Pathological findings of progressive renal involvement in a patient with TAFRO syndrome

Hiroataka Saito¹ · Kenichi Tanaka¹ · Momoko Fujiwara¹ · Tsuyoshi Iwasaki¹ · Tokutaro Numata¹ · Akira Oda¹ · Makoto Kanno¹ · Mizuko Tanaka² · Masaaki Eiro³ · Mamoru Satoh³ · Junichiro James Kazama¹

Received: 3 February 2019 / Accepted: 25 April 2019 / Published online: 10 May 2019
© Japanese Society of Nephrology 2019

Abstract

TAFRO syndrome (thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly) is thought of as an atypical type of idiopathic multicentric Castleman's disease. Interleukin-6, vascular endothelial growth factor (VEGF), and other cytokines are considered etiological factors. A 45-year-old woman was admitted to hospital with unknown fever and abdominal pain. She had thrombocytopenia, anasarca, proteinuria/hematuria, and slight hepatosplenomegaly. Based on her clinical course and laboratory data, she was diagnosed as having TAFRO syndrome. Kidney biopsy showed a membranoproliferative glomerulonephritis (MPGN)-like lesion containing lobulations of glomeruli, endothelial cell swelling, double contours of the glomerular basement membrane, and mesangiolytic. She was treated with methylprednisolone pulse (500 mg/day) and oral prednisolone (60 mg/day) therapy. The pleural effusion and ascites disappeared, and renal function normalized. Cyclosporine was added to prevent relapse. She went home, with no relapse 8 months after hospitalization. MPGN-like lesions were found frequently in patients with TAFRO syndrome in recent reports. However, there are few reports of pathologically confirmed cases of progressive renal involvement in TAFRO syndrome. The relationship between VEGF expression in renal tissue and the pathogenesis of renal injury in TAFRO syndrome was investigated in the present case.

Keywords TAFRO syndrome · Vascular endothelial growth factor · Thrombotic microangiopathy · Kidney biopsy

Introduction

TAFRO syndrome is a systemic inflammatory disorder characterized by thrombocytopenia, anasarca, fever, reticulin myelofibrosis, and organomegaly, first described in 2010 by Takai et al. [1]. Although progressive renal insufficiency is a common clinical feature of TAFRO syndrome, kidney biopsy is rarely performed because of thrombocytopenia. In the past case reports of TAFRO syndrome, a membranoproliferative glomerulonephritis (MPGN)-like lesion was detected histologically, with glomerular lobulations, capillary occlusions by endothelial cell swelling, double contours

of the glomerular basement membrane (GBM), and mesangiolytic [2–4]. Thus, the injury of endothelial cells makes a lesion similar to that of thrombotic microangiopathy (TMA) in TAFRO syndrome, but its pathogenesis is still unknown.

TAFRO syndrome has common characteristics with multicentric Castleman's disease and is considered to be a clinicopathologic subtype of it. Serum vascular endothelial growth factor (VEGF) and interleukin (IL)-6 levels are frequently elevated in both diseases and considered likely pathogenic factors [2]. Karoui et al. reported that decreased expression of glomerular VEGF was observed in some patients with renal involvement in Castleman's disease [5]. Furthermore, renal TMA lesions in patients who were treated with bevacizumab were thought to result from direct targeting of VEGF by antiangiogenic therapy [6]. They showed that local reduction of VEGF within the kidney resulted in TMA in mouse models of podocyte-specific VEGF deletion. The level of renal VEGF expression might be related to the pathogenesis of TMA-like lesions, but renal pathology has not been sufficiently evaluated in patients with TAFRO syndrome. A pathologically confirmed case

✉ Kenichi Tanaka
kennichi@fmu.ac.jp

¹ Department of Nephrology and Hypertension, Fukushima Medical University, 1, Hikarigaoka, Fukushima, Japan

² Department of Basic Pathology, Fukushima Medical University, Fukushima, Japan

³ Department of Nephrology, Ohta Nishinouchi Hospital, Koriyama, Japan

of a patient with progressive renal involvement in TAFRO syndrome is presented along with an examination of VEGF expression in renal tissue.

