CASE REPORT

Successful treatment by tocilizumab without steroid in a very severe case of TAFRO syndrome

Tamami Fujiki¹ · Suguru Hirasawa¹ · Seishi Watanabe¹ · Shunsuke Iwamoto¹ · Ryoichi Ando¹

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Abstract Successful use of tocilizumab (TCZ) to treat TAFRO syndrome has recently been reported. In those cases, TCZ was used with steroid. We present herein the case of a 59-year-old man with very severe TAFRO syndrome who was successfully treated using TCZ without steroid. He showed rapidly progressive anasarca, acute renal failure and very severe thrombocytopenia. We initially used steroid, but its efficacy was limited. Moreover, steroid use had to be stopped as soon as possible, because hemorrhagic shock developed due to severe duodenal ulcer. After overcoming infections (about 40 days after stopping steroid), administration of TCZ was started and the patient was discharged in clinical remission.

Keywords TAFRO syndrome · Renal failure · Steroid · Tocilizumab

Introduction

TAFRO syndrome is a new variant of multicentric Castleman's disease (MCD). This systemic inflammatory disorder is characterized by Thrombocytopenia, Anasarca, Fever, Renal insufficiency and Organomegaly [1]. As of August 2016, few cases have been reported from around the world. Most such cases have been reported from Japan. The mechanisms underlying TAFRO syndrome have yet to be elucidated. We report herein a very severe case of TAFRO

syndrome that was successfully treated using TCZ without steroid.

Case presentation

A 59-year-old Japanese man was admitted to our hospital with leg edema, fatigue and fever. He had a past medical history of duodenal ulcer, fatty liver, hyperuricemia and positive rheumatoid factor, but was not receiving any medication. His son had died 2 years prior to this admission after following a clinical course that suggested TAFRO syndrome.

The patient showed mild fever (about 37–38 °C), polypnea and severe leg edema on admission. Chest examination revealed decreased breath sounds in the right lung. No superficial lymph nodes were palpable. Laboratory tests on admission revealed mild thrombocytopenia, hypoproteinemia, elevation of C-reactive protein (CRP), alkaline phosphatase (ALP), creatinine (Cr), and urine *N*-acetyl- β -D-glucosaminidase (NAG) (Table 1). Urine testing showed granular casts without proteinuria or hematuria. Concentrations of aspartate aminotransferase (AST) and alanine transaminase (ALT) were elevated, but unchanged compared with the results of a medical check 6 months before admission, and so were attributed to fatty liver. Chest X-ray and computed tomography (CT) showed mild lymphadenopathy in the mediastinum, bilateral pleural effusion and ascites (Fig. 1).

Blood, sputum and urine culture tests were all negative and no other infectious diseases were present. Negative results were obtained for all autoantibodies. Among the tumor markers, only soluble interleukin-2 receptor (sIL-2R) was elevated. Bone marrow biopsy was performed to rule out malignant lymphoma, revealing normocellular

✉ Tamami Fujiki
shilfy213@gmail.com

¹ Japanese Red Cross Musashino Hospital, Kyonancho 1-26-1, Musashino, Tokyo, Japan

Table 1 Laboratory data on admission

[Urine test]		[Biochemistry]		[Infectious disease test]	
Specific gravity	1.023	TP	6.3 g/dl	RPR	(–)
pH	5.5	Alb	2.8 g/dl	TPHA	(–)
UP	(2+)	AST	50 IU/l	HBsAg	(–)
OB	(2+)	ALT	55 IU/l	HCVAb	(–)
UPCR	0.42 g/gCr	LDH	364 IU/l	β-D-Glucan	(–)
Protein	0.32 g/day	ALP	1359 IU/l	Tb-IFN-γ	(–)
RBC	1–4/HF	T-Bil	1.2 mg/dl	[Immunologic test]	
Granular cast	50–99/WF	BUN	19.8 mg/dl	ASLO	<20 IU/ml
β2MG	77 μg/l (NR 0–230)	Cr	1.36 mg/dl	RF	165.0 IU/ml
NAG	40.1 U/l (NR <11.5)	UA	8.6 mg/dl	IgG	865.6 mg/dl
[Blood cell count]		Na	140 mEq/l	IgA	172.8 mg/dl
WBC	8400/μl	K	4.6 mEq/l	IgM	156.8 mg/dl
Hb	17.3 g/dl	Cl	104 mEq/l	C3	170.2 mg/dl
Plt	14.9×4.4/μl	Ca	8.3 mg/dl	C4	30.0 mg/dl
[Coagulation test]		CRP	19.32 mg/dl	CH50	74.4 ch50U/ml
PT	13.9 s	Lysozyme	9.4 μg/ml	ANA	<40
APTT	34.4 s	ACE	11.6 IU/l (NR 7.7–29.4)	GBM	(–)
Fib	≥600 mg/dl	IL-6	15.2 pg/ml (NR <4)	PR3-ANCA	(–)
D-Dimer	4.9 μg/ml	VEGF	52 pg/ml (NR <38.3)	MPO-ANCA	(–)
		sIL-2R	1480 U/ml (NR 124–466)		

