Thrombotic microangiopathy on kidney biopsy in a patient with TAFRO syndrome

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Abstract

TAFRO syndrome represents a characteristic constellation of symptoms comprising Thrombocytopenia, Anasarca, myeloFibrosis, Renal dysfunction, and Organomegaly, and is considered to be a clinicopathologic variant of idiopathic multicentric Castleman disease. A 51-year-old woman was admitted to the hospital complaining of abdominal distension. Findings on physical examination were indicative of anasarca. Computed tomography revealed mild splenomegaly, pericardial effusion, pleural effusion, ascites, and paraaortic lymphadenopathy. Blood tests showed thrombocytopenia, and urinalysis demonstrated hematuria, proteinuria, and worsening renal function. Kidney biopsy was performed and revealed thrombotic microangiopathy-like lesions with global sclerosis of 1 of the 16 glomeruli on light microscopy. The remaining glomeruli had a distinct lobular pattern, with mesangiolysis, double contours of the glomerular basement membranes, and marked endothelial swelling. Immunofluorescence studies for IgG, IgM, IgA, C1q, C3, C4, κ -light chains, and λ -light chains were indeterminate. Electron microscopy showed marked endothelial swelling. We made a diagnosis of TAFRO syndrome and started steroid treatment, following which her symptoms gradually improved. There are few reports describing renal pathology in a patient with TAFRO syndrome.

Keywords TAFRO syndrome · Renal pathology · Thrombotic microangiopathy

Introduction

TAFRO syndrome characteristically presents as a constellation of symptoms comprising Thrombocytopenia, Anasarca, myeloFibrosis, Renal dysfunction, and Organomegaly, and is considered to be a clinicopathologic variant of idiopathic multicentric Castleman disease. The condition was first described in 2010 [1]. Subsequently, several reports about TAFRO syndrome were published [2–5] and the typical clinical course and effective treatment modalities have gradually been unraveled in recent years. However, there have been few reports about renal injury in a patient with TAFRO syndrome, and the pathogenesis of renal injury has remained unknown. Here, we present a case report about a patient with TAFRO syndrome who underwent kidney biopsy,

which revealed thrombotic microangiopathy (TMA)-like pathological findings.

Case report

A 51-year-old woman was admitted to the hospital, complaining of abdominal distension. Two months earlier, she noticed swelling of her legs and was prescribed furosemide, but her symptoms persisted. Urinalysis showed hematuria and proteinuria. Also, 20 days before presentation, she had influenza but recovered within 1 week. Her past medical history was unremarkable. She was not receiving any regular medication. The abdominal distension gradually worsened, so she was admitted to the hospital for further examination and treatment.

Her height was 160 cm and weight 60.9 kg, although her usual body weight was 50 kg. Vital signs on arrival were blood pressure of 153/72 mmHg, heart rate of 89 beats per minute, temperature of 36.6 °C, oxygen saturation of 98% on room air, respiratory rate of 20 breaths per minute, and her sensorium was clear. Findings on physical examination

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were significant for anasarca. Initial laboratory test results are shown in Table 1. Blood tests showed thrombocytopenia, and urinalysis revealed hematuria, proteinuria, and worsening renal function. No casts were seen on urinalysis. Serum electrophoresis and urine electrophoresis did not show M-protein. Serum IL-6 was 21.2 pg/mL (normal reference values: 0.0–4.0 pg/mL) and serum VEGF was 198 pg/mL

(normal reference values: 0.0–38.3 pg/mL). Blood, sputum, urine, and stool culture tests yielded no growth. A left pleural effusion was detected on chest X-ray with a cardiothoracic ratio of 60%. Computed tomography revealed mild splenomegaly, pericardial effusion, pleural effusion, ascites, and paraaortic lymphadenopathy (Fig. 1). Kidney size was normal bilaterally.

Table 1 The results of laboratory tests on admission

Blood test					Urinalysis		
TP	5.9	g/dL	ANA	Negative	Specific gravity	1.001	
Alb	2.5	g/dL	MPO-ANCA	Negative	pH	5.5	
BUN	12.7	mg/dL	PR3-ANCA	Negative	Glu	–	
Cr	1.03	mg/dL	IgG	1414	RBC	10–19	/HPF
Na	137	mEq/L	IgA	251	WBC	1–4	/HPF
K	3.8	mEq/L	IgM	66	Protein/Cr	0.52	g/gCr
Cl	101	mEq/L	C3	98			
Ca	7.7	mg/dl	C4	35			
UA	10.5	mg/dL	Hb	10.8			
Glu	82	mg/dL	Ht	31.6			
AST	14	U/L	Plt	9.5×10^4			
ALT	5	U/L	WBC	5600			
ALP	254	U/L	Neu	65			
LDH	186	U/L	Lymph	22			
CRP	4.58	mg/dL	Mono	10			
VEGF	198	pg/mL	Eos	2.2			
IL-6	21.2	pg/mL	PT-INR	1.39			
Soluble IL-2 R	1191	U/mL	PT%	63			
Folic acid	4.4	ng/mL	APTT	37			
Vitamin B12	635	pg/mL	Fib	310			
Ferritin	246	ng/mL	FDP	18.9			
Haptoglobin	262	mg/dL					

Normal reference values for IL-6 were 0.0–4.0 pg/mL and normal reference values for VEGF were 0.0–8.3 pg/mL

Fig. 1 Abdominal computed tomography on admission showed pleural effusion, ascites, splenomegaly (a), and paraaortic lymph node swelling (arrow, b)

Thoracentesis yielded a pale yellow fluid with a white blood cell (WBC) count of 200 cells/ μ L. Biochemical analysis showed glucose 127 mg/dL, lactate dehydrogenase 81 IU/L, and total protein 3.3 g/dL. Culture for pyogenes and acid-fast bacilli was negative. Cytologic examination of the pleural fluid showed no malignant cells.