Case report

A 45-year-old Japanese woman was admitted to hospital with a 2-week history of abdominal pain, nausea, and fever. On admission, her height was 157.3 cm and weight was 70 kg. Vital signs were blood pressure of 125/77 mmHg, heart rate of 111 beats/min, and temperature of 37.8 °C. Physical examination showed pitting edema of both legs and palpable lymph nodes in her neck and armpits. The skin lesions and neurologic examination findings of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) syndrome were not present. On laboratory tests, her serum creatinine (Cre) level was 0.64 mg/dL, almost the lower level of the normal range. They also showed hypoalbuminemia (1.8 mg/dL), and elevated alkaline phosphatase (ALP; 805 IU/L) and C-reactive protein (CRP; 11.3 mg/dL) concentrations. The complete blood count showed thrombocytopenia (108,000/ μ L), an increased white blood cell count (17,000/ μ L), and anemia (hemoglobin 10.5 g/dL). On urinalysis, protein was $\pm$, and there was microscopic hematuria (10–19 RBCs/high power field), with red cell blood casts. Epstein–Barr virus and human immunodeficiency virus serologies, and human herpes virus 8 polymerase chain reaction were negative. Immunoglobulin and complement were normal, and there was no paraproteinemia. Antinuclear antibody was elevated (320 $\times$, homogeneous and speckled staining patterns), but other antibodies such as anti-double-stranded deoxyribonucleic acid (ds-DNA) antibodies, anti-SSA/SSB antibodies, anti-neutrophil cytoplasmic antibodies (ANCA), and anti-glomerular basement membrane (GBM) antibodies were negative, suggesting that collagen diseases or vasculitis was unlikely (Table 1). Computed tomography (CT) showed hepatosplenomegaly and lymphadenopathy, but a pleural effusion or ascites, among the major criteria necessary for the diagnosis of TAFRO syndrome, was not apparent. Thus, it was difficult to make the diagnosis at this point.

She was followed with no medication. Thrombocytopenia had progressed to 39,000/ μ L at its minimum. Bone marrow examination showed a hypercellular marrow. No increase of megakaryocytes or myelofibrosis was observed. Surgical biopsy of an enlarged cervical lymph node was performed and showed lymphoid hyperplasia with involution and hyalinization of the germinal center, suggesting the hyaline vascular subtype of Castleman's disease.

The elevation of CRP and thrombocytopenia improved during the natural course after about 1 month of hospitalization and she was discharged. However, 1 month after

Table 1 Laboratory data on the first and second hospitalizations

	1st	2nd	
Biochemistry			
TP	5.8	6.4	g/dL
Alb	1.8	2.5	g/dL
UN	6.8	19.4	mg/dL
Cr	0.64	0.93	mg/dL
Na	141	145	mEq/L
K	3.9	4.8	mEq/L
Cl	100	110	mEq/L
Ca	7.8		mg/dL
UA	5.7	8.2	mg/dL
Glu	108		mg/dL
HbA1c	5.9		%
AST	19	10	U/L
ALT	6	2	U/L
ALP	805	378	U/L
LDH	272	175	U/L
CRP	11.3	2.93	mg/dL
Immunochemistry			
ANA	$\times 320$		
MPO–ANCA	Negative		
PR3–ANCA	Negative		
anti-GBM Ab	Negative		
IgG	1164	1365	mg/dL
IgA	160	134	mg/dL
IgM	100	101	mg/dL
C3	116	108	mg/dL
C4	42.6	32.2	mg/dL
Anti-ds-DNA Ab	2.0		IU/ml
Anti-SS-A Ab	Negative		
Anti-SS-B Ab	Negative		
Soluble IL-2 R	3390		U/mL
VEGF		999	pg/mL
IL-6		12	pg/mL
Completed blood cell			
RBC	417	393	$\times 10^4/\mu$ L
Hb	10.5	8.6	g/dL
Hct	34	29.4	%
Plt	108,000	238,000	/ μ L
WBC	10,700	8400	/ μ L
Neu	77.6	71.6	%
Lymph	14.4	22.9	%
Mono	7.5	5	%
Eos	0.4	0.4	%
Coagulation test			
PT-INR	1.18	1.21	
PT	72	68.5	%
APTT	28.6	31.3	s
Fib	482		mg/dL
FDP	24.2	26.8	μ g/dL
D-dimer	8.9	8.2	μ g/dL

