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CASE REPORT

Successful treatment of TAFRO syndrome, a variant type of multicentric Castleman disease with thrombotic microangiopathy, with anti-IL-6 receptor antibody and steroids

Shiho Fujiwara[1] · Hiromi Mochinaga[1] · Hirotomo Nakata[1] · Koichi Ohshima[2] · Masanori Matsumoto[3] · Mitsuhiro Uchiba[4] · Yoshiki Mikami[5] · Hiroyuki Hata[6] · Yutaka Okuno[1] · Hiroaki Mitsuya[1] · Kisato Nosaka[1,7]

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Abstract TAFRO syndrome is a rare variant type of multicentric Castleman disease, which is characterized by thrombocytopenia, anasarca, reticulin fibrosis of bone marrow, renal dysfunction and organomegaly. Here, we report a case of TAFRO syndrome that was successfully treated with tocilizumab. A 50-year-old man, who presented with fever, epigastric pain, abdominal fullness, and massive edema of the extremities, was admitted to our hospital. Computed tomography revealed bilateral pleural effusions, ascites, and lymphadenopathy. Laboratory data showed renal dysfunction, anemia, and thrombocytopenia. Examination of bone marrow and cervical lymph nodes led to a diagnosis of hyaline vascular-type Castleman disease. The level of serum interleukin (IL)-6 was extremely high. TAFRO syndrome was finally diagnosed. The patient was treated weekly with tocilizumab, an anti-IL-6 receptor antibody and steroids. In 4 weeks, all symptoms disappeared and serum IL-6 level returned to normal. Activity of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), which was significantly decreased (9.9 %) prior to treatment, increased after treatment with tocilizumab. The present case suggests that tocilizumab is an effective therapeutic agent for TAFRO syndrome. We suggest that hypercytokinemia in TAFRO syndrome inhibits ADAMTS13 activity, thereby inducing thrombotic microangiopathy.

Keywords TAFRO syndrome · Castleman disease · Tocilizumab · ADAMTS13

Introduction

Castleman disease (CD) is a rare lymphoproliferative disorder with hyperplastic lymph nodes, which was first described by Castleman et al. in 1954 [1]. There are four classifications according to histopathological findings: hyaline vascular type, plasma cell type, mixed type, and plasmablastic type [2–4]. In addition, CD is divided into two clinical subtypes, unicentric variant CD (UCD), and systematic or multicentric variant CD (MCD). The former is a localized and common type of the disease with favorable prognosis, and the latter is an aggressive form with autoimmune symptoms. The hyaline–vascular type is most common in UCD and the plasma cell variant is common in MCD [5].

Recently, a variant type of MCD was described [6, 7]. This variant type was characterized by five symptoms and signs: thrombocytopenia (T), anasarca (A), reticulin fibrosis of bone marrow (F), renal dysfunction (R), and organomegaly (O). Therefore, it is called TAFRO syndrome. It is

✉ Kisato Nosaka
knosaka95@gmail.com

1 Department of Hematology, Kumamoto University School of Medicine, 1-1-1 Honjo, Tyuou-ku, Kumamoto, Japan

2 Department of Pathology, Kurume University School of Medicine, Fukuoka, Japan

3 Department of Blood Transfusion Medicine, Nara Medical University, Nara, Japan

4 Department of Blood Transfusion and Cell Therapy, Kumamoto University Hospital, Kumamoto, Japan

5 Department of Surgical Pathology, Kumamoto University Hospital, Kumamoto, Japan

6 Division of Informative Clinical Sciences, Faculty of Medical Sciences, Kumamoto University School of Medicine, Kumamoto, Japan

