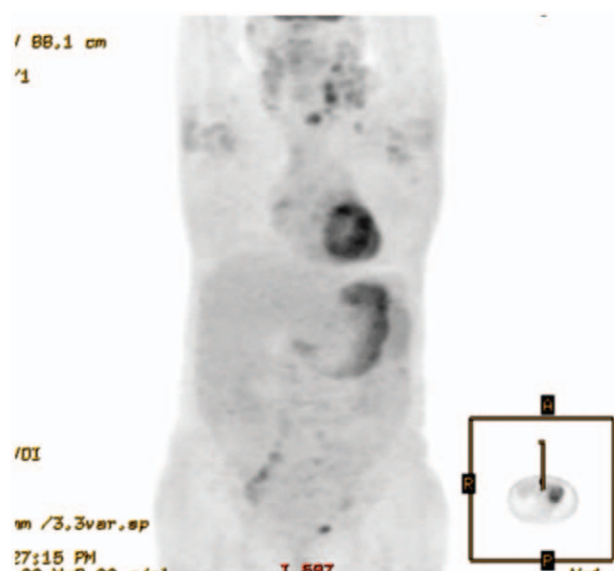


Figure 2. ^{18}F FDG-positron emission tomography scan showing abnormal accumulation of FDG in the lymph nodes.

histological findings as the resected tumor. At this time, the patient was diagnosed with MCD based on the clinical picture of multiple enlarged lymph nodes, fever, anemia, renal dysfunction, and oedema.

After resection of the lesion in January 2015, the patient's response to the diuretics improved significantly, and her body weight decreased from 81.6 kg at admission to 55 kg. The oedema, respiratory, and renal functions all rapidly improved and the patient was discharged. However, the enlarged lymph nodes persisted, so the patient was closely monitored in anticipation of recurrence.

2.2. Clinical course during second hospitalisation

In July 2015, the patient's creatinine (Cr) was 0.69 mg/dL, and proteinuria was negative. One month later, in August 2015, the patient developed proteinuria (536 mg/gCr), renal failure (Cr 2.1 mg/dL, estimated glomerular filtration rate [eGFR] 20 mL/min/1.73 m²), generalized anasarca, anemia (hemoglobin 5.9 g/dL),

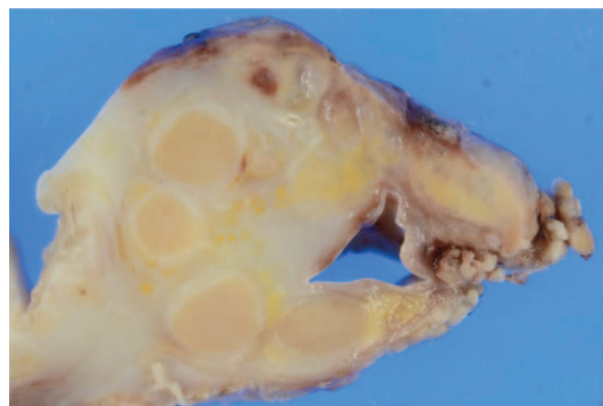


Figure 3. Gross appearance of the anterior mediastinal tumor. The anterior mediastinal tumor measured 65 × 25 mm and showed a multinodular lesion with fibrosis.

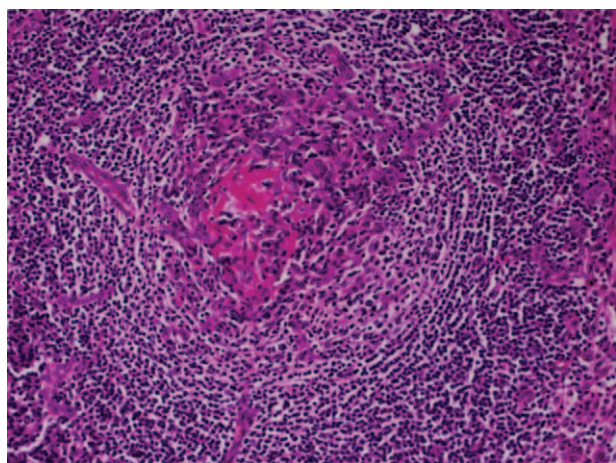


Figure 4. Light microgram showing the histological findings of the anterior mediastinal tumor × 20 hematoxylin–eosin stain.