Table 1 (continued)

	1st	2nd	
Viral test			
Anti-HIV Ab		Negative	
HHV-8 DNA		<2.0	× 10 copies
Urinalysis			
Specific gravity	1.016	1.028	
pH	6	5.5	
Glu	Negative	Negative	
RBC	10–19	10–19	/HPF
WBC	<1	1–4	/HPF
Protein/Cr	0.2	2.05	g/gCr
Cast	Negative		
RBC	Negative	Negative	
WBC	Negative	Negative	
Granular	Negative	2+	

TP total protein, *Alb* albumin, *UN* urea nitrogen, *Cr* creatinine, *Na* sodium, *K* potassium, *Cl* chlorine, *Ca* calcium, *UA* uric acid, *Glu* glucose, *HbA1c* hemoglobin A1c, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *LDH* lactate dehydrogenase, *CRP* C-reactive protein, *ANA* antinuclear antibody, *MPO-ANCA* myeloperoxidase–anti-neutrophil cytoplasmic antibodies, *PR3-ANCA* proteinase-3–anti-neutrophil cytoplasmic antibodies, *anti-GBM Ab* anti-glomerular basement membrane antibodies, *IgG* immunoglobulin G, *IgA* immunoglobulin A, *IgM* immunoglobulin M, *C3* complement 3, *C4* complement 4, *anti-ds-DNA Ab* anti-double-stranded DNA antibodies, *anti-SSA Ab* anti-SSA antibodies, *anti-SSB Ab* anti-SSB antibodies, *soluble IL-2 R* soluble interleukin-2 receptor, *VEGF* vascular endothelial growth factor, *IL-6* interleukin-6, *RBC* red blood cell, *Hb* hemoglobin, *Hct* hematocrit, *Plt* platelet, *WBC* white blood cell, *Neu* neutrophils, *Lymph* lymphocytes, *Mono* monocytes, *Eos* eosinophils, *PT-INR* prothrombin time–international normalized ratio, *PT* prothrombin, *APTT* activated partial thromboplastin time, *Fib* fibrinogen, *FDP* fibrin degradation product, *D-dimer* d-dimer, *anti-HIV Ab* anti-human immunodeficiency virus antibodies, *HHV-8 DNA* human herpesvirus 8 deoxyribonucleic acid

discharge, the CRP level was again elevated (2.93 mg/dL), and renal insufficiency had progressed (serum Cre 0.93 mg/dL). She was admitted again, and physical examination showed general pitting edema, and a CT scan showed a new pleural effusion and ascites, which were not found before. A diagnosis of TAFRO syndrome was then made based on her clinical and laboratory findings (day 85 after first admission). The plasma VEGF level was elevated at 999 pg/mL and serum interleukin-6 (IL-6) was 12.0 pg/mL.

A kidney biopsy was performed because the platelet count was preserved (238,000/μL) on hospital day 7. Of the 11 glomeruli, 1 was globally sclerosed. The remaining glomeruli showed diffuse lobulations with double contours of the GBM and mesangiolysis. Glomerular capillary lumens were narrowed by endothelial cell swelling (Fig. 1a, b). There was no crescent formation. Immunofluorescence studies for IgG, IgA, IgM, C1q, C3, C4, and fibrinogen were all negative. Electron microscopy

Fig. 1 Histological findings. Light microscopy shows lobulations of glomeruli, mesangiolysis, double contours of the glomerular basement membrane, and swelling of endothelial cells (**a** periodic acid–Schiff stain, and **b** periodic acid–silver methenamine stain). On electron microscopy (**c**), endothelial swelling, widening of the sub-endothelial space, and double contours of the glomerular basement membrane are confirmed

showed glomerular endothelial swelling and widening of the subendothelial space (Fig. 1c). Electron-dense deposits were not observed. From these findings, a diagnosis of MPGN-like lesions was made, suggesting endothelial injury like the lesions of TMA. Moreover, the glomerular