7 Cancer Center of Kumamoto Medical School of Medicine, Kumamoto, Japan

Table 1 Laboratory findings

WBC	15,700/μL	TP	6.0 g/dL	HBs Ag	(−)	IgG	1536 mg/dL
Baso	0.0 %	AIb	2.2 g/dL	HBs Ab	(+)	IgA	360 mg/dL
Eosin	1.0 %	BUN	94.8 mg/dL	HBc Ab	(+)	IgM	45 mg/dL
Neut	88.0 %	Crea	2.26 mg/dL	HBV-DNA	(−)	IgG4	100 mg/dL
Lymp	7.0 %	eGFR	26 ml/min	HCV Ab	(−)	CH50	67 U/mL
Mono	5 %	T-Bil	0.5 mg/dL	HTLV- I Ab	(−)	C3c	119.2 mg/dL
Hgb	12.4 g/dL	AST	24 U/L	HIV Ab	(−)	C4	25.6 mg/dL
Hct	36.5 %	ALT	20 U/L	TPLA	(−)	ANA	<×40
PLT	67 × 103 /μL	LDH	235 U/L	RPR	(−)	RF	5 IU/mL
RET	1.82 %	γ-KT	235 U/L	QFT	(−)	MPO-ANCA	(−)
IPF	32 %	ALP	841 U/L	EBV-VCA IgG	<10	PR3-ANCA	(−)
		CRP	17.19 mg/dL	EBV-VCA IgM	×80	aCLAb	17 U/mL
PT	76 %	Fe	14 μg/dL	EBV-EBNA	×40	LA	(−)
PT-INR	1.17	UIBC	I38 μg/dL	Parvovirus IgM	(−)	aCL*β2GPI	(−)
APTT	44.7 s	Ferritin	788.7 ng/mL	Parvovirus IgM	(+)	PA-IgG	228 ng/10^7cells
Fib	>700 mg/dL	BNP	14.8 pg/mL	βDglucan	<6.0 pg/mL	Coombs	(−)
AT	86 %	HPG	286 mg/dL	SETS Ab	(−)	ACE	14.5 IU/L
FDP	19.6 μg/ml	SAA	184.5 μg/dL	HHV-8	<2.0 × 10 copy		
D-Dimer	15.9 μg/ml	CEA	0.3 ng/dL	IL-Iβ	19 pg/mL	Urine	
		CA19-9	11.4 U/mL	IL-6	2130 pg/mL	U-protein	(1+)
		PSA	0.373 ng/mL	TNFα	63.5 pg/mL	U-glucose	(−)
		SCC	0.9 ng/mL	VEGF	118 pg/mL	U-occult blood	(1+)
		CYFRA	1.5 ng/mL	TPO	4.69 Fmol/mL	RBC	5–9/HPF
		ProGRP	59.8 pg/mL				
		AFP	1.6 ng/mL				
		s-IL2R	3351 U/mL				

WBC white blood cells, *Baso* basophils, *Eosin* eosinophils, *Neut* neutrophils, *Lymp* lymphocytes, *Mono* monocytes, *Hgb* hemoglobin, *Hct* hematocrit, *Plt* platelets, *RET* reticulocytes, *IPF* immature platelet fraction, *PT* prothrombin time, *PT-INR* international normalized ratio of prothrombin time, *APTT* activated partial thromboplastin time, *Fib* fibrinogen, *AT* antithrombin, *FDP* fibrin degradation products, *TP* total protein, *Alb* albumin, *BUN* blood urea nitrogen, *Crea* creatinine, *eGFR* estimated glomerular filtration rate, *T-Bil* total bilirubin, *AST* aspartate transferase, *ALT* alanine transaminase, *LDH* lactate dehydrogenase, *γ-GTP* γ-glutamyltranspeptidase, *ALP* alkaline phosphatase, *CRP* C-reactive protein, *UIBC* unsaturated iron binding capacity, *BNP* brain natriuretic peptide, *HPG* haptoglobin, *SAA* serum amyloid A protein, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *PSA* prostate-specific antigen, *SCC* squamous cell carcinoma antigen, *CYFRA* cytokeratin 19 fragment, *ProGRP* pro-gastrin-releasing peptide, *AFP* α-fetoprotein, *s-IL2R* soluble interleukin-2 receptor, *HTLV-1* human T cell leukemia virus type 1, *HIV* human immunodeficiency virus, *TPLA* treponema pallidum latex agglutination, *QFT* interferon-γ release assay, *EBV* Epstein–Barr virus, *SFTS* severe fever with thrombocytopenia syndrome, *HHV-8* human herpesvirus-8, *IL-1β* interleukin 1β, *IL-6* interleukin-6, *TNFα* tumor necrosis factor α, *VEGF* vascular endothelial growth factor, *TPO* thrombopoietin, *ANA* anti-nuclear antibody, *RF* rheumatoid factor, *MPO-ANCA* myeloperoxidase anti-neutrophil cytoplasmic antibody, *PR3-ANCA* proteinase 3 anti-neutrophil cytoplasmic antibody, *aCL-β2 GPI* anti-cardiolipin-β2 glycoprotein I complex antibodies, *LA* lupus anticoagulants, *PA-IgG* platelet-associated IgG, *ACE* angiotensin converting enzyme