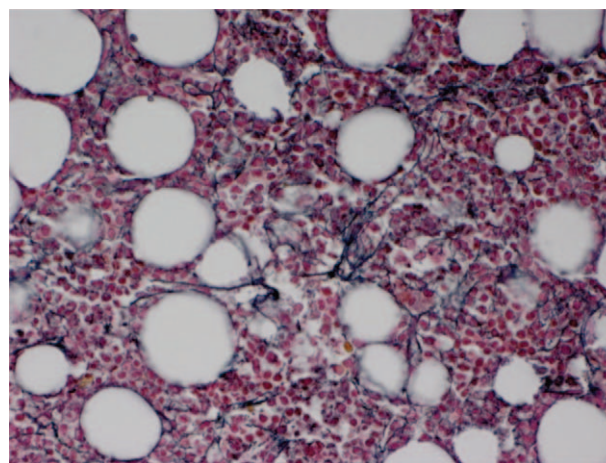


Figure 5. Light microgram showing the bone marrow findings × 100 Silver impregnation method: Mild fibrosis.

and thrombocytopenia (platelet count $6.9 \times 10^4/\mu\text{l}$). sIL-2R, platelet-associated IgG (PAIgG), IL-6, and vascular endothelial growth factor (VEGF) were all elevated (Table 2). The patient was readmitted for further enlargement of the residual lymph nodes and development of hepatosplenomegaly. A bone marrow biopsy showed increased megakaryocytes and mild myelofibrosis (Fig. 5), so the patient was diagnosed with TAFRO syndrome. The patient responded to pulse steroid therapy, followed by 60 mg/day oral prednisolone (PSL), and the steroid dose was reduced as the symptoms improved (Fig. 6).

In January 2016, during which the patient was receiving 10 mg/day PSL, a renal biopsy was performed to unveil the renal pathology. Light microscopy (Fig. 7) revealed hyalinization of 1/11 glomeruli, diffuse and global mesangial proliferation, and glomerular lobulation with partial duplication of the basement membrane. Stromal fibrosis with patchy tubular atrophy was noted, together with peripheral lymphocytic infiltration. Direct

fast scarlet staining was negative, and there was no amyloid deposition. Immunofluorescence was positive for IgM, which was partially granular, and negative for IgG, IgA, fibrinogen, C3, C4, and C1q. Electron microscopy revealed no electron dense deposits with partial disappearance of the podocyte foot processes. There was partial duplication of the basement membrane and mesangial interposition, which were consistent with MPGN-like findings. The patient’s subsequent clinical progress was favourable, and remission was maintained with oral steroid therapy (PSL 3 mg/day).

3. Discussion and conclusions

CD is a rare lymphoproliferative disorder first reported in 1956 by Castleman et al^[3] as thymoma-like mediastinal lymph node enlargement. After the first report, many other similar cases were reported, and the disease was classified into a number of different

Table 2

Laboratory data on the second admission.

Urinalysis		Biochemistry		Tumour marker	
Protein	1+	TP	6.1 g/dL	sIL-2R	1967 U/mL
Occult blood	(–)	Alb	2.7 g/dL	Immunologic test	
Protein content	536 mg/gCr	UA	9.1 mg/dL	PA-IgG	42.6 ng/10 ⁷ cells
Complete blood cell count		BUN	73.4 mg/dL	Cytokines	
White blood cell	3600/μl	Cr	2.1 mg/dL	IL-6	11.7 pg/mL
Neutrophil	69.5%	eGFR	20 mL/min/1.73 m ²	VEGF	464 pg/mL
Lymphocyte	15.5%	TB	0.2 mg/dL		
Monocyte	13.5%	AST	8 IU/L		
Eosinophil	0%	ALT	4 IU/L		
Red blood cell	$230 \times 10^4/\mu\text{l}$	ALP	360 IU/L		
Hemoglobin	5.9 g/dL	γ-GT	40 IU/L		
Hematocrit	18.4%	LDH	127 IU/L		
Platelet	$6.9 \times 10^4/\mu\text{l}$	Na	131 mEq/L		
		K	4.3 mEq/L		
		Cl	97 mEq/L		
		Ca	7.9 mg/dL		
		IP	4.4 mg/dL		
		Glu	117 mg/dL		
		CRP	4.1 mg/dL		

IL-6=interleukin-6 (normal value ≤ 4 pg/mL), PA-IgG=platelet-associated IgG (normal value < 27.6 ng/10⁷cells), sIL-2R=soluble IL-2 receptor (normal value 122–496 U/mL), VEGF=vascular endothelial growth factor (normal value ≤ 38.3 pg/mL).