Analysis of the ascitic transudate also yielded a pale yellow colored fluid with a WBC count of 200 cells/ μ L. Biochemical analysis showed glucose 130 mg/dL, lactate dehydrogenase 77 IU/L, and total protein 2.6 g/dL. Cultures for pyogenes and acid-fast bacilli were also negative. Cytologic examination of the pleural fluid showed no malignant cells.

Bone marrow aspiration revealed normal cellular distribution and maturation.

On day 8 after admission, kidney biopsy was performed. Light microscopy revealed global sclerosis of 1 of the 16 glomeruli. The remaining glomeruli appeared lobular with mesangiolysis, double contours of the glomerular basement membranes, and marked endothelial swelling (Fig. 2a, b). Partial infiltration of monocytes and plasma cells into the tubulointerstitial lesions could be seen. Immunofluorescence studies for IgG, IgM, IgA, C1q, C3, C4, κ -light chains, and λ -light chains were indeterminate. Electron microscopy showed marked endothelial swelling (Fig. 2c).

Fig. 2 Histopathological findings. **a** The glomeruli appeared lobular pattern, mesangiolysis, double contours of the glomerular basement membranes and marked endothelial swelling (periodic acid–Schiff stain, $\times 200$). **b** Glomerular basement membranes showed double

contours (periodic acid–sliver methenamine stain, $\times 200$). **c** Electron microscopy showed endothelial swelling and widening of the subendothelial space ($\times 3000$)

On day 11 after admission, we made a diagnosis of TAFRO syndrome, and methylprednisolone pulse therapy at a dose of 0.5 g/day for 3 days was initiated. The clinical course is shown in Fig. 3. The anasarca, serum CRP, and fever resolved considerably following steroid therapy. Platelet count remained low initially, but increased gradually after about a month.

Additionally, we performed immunohistological staining with a monoclonal mouse antibody to VEGF (clone C1, Santa Cruz Biotechnology, Santa Cruz, CA) in renal tissues from our patient, and we could not detect any abnormality (Fig. 4).

Discussion

The characteristic symptoms of TAFRO syndrome, namely, thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, and organomegaly, are generally thought to represent a clinicopathologic variant of idiopathic multicentric Castleman disease.

Diagnostic criteria for TAFRO syndrome were proposed in 2016 [6] and the present case met all the major categories of these criteria (anasarca, thrombocytopenia, and systemic inflammation). Also, our case met two out of four minor categories (organomegaly and progressive renal insufficiency). Thus, we made a diagnosis of TAFRO syndrome.

Fig. 4 Immunohistology of VEGF in renal tissues from our patients (×400). VEGF expression did not show any reduction

Regarding renal pathology, TMA-like lesions such as capillary-loop double contours and endotheliosis are the most common features of Castleman disease [7, 8]. In our case, kidney biopsy showed TMA-like lesions and the findings were the same as those seen in Castleman disease. Apart from our case, only one case report has described renal pathology in TAFRO syndrome [9]. In that study, renal pathology examination showed TMA-like lesion, with mesangial expansion and duplication of the glomerular

Fig. 3 Clinical course of the patient. BW body weight, Cr creatinine, CRP C-reactive protein, mPSL methylprednisolone, Plt platelet, PSL prednisolone, UTP urinary total protein

capillary basal membrane. These features were also similar to our case and we considered that renal injury in TAFRO syndrome might be caused mainly by TMA.

Renal TMA with endothelial swelling was also described in a patient receiving VEGF antibody therapy [10], and in a patient treated with sirolimus [11]. Glomerular VEGF is thought to play an important role in these conditions and glomerular VEGF loss contributes to the pathogenesis of TMA-like lesions [7, 10–12]. The production of VEGF by podocytes is required for maintenance of the adjacent glomerular endothelium. Glomerular endothelial cells contain fenestrations that are necessary for the permeability of the glomerular filtration barrier and VEGF induces the formation of them. Decreasing VEGF from the glomerulus causes a loss of fenestration and develops microvascular injury and TMA [10]. In our case, serum VEGF and IL-6 were elevated and cytokine storm could have occurred which is related to the pathogenesis of renal lesions. We hypothesized that glomerular VEGF levels might be decreased in TAFRO syndrome as well as in other disease conditions, and this might have led to the TMA-like pathological findings in the kidney in the present case. However, VEGF staining did not show any reduction. In TAFRO disease, other different mechanism might cause renal injury.

Conclusion

There are few reports describing renal pathology in a patient with TAFRO syndrome and to our knowledge this is the case first report on renal pathology in an Asian patient with TAFRO syndrome. The patient was successfully treated with immunosuppressive therapy. There is a need for more reports on renal pathology in patients with TAFRO syndrome.

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Compliance with ethical standards

Conflict of interest All the authors have declared no competing interest.

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 the case report.

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