thought that an immune-mediated mechanism contributes to the thrombocytopenia observed in TAFRO syndrome, however, the precise mechanisms are still unclear [8]. ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) is an important regulator of von Willebrand factor (vWF), and decreased ADAMTS13 is often observed in thrombotic microangiopathy (TMA) patients, who show thrombocytopenia and renal dysfunction.

Here, we report a case of MCD with thrombocytopenia, anasarca, and renal dysfunction showing features characteristic for TAFRO syndrome. We describe improvement of the disease, along with recovery of ADAMTS13 activity, by treatment with anti-interleukin (IL)-6 receptor antibody tocilizumab.

Case report

A 50-year-old Japanese man was admitted to our hospital because of fever, anasarca, renal dysfunction, and thrombocytopenia. He had been well until 4 weeks before admission. These symptoms lasted for 4 weeks.

On admission, he had epigastric pain, abdominal fullness, and edema of the extremities. The bilateral submandibular

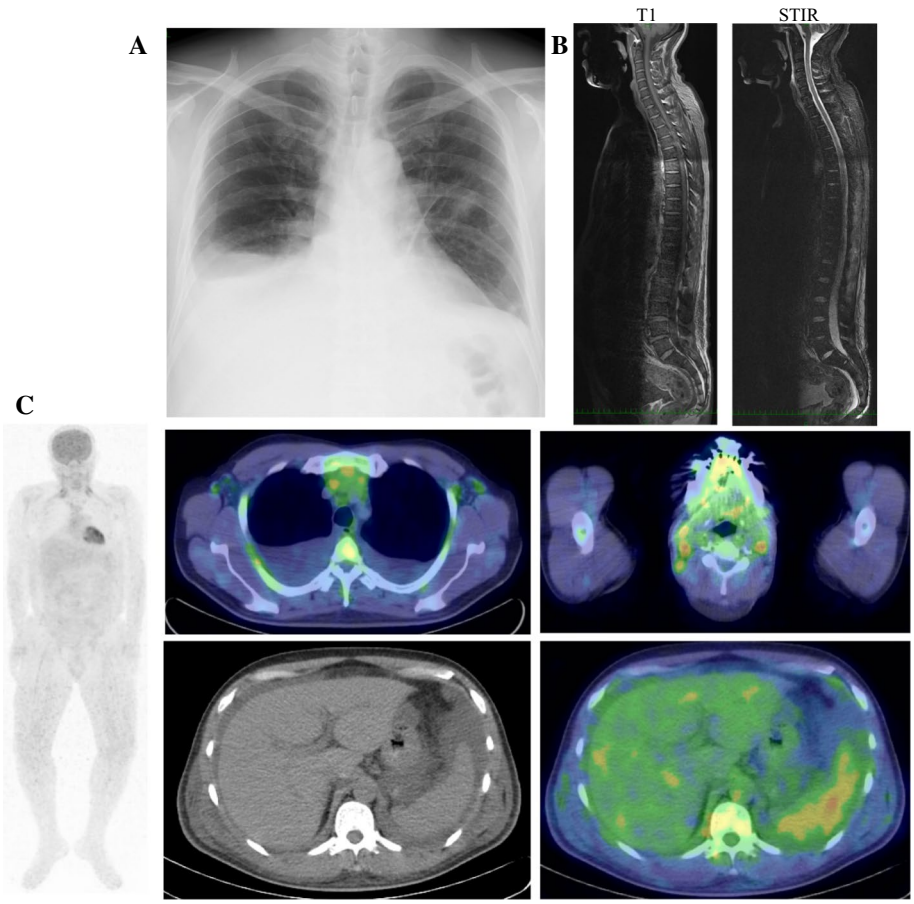

Fig. 1 Imaging findings. **a** Chest X-ray on admission showed pleural effusion. **b** Whole-spine magnetic resonance imaging: all vertebral bodies showed diffuse low intensity on T1 and short-T1 version recovery imaging. **c** ^{18}Fluorodeoxyglucose positron emission tomography/computed tomography showed bilateral pleural effusion, ascites, lymphoadenopathy and mild splenomegaly

and left cervical lymph nodes were swollen, with a maximum diameter of 1.5 cm. All laboratory findings are summarized in Table 1. His white blood cell count and C-reactive protein (CRP) levels were significantly elevated at 15700/μL and 17.19 mg/dL, respectively. He also had slight anemia (hemoglobin 12.4 g/dL), thrombocytopenia (platelet count 67 × 10^3/μL), renal dysfunction (estimated glomerular filtration rate 26 mL/min), and hypoalbuminemia (albumin 2.2 g/dL). Reticulocytes and immature platelet fraction (IPF) were elevated at 1.82 and 32 %, respectively, whereas schistocytes were not found. Neither lupus anticoagulant nor anti-cardiolipin–β2 glycoprotein I complex antibodies were found. The level of soluble IL-2 receptor was markedly elevated (3351 U/mL), while other tumor markers were normal. Mild proteinuria was observed.