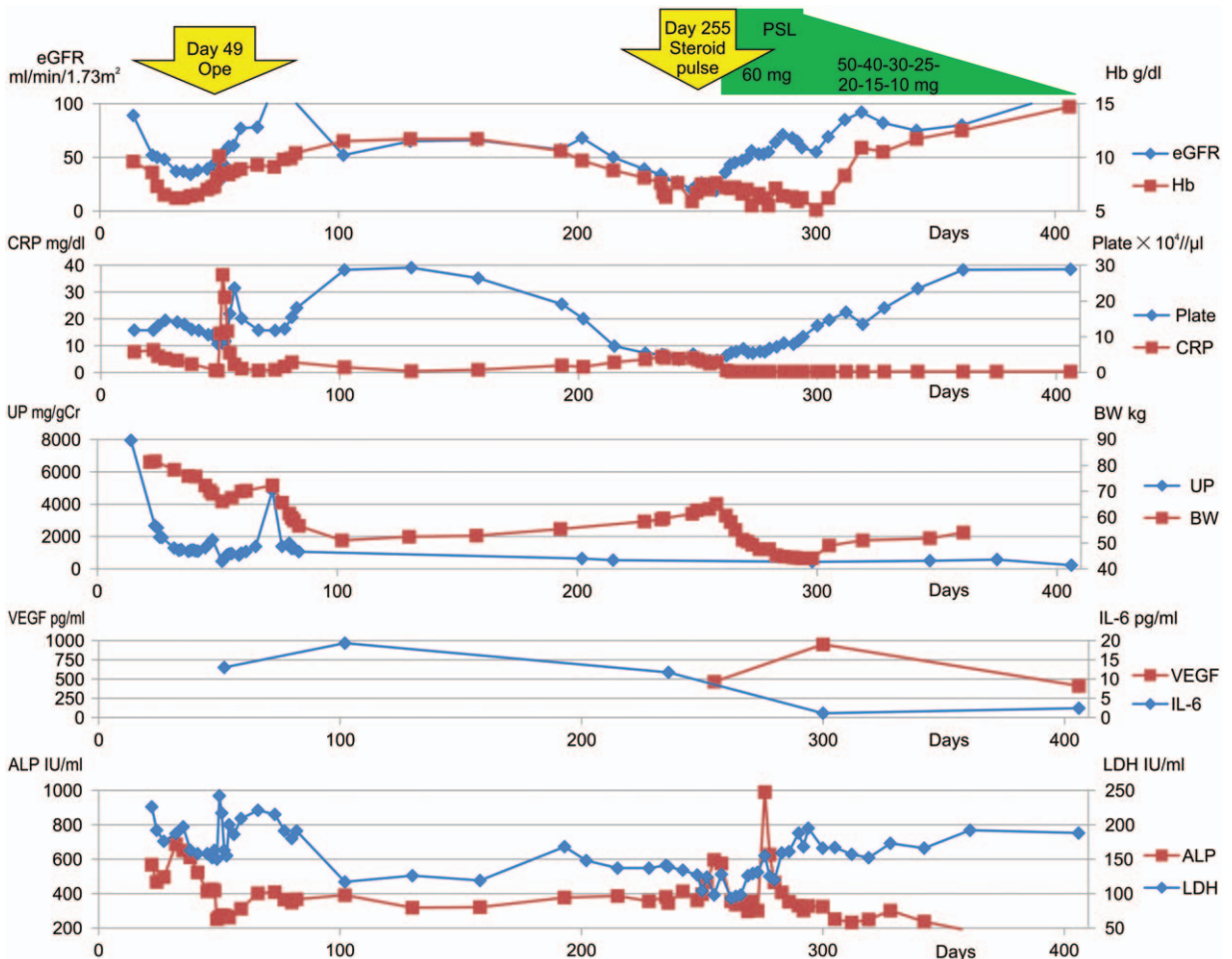


Figure 6. Treatment course. In this figure, the progression and the change of each clinical parameter with steroid therapy is illustrated. As shown, improvement of the different parameters was observed with steroid therapy. ALP = alkaline phosphatase (IU/L), BW = body weight (Kg), CRP = C-reactive protein (mg/dL), eGFR = estimated glomerular filtration rate (mL/min/1.73 m²), Hb = hemoglobin (g/dL), IL-6 = interleukin-6 (pg/mL), LDH = Lactate dehydrogenase (IU/L), Ope = Operation, PSL = prednisolone, UP = urine protein (mg/gCr), VEGF = vascular endothelial growth factor (pg/mL).