VEGF expression level was evaluated by immunolabelling of VEGF with a monoclonal mouse VEGF antibody (VG1, Novus Biologicals, Centennial, CO, USA). An independent archived biopsy specimen (normal renal tissue of isolated kidney of renal cell carcinoma) was used as a positive control (Fig. 2a). Second, specimens of the present patient were immunolabelled, as were archived biopsy samples of IgA nephritis and minimal change nephrotic syndrome as controls. The results showed staining of VEGF in podocytes in many samples, and VEGF labelling was not decreased in TAFRO syndrome compared to controls (Fig. 2b–d).

Three days after hospital admission, the patient received methylprednisolone pulse therapy (500 mg daily for 3 days), followed by 60 mg/day of prednisolone (1.0 mg/kg/day). The clinical course is shown in Fig. 3. Steroid therapy immediately improved the systemic inflammation, pleural effusion, and ascites. On day 25, cyclosporine 100 mg/day was added to prevent relapse. Renal function returned to normal within 1 month. By 6 months after the first admission, the steroid had been tapered to 10 mg, with no recurrence.

Discussion

TAFRO syndrome has been reported mostly in Japan, though it has recently been reported in other countries as well. Masaki et al. proposed diagnostic criteria in 2016 [7]. According to these criteria, all of the three major criteria and at least two of the four minor criteria are necessary for the diagnosis of TAFRO syndrome. Furthermore, diseases such as POEMS syndrome, malignancies, viral infections, and so on must be ruled out. The present case met all the major criteria and three of the minor ones (organomegaly, progressive renal insufficiency, and lymph node histology), so a diagnosis of TAFRO syndrome was made. In particular, the present case was self-limited, which was a different clinical course from previous reports. Systemic inflammation and thrombocytopenia disappeared early in the natural course, and after a few months, inflammation relapsed with a pleural effusion and ascites. At first, the patient was suspected of having viral infections or malignant lymphoma, but viral screening and the results of lymph node biopsy did not support those diagnoses.

Furuto et al. also reported an atypical clinical course of TAFRO syndrome [8]. The patient had an anterior mediastinal tumor that showed lymphocytic proliferation without

Fig. 2 Immunohistology of VEGF in renal tissues of the patient. **a** The patient, **b** normal renal tissue of isolated kidney of renal cell carcinoma, **c** IgA nephritis, **d** minimal change nephrotic syndrome. Podocyte VEGF expression does not show a reduction in any samples

Fig. 3 Clinical course of the patient. *Cr* creatinine, *CRP* C-reactive protein, *mPSL* methylprednisolone, *Plt* platelets, *PSL* prednisolone

signs of malignancy, initially diagnosed as multicentric Castleman's disease. After resection of the tumor, generalized anasarca and renal insufficiency improved. However, 6 months after surgery, they recurred and thrombocytopenia developed, and so she was diagnosed with TAFRO syndrome. This slowly progressive clinical course is atypical for TAFRO syndrome. In the present case, thrombocytopenia improved spontaneously and did not worsen at the second admission. Platelet-associated immunoglobulin G is often elevated in TAFRO syndrome [8], so it might have resulted from a change of the immune response to an etiological factor of TAFRO syndrome.

Renal insufficiency, one of the minor criteria, is often progressive and rarely requires hemodialysis [2, 3, 9–12]. Iwaki et al. reported that renal involvement was seen in about 55% of cases of TAFRO syndrome [13]. Although the evidence for the treatment of TAFRO syndrome has not been established, steroid therapy was chosen in almost all cases. Cyclosporine, tocilizumab, anti-IL-6 antibodies, or rituximab are also used in such cases that are steroid resistant.