The IL-6 level was high (2130 pg/mL), but levels of several other cytokines [vascular endothelial growth factor (VEGF), IL-1β and tumor necrosis factor (TNF)-α] were only slightly elevated. Tests for HIV, human herpesvirus-8, Epstein–Barr virus, parvovirus, severe fever with thrombocytopenia syndrome virus, and *Mycobacterium tuberculosis* were all negative. Complement titer and all examinations for antinuclear antibody, IgG rheumatoid factors, myeloperoxidase anti-neutrophil cytoplasmic antibody (ANCA), cytoplasmic ANCA, angiotensin-converting enzyme (ACE), and IgG4 were normal. The level of immunoglobulin was normal, and monoclonal immunoglobulin was not detected by immune fixation tests.

Chest X-ray showed pleural effusion on admission. ^{18}Fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography revealed mildly abnormal accumulation of ^{18}FDG in bilateral pleural effusion, ascites, and lymphadenopathy (cervical, subclavian, axillary, mediastinal, para-aortic and inguinal lymph nodes) (maximum standard uptake value: 3.4) (Fig. 1a, c). The intensity of bone marrow was low on T1 and short-T1 version recovery imaging of whole-spine magnetic resonance imaging, suggesting hypercellularity of bone marrow or myelofibrosis (Fig. 1b). Bone marrow biopsy revealed a normocellular bone marrow with mild reticulin fibrosis (Fig. 2a, b). Biopsy of a cervical lymph node showed atrophic germinal centers with interfollicular enlargement and hyalinized vessels in germinal centers (Fig. 2c, d). These findings suggested that the patient had hyaline vascular type of Castleman disease. ADAMTS13 activity was significantly decreased (9.9 %), whereas its inhibitor was not found (Table 2). Taking these findings together, we proposed a diagnosis of TAFRO syndrome (Fig. 3).