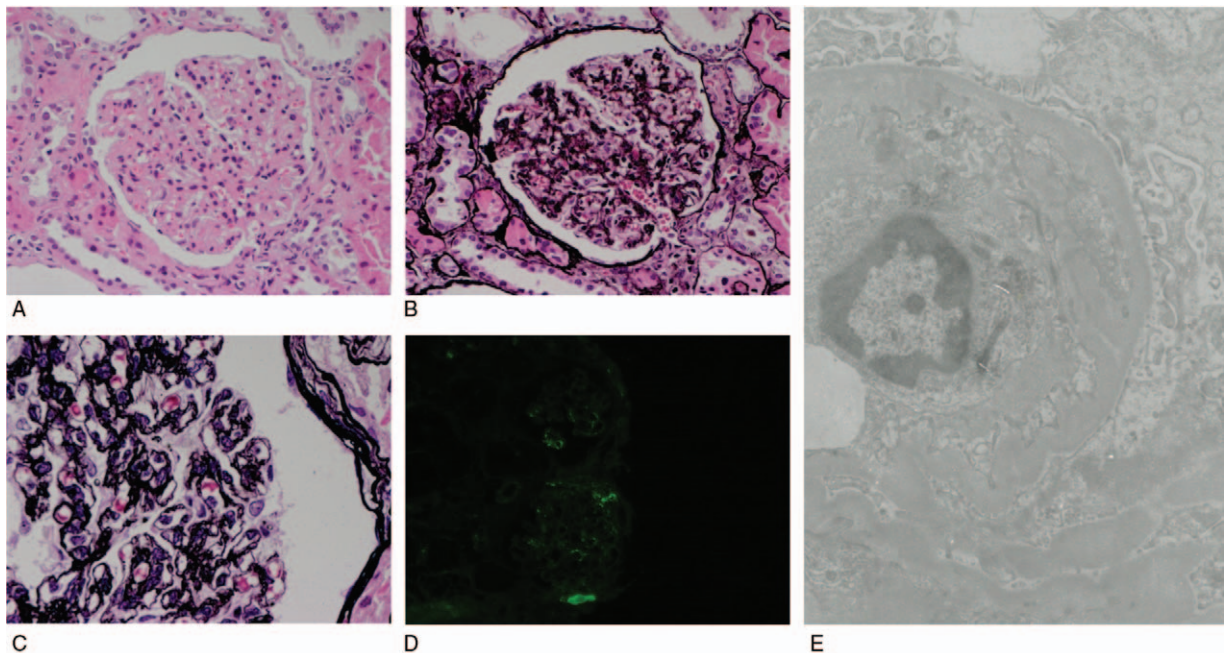


Figure 7. Renal histopathological findings. (A) Light microgram ×400 hematoxylin-eosin stain, (B) ×400 periodic acid silver-methenamine stain, (C) ×1000 periodic acid silver-methenamine stain, (D) Fluorescent antibody technique ×20 IgM, (E) electron micrograph ×5000.

types.^[4,5] CD is classified according to the histopathological findings into HV type, plasma cell (PC) type, and mixed type. Clinically, the disease is classified as unicentric Castleman disease (UCD), where the enlarged lymph nodes are localized; and MCD, where the enlarged lymph nodes are generalized. Many of the patients with UCD have the HV type with asymptomatic mediastinal lymph node enlargement; however, a rarity may have associated clinical symptoms. If the entire mass is resected, the prognosis is good, and reports show that resection of the lesion can improve the condition, as it is associated with reduction in IL-6.^[6] On the other hand, MCD is usually of the PC or mixed type, this condition often recurs and the prognosis is poor.

In terms of the cause of MCD, in Europe and the United States it is known to be a disease that develops in conjunction with infections such as HIV and HHV-8, but in Japan, almost all the reported cases with MCD test negative for HIV and HHV-8, so it is presumed that the pathology of MCD in Japan may differ from that in Europe and the U.S. MCD is often associated with systemic symptoms including fever, malaise, C-reactive protein (CRP) elevation, serum amyloid A (SAA) elevation, anemia, polyclonal gammopathy, liver damage, and renal dysfunction. The kidney damage associated with MCD ranges from minor renal function test abnormalities with only hematuria and/or proteinuria, to serious conditions including nephritis, nephrotic syndrome, acute renal failure, and chronic renal failure, necessitating hemodialysis.^[7] The cause is reported to involve the production of IL-6 from lymph nodes.^[8] IL-6 is thought to cause amyloid deposition through increasing the AA amyloid precursor SAA protein, which accumulates in hepatocytes,^[9] and cause an increase in proliferation of renal mesangial cells^[10] and hyperviscosity syndrome associated with gammopathy.^[11–13] A number of reports examined multiple cases with renal tissue lesions in France^[8] and China.^[7,14] Yuan et al^[14] examined 49 cases with MCD; the renal histology was thrombotic microangiopathy (n=12), amyloidosis (n=9), MPGN (n=7), and other (n=21). Xu et al^[7] examined CD, combining MCD and UCD, to investigate the renal histological types in a total of 94 patients, comprised of 64 cases reported to date, 11 of their own cases and 19 cases reported by El Karoui et al.^[8] The reported histological types were diverse and included amyloidosis (n=29), small vessel lesion with MPGN and thrombotic microangiopathy (n=27), interstitial nephritis (n=7), mesangioproliferative glomerulonephritis (n=5), crescentic glomerulonephritis (n=5), focal segmental glomerulosclerosis (n=4), membranous nephropathy (n=4), minimal change disease (n=3), and other (n=11), with amyloidosis being the most common.^[7]