The level of serum IL-6 or plasma VEGF is frequently elevated in TAFRO syndrome, as well as in Castleman's disease [7]. Renal VEGF is considered to play an important role in maintaining glomerular endothelial cells. In human kidneys, VEGF mRNA and/or protein was detected predominantly in glomerular podocytes, distal tubules, and collecting ducts [14]. VEGF expression is stimulated by hypoxia and some growth factors and cytokines, such as IL-6 and others. VEGF increases the production of nitric oxide, upregulating the expression of endothelial nitric oxide synthase 3 [14]. In experimental rats, administration of VEGF₁₂₁ protects against renal infarction in TMA [15].

It is considered that maintenance of endothelial nitric oxide production by VEGF may prevent endothelial cell apoptosis.

In past reports, similar MPGN-like lesions were observed in multicentric Castleman's disease. Karoui et al. examined podocyte VEGF expression levels in Castleman's disease with renal involvement using a monoclonal mouse VEGF antibody [5]. They reported that a reduction of the glomerular VEGF level was observed in patients with small-vessel lesions, which showed endothelial swelling, double contours of the GBM, and mesangiolysis. Furthermore, the loss of glomerular VEGF was negatively correlated with the plasma CRP level reflecting the activity of Castleman's disease, suggesting that downregulation of glomerular VEGF may be induced by lymphoproliferation through the action of undetermined circulating factors.

We hypothesized that podocyte VEGF expression in TAFRO syndrome might also be decreased. Renal VEGF expression in TAFRO syndrome has not been sufficiently evaluated so far. Two previous case reports had already investigated them. In the case reported by Noda-Narita et al. [16], renal biopsy showed diffuse endocapillary proliferative glomerulonephritis, and immunohistochemical staining showed that podocytes were weakly positive for IL-6, but negative for VEGF. However, the patient met the criteria of not only TAFRO syndrome, but also of POEMS syndrome. Therefore, one must interpret the results of renal pathology carefully. On the other hand, in the case reported by Ozeki et al. [17], although renal pathology showed TMA-like lesions, as in the present case, VEGF staining of the glomeruli did not show any reduction. They considered that other mechanisms might have caused renal injury. In the present case, there was no reduction of podocyte VEGF expression. Some reasons for this result can be assumed. First, the

specimens were taken 4 days after administration of steroid therapy. The patient showed a good response to steroid therapy, and recovery of VEGF production from podocytes may have occurred before renal biopsy.

Second, the CRP level improved to 1.59 mg/dL the day after kidney biopsy. As mentioned above, if the level of VEGF production from podocytes is related to the CRP level that could have affected VEGF labelling. The patient showed CRP elevation to at most 17.7 mg/dL, when the podocyte VEGF expression might have been decreased. Although what inhibits the production of VEGF by podocytes is unclear, IL-6 and other cytokines could be involved.

Finally, apart from the reduction of podocyte VEGF, other mechanisms might cause renal involvement in TAFRO syndrome. Kurose et al. [18] confirmed that mesangial cells were positive for IL-6 immunostaining in patients with idiopathic multicentric Castleman's disease with TAFRO syndrome. Since IL-6 contributes to mesangial cell proliferation in human kidneys [19], the overproduction of IL-6 itself may be related to renal lesions in TAFRO syndrome. Further research of this issue is also needed.

Consequently, it was not possible to obtain results supporting our hypothesis that the reduction of podocyte VEGF expression causes the renal TMA lesions in TAFRO syndrome. It is important to confirm podocyte VEGF expression in the active phase before treatment, including steroid therapy. However, the clinical course of TAFRO syndrome is often acute and progressive, and so an early diagnosis must be made and treatment started. Kidney biopsy is not essential in TAFRO syndrome and must be conducted carefully because of the associated thrombocytopenia. Furthermore, based on the present case, it appears that the clinical features of TAFRO syndrome such as thrombocytopenia, pleural effusion or ascites, and renal dysfunction may not necessarily develop at the same time. Several variant types of TAFRO syndrome may exist, and further study is still needed to identify them.