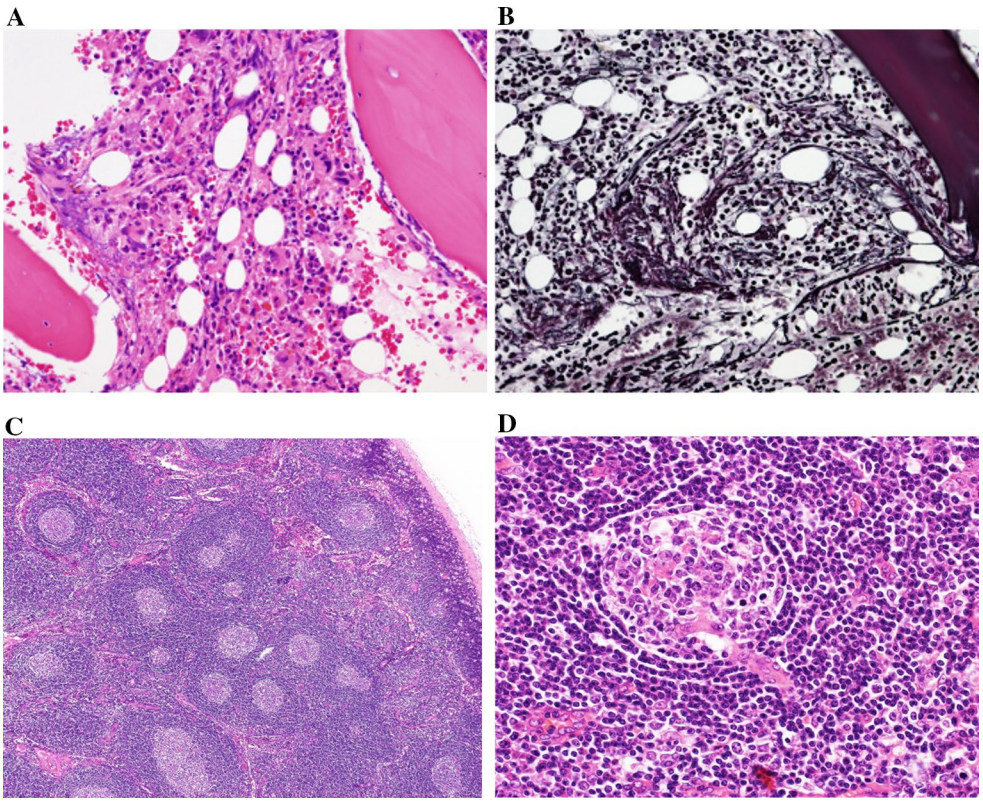

Fig. 2 Histological findings. Bone marrow biopsy: **a** hematoxylin and eosin staining showing normocellular bone marrow; **b** silver impregnation stain showing mild myelofibrosis. Lymph node biopsy: **c** atrophic germinal centers and enlarged interfollicules; **d** hyaline vessels in germinal centers

Table 2 ADAMTS13 activity in clinical course

	ADAMTS13 activity (%)	ADAMTS13 inhibitor (Bethesda unit/mL)	vWF antigen	vWF collagen binding
Day 5	9.9	<0.5	219.7	367
Day 39	15.1	<0.5	163	265
Day 53	26.9	<0.5		
Day 84	41.9	<0.5		
Day 124	60.8	<0.5		
Day 173	75.4	<0.5		
Day 224	70.1	<0.5		
Day 259	71.8	<0.5		

ADAMTS13 a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13; *vWF* von Willibrand factor

After admission, renal failure, anemia, and thrombocytopenia progressed rapidly. On day 6, high-dose methylprednisolone (1 g/body/day, 3 days) was administered and prednisolone was started at 1 mg/kg from day 9. In addition, hemodialysis was performed because of oliguric renal failure. Although platelet count was temporarily increased from 26×10^3 to 74×10^3/μL and serum IL-6 level decreased (11.4 pg/mL), renal function and anasarca were not improved. The subsequent reduction in platelet count (to 29×10^3/μL) indicated that steroid treatment was insufficiently effective. Therefore, starting on day 21, the patient was also administered weekly injections of anti-IL-6 receptor antibody (tocilizumab 8 mg/kg), along with steroids.