The histopathology of the lymph nodes in our case was consistent with HV-type CD, and the condition was initially diagnosed as MCD based on the clinical picture of multiple enlarged lymph nodes, fever, anemia, renal dysfunction, and oedema. The patient also presented with generalized anasarca, proteinuria, and renal failure, but these symptoms improved after resection of the lesion. Moreover, IL-6 and VEGF levels decreased with reduction in the size of the lesion. Therefore, we postulated that the increased vascular permeability improved. In general, HV-type CD is often unicentric, and we considered the complication of systemic symptoms with multiple enlarged lymph nodes to be atypical. Furthermore, enlarged lymph nodes other than the resected mass persisted after surgery, and generalized anasarca, proteinuria, and renal failure recurred approximately 6 months after resection, which was also associated with thrombocytopenia. Therefore, we considered

that our case represent a typical clinical picture of TS, with T: thrombocytopenia, A: anasarca, F: myelofibrosis, R: renal dysfunction, and O: organomegaly; consequently, the patient was treated with steroid therapy. This resulted in shrinkage of the generalized lymphadenopathy, improvement in renal function, resolution of proteinuria, and clinical improvement, including normalization of the levels of serum protein and albumin.

The background of establishing the disease concept of TS is as follows: In 2008, Kojima et al^[15] reported cases with MCD-like pathology, which lacked IPL (idiopathic plasmacytic lymphadenopathy)-like gammopathy. Lymph node biopsies were consistent with the HV type rather than the PC type, and there were high rates of pleural effusion, ascites, and thrombocytopenia, so these cases were diagnosed as non-IPL.^[15] Then in 2010, Takai et al^[2] reported cases with TS, and in 2013, Kawabata et al^[16] reported 3 out of 21 MCD cases that had TS-like symptoms. There were many similarities in the cases described in these three reports,^[2,16] and in 2013 a new systemic inflammatory disease was jointly proposed and announced as Castleman–Kojima disease/TAFRO syndrome.^[17] TS is a disease concept that was recently proposed in Japan, and much of the lymph node pathologies are consistent with mixed type,^[18] but there are also a number of reports with pathology findings consistent with HV type.^[19,20] This condition is more commonly reported in Japan than overseas, with a few reports from India,^[21] Italy,^[22,23] and France,^[24] which might be explained by the unawareness of this disease overseas.

In 2015, Masaki et al^[1] examined 28 cases with TS, and updated the diagnostic criteria (Table 3). In these diagnostic criteria, they established three major categories: anasarca, thrombocytopenia, and systemic inflammation, and 4 minor categories: CD-like features on lymph node biopsy, reticulin myelofibrosis and/or increased number of megakaryocytes in bone marrow, mild organomegaly, and progressive renal insufficiency. Patients that meet 3 of the major categories and 2 of the minor categories may be diagnosed as TS. Our case was diagnosed with TS based on these diagnostic criteria. Our case developed thrombocytopenia approximately 8 months after onset, so this case progressed slowly.

A comparison of the characteristics of this case and TS cases from multiple facilities in Japan is shown in Table 4.^[18] TS is common in middle-aged women, and the characteristic clinical data include generalized anasarca, fever, inflammation, thrombocytopenia, anemia (normo- to microcytic), ALP elevation, low level of lactate dehydrogenase, and renal dysfunction, and often a bone marrow puncture will yield a dry tap with myelofibrosis and increased megakaryocytes. Clinically, patients present with hepatosplenomegaly. Multiple enlarged lymph nodes are also seen, but are commonly only mildly enlarged measuring 1.5 cm or smaller, and there is also mild elevation of polyclonal gamma globulins. Other characteristics are elevated IL-6, VEGF, and sIL-2R; negativity for HHV-8, EBV, and HIV; uptake seen on PET scans, and occasionally a case might be positive for auto-antibodies, but without satisfying the diagnostic criteria of autoimmune diseases or other diseases,^[25] and many cases are acute or subacute.^[26] In TS thrombocytopenia, Pa-IgG (platelet associated immunoglobulin G) is often elevated,^[25] so it is suspected that there is some sort of immune mechanism at work.^[20,27] There are some cases of TS with poor prognoses, so it is important to intervene with treatment early,^[1] and TS usually responds well to steroids, cyclosporin (CyA), the anti-IL-6 receptor antibodies tocilizumab, and rituximab.^[20,28,29]

Table 3

Diagnostic criteria of TAFRO syndrome (2015).

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 pretreatment platelet count $\leq 100,000/\mu\text{l}$
- (3) Systemic inflammation, defined as fever of unknown etiology above 37.5°C and/or serum C-reactive protein concentration ≥ 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, etc.
- (3) Infectious disorders, including acid fast bacterial infection, rickettsial disease, lyme disease, severe fever with thrombocytopenia syndrome (SFTS), etc.
- (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

Modified from reference (25).