In conclusion, there are few reports of renal VEGF expression in TAFRO syndrome. In the present case, the patient had an atypical clinical course of TAFRO syndrome, and reduction of podocyte VEGF expression could not be confirmed. Further investigation including VEGF/IL-6 expressions in renal lesions and analyzing the pattern of the clinical course is required to elucidate the renal pathogenesis and etiology of TAFRO syndrome.

Compliance with ethical standards

Conflict of interest All authors have no conflicts of interests affecting the present study.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from the patient in this case report.

References

1. Takai K, Nikkuni K, Shibuya H, Hashidate H. Thrombocytopenia with mild bone marrow fibrosis accompanied by fever, pleural effusion, ascites and hepatosplenomegaly. *Jpn J Clin Hematol*. 2010;51:320–5.
2. Tanaka M, Tsujimoto H, Yamamoto K, et al. Clinicopathological features of progressive renal involvement in TAFRO syndrome: a case report and literature review. *Medicine*. 2017;96:e8216.
3. Jose FF, Kerbaux LN, Perini GF, et al. A life-threatening case of TAFRO syndrome with dramatic response to tocilizumab, rituximab, and pulse steroids: the first case report in Latin America. *Medicine*. 2017;96:e6271.
4. Kawashima M, Usui T, Okada H, et al. TAFRO syndrome: 2 cases and review of the literature. *Mod Rheumatol*. 2017;27:1093–7.
5. El Karoui K, Vuiblet V, Dion D, et al. Renal involvement in Castleman disease. *Nephrol Dial Transplant*. 2011;26:599–609.
6. Eremina V, Jefferson JA, Kowalewska J, et al. VEGF inhibition and renal thrombotic microangiopathy. *N Eng J Med*. 2008;358:1129–36.
7. 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.
8. Furuto Y, Hashimoto H, Horiuti H, et al. Membranoproliferative glomerulonephritis-like findings for TAFRO syndrome, associated with an anterior mediastinal tumor. *Medicine*. 2018;97:e11057.
9. Sakai K, Maeda T, Kuriyama A, et al. TAFRO syndrome successfully treated with tocilizumab: a case report and systematic review. *Mod Rheumatol*. 2018;28:564–9.
10. Kikuchi T, Shimizu T, Toyama T, et al. Successful treatment of TAFRO syndrome with tocilizumab, prednisone, and cyclophosphamide. *Intern Med*. 2017;56:2205–11.
11. Fujiwara S, Mochinaga H, Nakata H, et al. Successful treatment of TAFRO syndrome, a variant type of multicentric Castleman disease with thrombotic microangiopathy, with anti-IL-6 receptor antibody and steroids. *Int J Hematol*. 2016;103:718–23.
12. Ohya E, Mizutani M, Sakaguchi H, et al. Diffuse large B-cell lymphoma during corticosteroid therapy for TAFRO syndrome. *Intern Med*. 2015;55:2861–7.
13. 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.
14. Schrijvers BF, Flyvbjerg A, De Zeeuw AS. The role of vascular endothelial growth factor (VEGF) in renal pathophysiology. *Kidney Int*. 2004;65:2003–17.
15. Suga S, Kim YG, Joly A, et al. Vascular endothelial growth factor (VEGF121) protects rats from renal infarction in thrombotic microangiopathy. *Kidney Int*. 2001;60:1297–308.
16. Noda-Narita S, Sumida K, Hoshino A, et al. TAFRO syndrome with refractory thrombocytopenia responding to tocilizumab and romiplostim: a case report. *CEN Case Rep*. 2018;7:162–8.
17. Ozeki T, Tsuji M, Yamamoto J, et al. Thrombotic microangiopathy on kidney biopsy in a patient with TAFRO syndrome. *CEN Case Rep*. 2018;7:243–7.

18. Kurose N, Mizutani K, Kumagai M, et al. An extranodal histopathological analysis of idiopathic multicentric Castleman disease with and without TAFRO syndrome. *Pathol Res Pract*. 2019;215:410–3.
19. Matsumura N. Distribution of interleukin-6 in human proliferative glomerulonephritides. *J Nara Med*. 1992;43:284–96.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.