In spite of anti-IL-6 therapy with steroids, renal dysfunction, anemia, and thrombocytopenia, with bleeding in the oral mucosa and petechia persisted for the subsequent 4 weeks. However, from day 51, platelet count and hemoglobin level improved gradually along with an increase of urine volume. On day 91, both anasarca and ascites

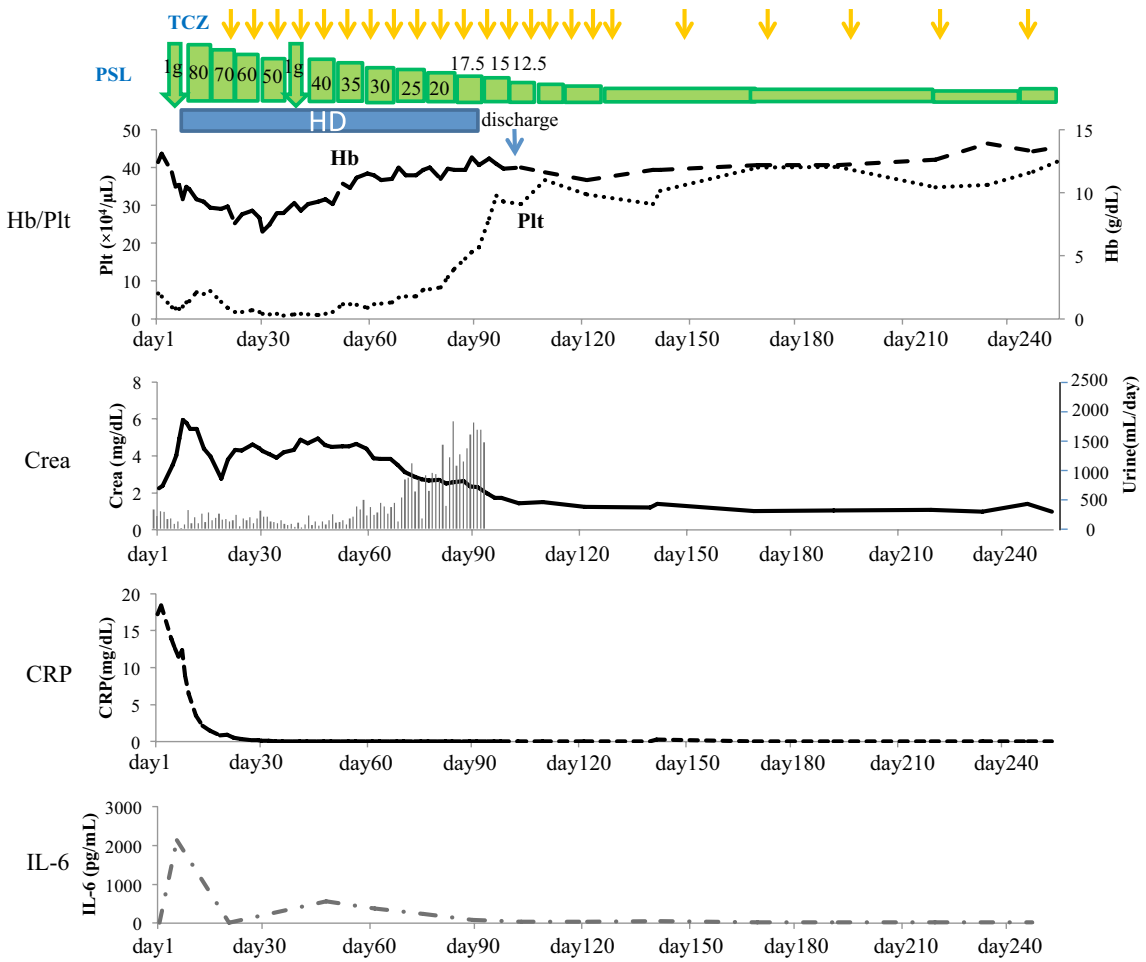

Fig. 3 Clinical course. *Crea* creatinine, *CRP* C-reactive protein, *Hb* hemoglobin, *HD* hemodialysis, *IL-6* interleukin-6, *Plt* platelet, *PSL* prednisolone, *TCZ* tocilizumab

disappeared and hemodialysis was discontinued. The level of serum IL-6 has been stable (15–25 pg/mL) and the patient has been free of symptoms, with continuous tocilizumab therapy (8 mg/kg) every 3 weeks in combination with prednisolone (5 mg/day). ADAMTS13 activity increased after therapy (Table 2).