Table 4

TS: Comparison of our case and the characteristics of the 37 cases from multiple centres.

	37 cases from multiple facilities in Japan	Our case
Age	Mean age 52 years	55 years
Sex M:F	13: 24	F
Clinical characteristics	Generalized oedema	Generalized oedema
Laboratory data	Pleural effusion and ascites	Pleural effusion and ascites
	Fever and strong inflammatory response	Low-grade fever and elevated inflammatory response
	Thrombocytopenia and anemia (normo- to microcytic)	Thrombocytopenia and anemia
	Elevated ALP	Elevated ALP
	Low LDH	Normal LDH
	Renal dysfunction	Renal dysfunction
Bone marrow puncture	Dry tap	Normal
Bone marrow biopsy	Myelofibrosis with megakaryocytic proliferation	Megakaryocytic proliferation
Organomegaly	Hepatosplenomegaly	Hepatosplenomegaly
Multiple enlarged lymph nodes	Less than 1.5 cm diameter	Around 1 cm in diameter
Histology	Many were mixed type, some were HV type	HV type
Polyclonal hypergammaglobulinemia	Mild (IgG ≤ 4000 mg/dL)	IgG 1140 mg/dL
Treatment	Steroids, CyA, tocilizumab	Resection, steroids
Prognosis	Some cases had rapid deterioration of general condition, with poor prognosis	Good

ALP = alkaline phosphatase, CyA = ciclosporin, HV = hyaline vascular, LDH = lactate dehydrogenase. Modified from Masaki et al.^[18]

Recently there have been reports that pathologically differentiate TS from the conventional PC type MCD, as lymph node biopsies in TS revealed atrophic germinal centres with enlarged nuclei of endothelial cells and proliferation of endothelial venules in the interfollicular zone (Table 5).^[30] Other reports showed that some cases with TS were difficult to treat with tocilizumab but responded well to CyA, suggesting the involvement of IL-2 as well as IL-6 in TS.^[28] Therefore, TS should be thought of as an independent disease, as it differs from MCD.

TS are also thought to have a different aetiology from MCD based on renal histology. The renal histologies in 9 patients with TS in Japan, including our case, are shown in Table 6.^[26,31–36] The most common finding was MPGN-like histology, and there were no reports of amyloidosis. MPGN-like findings were significantly common in TS when considering these 9 cases of TS, and when considering the renal pathology reports of the aforementioned 49 cases of MCD examined by Yuan et al.^[14] As mentioned above, IL-6 is considered to be one of the causes of

Table 5

Histological findings of lymph nodes.

	TAFRO	MCD (PC type)
Germinal centres	Atrophic germinal centres with enlarged nuclei of endothelial cell	Hyperplastic germinal centres of varying sizes
Interfollicular zone	Proliferation of endothelial venules, small numbers of mature plasma cells	Sheets of proliferating mature plasma cells

Modified from Iwaki et al.^[30]
MCD = multicentric Castleman disease.

Table 6**Renal histology reports of TS cases in Japan.**

	Age Sex	Urinalysis findings, renal function	Renal histology findings	Treatment
2015 Hamada et al ^[25]	77 F	Proteinuria, Urine occult blood Cr 0.83 mg/dL	Membranoproliferative glomerulonephritis-like	Diagnosed with Castleman disease 14 years earlier, treated with steroids
2016 Sasaki et al ^[31]	49 F	Proteinuria, urine occult blood Cr 2.45 mg/dL	Thrombotic microangiopathy	No improvement with Tocilizumab Condition eased with steroids
2015 Takahasi et al ^[32]	34 M	Proteinuria 1.65 g/gCr Urine occult blood Cr 1.77 mg/dL	Thrombotic microangiopathy	Steroid therapy was effective
2014 Tsukada et al ^[33]	69 M	Proteinuria 1.7 g/day Cr 2.8 mg/dL	Membranoproliferative glomerulonephritis-like	Treated with steroids/HD/PE, but the patient died
2013 Shibufuji et al ^[34]	64 F	Proteinuria, urine occult blood	Enlarged glomerulus Poor deposition with fluorescent antibody technique	Initially suspected SLE Responded well to steroids/CyA
2016 Kakeshita et al ^[35]	69 F	Proteinuria 4 g/gCr Cr 1.2 mg/dL	Membranoproliferative glomerulonephritis-like	Treated with steroids /CyA, but the patient died
2015 Fujita et al ^[36]	49 F	renal Renal dysfunction	Mesangioproliferative glomerulonephritis	Responded well to steroids/CyA
2015 Fujita ^[36]	65 F	Proteinuria	Minor abnormality with minimal immune complex deposition	Responded well to steroids/CyA
Our Case	55 F	Proteinuria	Membranoproliferative glomerulonephritis-like	Steroid therapy was effective

CyA=cyclosporin, HD=hemodialysis, PE=plasma exchange, SLE=systemic lupus erythematosus.

renal amyloidosis in MCD, but there are reports of TS with only mild elevation of IL-6,^[19] and other reports where the levels were not necessarily high,^[1,26,31] suggesting that the low incidence of renal amyloidosis may be related to TS. In fact, in our case also, IL-6 was not markedly elevated. The aetiology of TS is still unknown,^[1] so it is important to study more cases of TS and analyze the renal pathology profile.

In conclusion, we encountered a case that we initially diagnosed as HV type MCD, but the patient developed thrombocytopenia in the course of the disease and ultimately the condition was diagnosed as TS. The renal histopathological profile of TS presents with MPGN-like findings, and when comparing our case to previous reports, it was found that MPGN-like findings were found in many patients with TS. Our case reiterated the importance of careful monitoring of patients as the characteristic TS findings might present over the course of time.

Acknowledgments

We would like to thank Editage (www.editage.jp) for English language editing. An article about the same patient has been previously published (Masaaki Nagano and Jun Matsumoto, A case of TAFRO syndrome with a large mediastinal mass treated with debulking surgery, *Surgical Case Reports* 2016;2:61). However, the contents of the previously published report are different from the contents of this article, as the nephrological aspects and renal pathology findings of TAFRO syndrome were not discussed in the previous report.

Author contributions

Conceptualization: Yoshitaka Furuto.

Data curation: Yoshitaka Furuto.

Formal analysis: Yoshitaka Furuto.

Investigation: Yoshitaka Furuto.

Methodology: Yoshitaka Furuto.

Project administration: Yoshitaka Furuto.

Supervision: Yuko Shibuya.

Validation: Yoshitaka Furuto, Hirotsugu Hashimoto, Hajima Horiuti, Yuko Shibuya.

Visualization: Yoshitaka Furuto.

Writing – original draft: Yoshitaka Furuto.

Writing – review & editing: Yoshitaka Furuto, Hirotsugu Hashimoto, Hajima Horiuti, Yuko Shibuya.

References

- Masaki Y, Kawabata H, Takai K, et al. Proposed diagnostic criteria, disease severity classification and treatment strategy for TAFRO syndrome, 2015 version. *Int J Hematol* 2016;103:686–92.
- Takai K, Nikkuni K, Shibuya H, et al. Thrombocytopenia with mild bone marrow fibrosis accompanied by fever, pleural effusion, ascites and hepatosplenomegaly. *Rinsho Ketsueki* 2010;51:320–5.
- Castleman B, Iverson L, Menendez VP. Localised mediastinal lymphnode hyperplasia resembling thymoma. *Cancer* 1956;9: 822–30.
- Keller AR, Hochholzer L, Castleman B. Hyaline Vascular and Plasma cell types of giant lymph node hyperplasia of the mediastinum and other locations. *Cancer* 1972;29:670–83.
- Chen KTK. Multicentric Castleman's disease and Kaposi's sarcoma. *Am J Surg Pathol* 1984;8:287.