Discussion

Although the actual mechanism of thrombocytopenia and anemia in TAFRO syndrome is still unclear, autoimmune mechanisms of CD are suggested in previous reports [9–12]. In our case, we observed severe thrombocytopenia with oral bleeding and petechia. We considered that an autoimmune mechanism contributed to the thrombocytopenia in our case, given that the bone marrow was normocellular and levels of IPF and platelet-associated IgG (PAIgG) were elevated. However, severe thrombocytopenia persisted in spite of steroid therapy. ADAMTS13 activity was significantly decreased (9.9 %), while ADAMTS13 inhibitor was not detected. ADAMTS13 activity increased as platelet count improved, indicating that the activity of ADAMTS13 may play a role in TAFRO syndrome. In contrast, ADAMTS13 activity was normal (50.9 %) in another case of typical MCD without showing features for TAFRO syndrome in our institution.

vWF is synthesized by endothelial cells and megakaryocytes. It is stored in Weidel–Palade bodies and platelet α granules as ultralarge multimer vWF (UL-VWF). UL-VWF is released from Weidel–Palade bodies into the circulation upon stimulation by cytokines, hypoxia, desmopressin, and epinephrine [13, 14].

Previous studies have reported that several cytokines, such as IL-2, IL-6, IL-8 and TNF-α stimulate vWF release [15, 16]. Bernardo et al. reported that TNF-α and IL-8 (but not IL-6) stimulate the release of UL-vWF strings from human umbilical vein endothelial cells in a dose-dependent manner. IL-6 (but not IL-8 or TNF-α) inhibits the cleavage of UL-vWF strings by ADAMTS13 [15].

Cao et al. demonstrated that inflammatory cytokines (IL-4, interferon-γ and TNF-α) inhibit ADAMTS13 synthesis without affecting vWF secretion [17].

Yoshizaki et al. were the first to report IL-6 production in lymph nodes of patients with CD [18]. Several other cytokines play an important role in MCD, such as VEGF, IL-1 and TNF-α [4]. Kawabata et al. reported that various cytokines were elevated in an adolescent case of TAFRO syndrome [8]. In this patient, elevated IL-6 was accompanied by elevated TNF-α and VEGF, suggesting that these cytokines stimulated vWF release and inhibited ADAMTS13 synthesis. Our results suggest that the mechanism of thrombocytopenia in TAFRO syndrome is associated with thrombotic microangiopathy induced by hypercytokinemia. ADAMTS13 activity recovered as IL-6 and CRP levels improved.

The effects of anti-IL-6 receptor antibody in patients with TAFRO syndrome have been described [19, 20]. In those reports, patients with TAFRO syndrome showed rapid improvements by treatment with tocilizumab and steroids or with tocilizumab followed by rituximab and chemotherapy. In the patient described here, aspects of TAFRO syndrome, such as thrombocytopenia and renal dysfunction, persisted for 1 month after the addition of tocilizumab to steroid treatment. Improvements in these symptoms, as well as increased platelet counts, were observed beginning on day 51.

In conclusion, we report a case of TAFRO syndrome that was successfully treated with steroids and tocilizumab. These findings suggest that thrombotic microangiopathy in TAFRO syndrome may be partially caused by reduced ADAMTS13 activity, which is driven by excess IL-6 and other cytokines. Control of IL-6 by anti-IL-6 receptor antibody and of other cytokines by steroids may be a suitable therapeutic modality for patients with TAFRO syndrome.

Compliance with ethical standards

Conflict of interest K. N. has received honoraria for lecture from Chugai Pharmaceutical.

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