- [6] Yoshizaki K, Matsuda T, Nishimoto N, et al. Pathogenic significance of interleukin-6(IL6/BSF-2) in Castleman's disease. *Blood* 1989;74:1360–7.
- [7] Xu D, Lv J, Dong Y, et al. Renal involvement in a large cohort of Chinese patients with Castleman disease. *Nephrol Dial Transplant* 2012;27 (suppl 3):iii119–25.
- [8] El Karoui K, Vuilbet V, Dion D, et al. Renal involvement in Castleman disease. *Nephrol Dial Transplant* 2011;26:599–609.
- [9] Tanaka K, Horita M, Shibayama H, et al. Secondary amyloidosis associated with Castleman disease. *Intern Med* 1995;34:122–6.
- [10] Suematsu S, Matsuda T, Aozasa K, et al. IgG1 plasmacytosis in interleukin 6 transgenic mice. *Proc Natl Acad Sci USA* 1989;86:7547–51.
- [11] Couch WD. Giant lymph node hyperplasia associated with thrombocytopenic purpura. *Am J Clin Pathol* 1980;74:340–4.
- [12] Jones CH, Will EJ. Angiofollicular lymph node hyperplasia, accelerated hypertension, and acute renal failure: a case report. *Nephrol Dial Transplant* 1996;11:352–4.
- [13] Lajoie G, Kumar S, Min KW, et al. Renal Thrombotic microangiopathy associated with multicentric Castleman disease. Report of two cases. *Am J Surg Pathol* 1995;19:1021–8.
- [14] Yuan XG, Hu W, Chen FF, et al. Renal complications of Castleman's disease: report of two cases and analysis of 75 cases. *Clin Exp Nephrol* 2011;15:921–6.
- [15] Kojima M, Nakamura N, Tsukamoto N, et al. Clinical implications of idiopathic multicentric Castleman disease among Japanese: a report of 28 cases. *Int J Surg Pathol* 2008;16:391–8.
- [16] Kawabata H, Kadowaki N, Nishikori M, 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.
- [17] Kawabata H, Takai K, Kojima M, et al. Castleman-Kojima disease (TAFRO syndrome): a novel systemic inflammatory disease characterised 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.
- [18] Masaki Y. New disease concept: TAFRO syndrome—one subtype of multicentric Castleman disease with thoracic and abdominal ascites and thrombocytopenia. *Hematol* 2014;68:97–102.
- [19] Ozawa T, Kosugi S, Kito M, et al. Efficacy of rituximab for TAFRO syndrome, a variant type of multicentric Castleman's disease. *Jpn J Clin Hematol* 2014;55:350–5.
- [20] Iwaki N, Sato Y, Takata K, et al. Atypical hyaline vascular type Castleman disease with thrombocytopenia, anasarca, fever, and systemic lymphadenopathy. *J Clin Exp Hematop* 2013;53:87–93.
- [21] Kodari PR, Parvez M, Kaza S, et al. Castleman–Kojima disease in a south Asian Adolescent. *J Clin Exp Hematop* 2014;54:163–6.
- [22] Tedesco S, Postacchini L, Manfredi L, et al. Successful treatment of a Caucasian case of multifocal Castleman's disease with TAFRO syndrome with a pathophysiology targeted therapy—a case report. *Exp Hematol Oncol* 2015;4:3.
- [23] Carbone A, Pantanowitz L. TAFRO syndrome: an atypical variant of KSHV-negative multicentric Castleman disease. *Am J Hematol* 2016; 91:171–2.
- [24] Jouvray M, Terriou L, Meignin V, et al. Pseudo-adult Still's disease, anasarca, thrombotic thrombocytopenic purpura and dysautonomia: an atypical presentation of multicentric Castleman's disease. Discussion of TAFRO syndrome. *Rev Med Interne* 2016;37:53–7.
- [25] Hamada M, Takeuchi Y, Yamazaki D, et al. A case of TAFRO syndrome which presented the kidney pathology image of membranoproliferative glomerulonephritis-like. *Jpn J Nephrol* 2015;57: 1136-O-206.
- [26] Masaki Y, Kawabata H, Takai K, et al. Proposed diagnostic criteria, disease severity classification, and treatment strategy for a novel disorder; TAFRO syndrome. *Jpn J Clin Hepatol* 2016;57:2029–37.
- [27] Inoue M, Ankou M, Hua J, et al. Complete resolution of TAFRO syndrome (thrombocytopenia, anasarca, fever, reticulin fibrosis and organomegaly) after immunosuppressive therapies using corticosteroids and cyclosporine A: a case report. *J Clin Exp Hematop* 2013;53:95–9.
- [28] Konishi Y, Takahashi S, Nishi K, et al. Successful treatment of TAFRO syndrome, a variant of multicentric Castleman's disease, with cyclosporine A: possible pathogenetic contribution of interleukin-2. *Tohoku J Exp Med* 2015;236:289–95.
- [29] Kawabata H, Kotani S, Matsumura Y, 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.
- [30] Iwaki N, Fajgenbaum DC, Nabel CS, et al. Clinicopathologic analysis of TAFRO syndrome demonstrates a distinct subtype of HHV-8-negative multicentric Castleman disease. *Am J Hematol* 2016;91:220–6.
- [31] Sasaki T, Naito Y, Yamashiro Y, et al. A case of the TAFRO syndrome which presented the kidney pathology image of thrombotic microangiopathy. *Jpn J Nephrol* 2016;58: 774-O-127.
- [32] Takahashi D, Tanaka M, Yasuko Y, et al. A case of TAFRO syndrome treated effectively with steroid therapy. *Jpn J Nephrol* 2015;7: 950-O-024.
- [33] Tsukada Y, Hara S, Yoshida T, et al. A case of the TAFRO syndrome which examined kidney histology by autopsy. *Jpn J Nephrol* 2014;56: 394-P-396.
- [34] Shibufuji N, Maruyama K, Syoujima S, et al. A case of the TAFRO syndrome improved by steroid and cyclosporine therapy. *Jpn J Nephrol* 2013;55: 1222-P-121.
- [35] Kakeshita K, Shiroishi S, Fujioka H, et al. A case of the TAFRO syndrome which caused membranoproliferative glomerulonephritis. *Jpn J Nephrol* 2016;58: 910-O-018.
- [36] Fujita K, Shibuto N, Yamamura Y, et al. TAFRO syndrome: a unique mimicker of systemic lupus erythematosus. *Ann Rheum Dis* 2015; 74:855.