NR normal range, UP urinary protein, OB occult blood, UPCR urine protein-to-creatinine ratio, RBC red blood cell, β2MG β2-microglobulin, NAG N-acetyl-β-D-glucosaminidase, WBC white blood cell, Hb hemoglobin, Ht hematocrit, Plt platelet cells, PT prothrombin time, APTT activated partial thromboplastin time, Fib fibrinogen, TP total protein, Alb albumin, AST aspartate aminotransferase, ALT alanine transaminase, LDH lactate dehydrogenase, ALP alkaline phosphatase, T-Bil total bilirubin, BUN blood urea nitrogen, Cr creatinine, UA uric acid, CRP C-reactive protein, ACE angiotensin-converting enzyme, IL-6 interleukin 6, VEGF vascular endothelial growth factor, sIL-2R soluble interleukin-2 receptor, RPR rapid plasma regain test, TPHA *Treponema pallidum* hemagglutination test, HBsAg hepatic B surface antigen, HCVAb hepatitis C virus antibody, Tb-IFN-γ tuberculosis interferon-γ, ASLO anti-streptolysin-O, RF rheumatoid factor, Ig immunoglobulin, C complement, CH hemolytic complement activity, ANA anti-nuclear antibody, GBM anti-glomerular basement antibody, PR3-ANCA proteinase-3 anti-neutrophil cytoplasmic antibody, MPO-ANCA myeloperoxidase anti-neutrophil cytoplasmic antibody

bone marrow with increased megakaryocytes and mild hyperplasia of reticulin fibers. Weak accumulation of gallium on scintigraphy was seen in the kidneys (Fig. 2). Considering this finding together with the results of urine testing, interstitial nephritis was suspected. However, various tests failed to identify a cause for interstitial nephritis (such as sarcoidosis). Levels of interleukin (IL)-6 and vascular endothelial growth factor (VEGF) were slightly elevated. These findings led to a suspicion of MCD. However, mild lymphadenopathy (maximum diameter <1.5 cm) and lack of hypergammaglobulinemia were atypical findings in MCD. We were unable to make a definite diagnosis at that time, because the lymph nodes were too small to biopsy. After admission, fever and high concentrations of CRP (CRP >15 mg/dl) persisted and renal function rapidly deteriorated (Fig. 3). Furthermore, ascites and pleural effusion increased. The ascites and pleural effusion showed biochemical exudative characteristics but were sterile, and no malignant cells were detected. On hospital day 21, high-dose steroid therapy (intravenous methylprednisolone at 1 g/day for 3 days, then oral prednisolone at 50 mg/day)

was started. Steroid therapy improved the fever, level of CRP, and renal function, but anasarca and dyspnea worsened day by day. Moreover, the platelet count dropped significantly ($0.2\text{--}3 \times 10^4/\mu\text{l}$) and platelet transfusions failed to improve platelet count. After several tests (Table 2), TAFRO syndrome was diagnosed.

During steroid therapy, the patient developed hemorrhagic shock because of severe duodenal ulcers and we, therefore, had to reduce and stop steroid administration as soon as possible. Bleeding from the duodenal ulcers was stopped after transcatheter arterial embolization. Nevertheless, various infections recurred after that life-threatening event (Fig. 4), preventing immunosuppressive treatments. His general condition improved slightly with antibiotics, transfusion, artificial respiration, drainage for pleural effusions and ascites, and hemodialysis. On hospital day 135, after confirming negative blood cultures, treatment with TCZ was started at 8 mg/kg/2 weeks. After 2 months from initiation of TCZ, severe anasarca gradually resolved (body weight decreased from 90 to 50 kg), and he was weaned from ventilator support. Albumin concentrations and

Fig. 1 Chest X-ray photograph and CT on admission. He had bilateral pleural effusion (a), mild lymphadenopathy in the mediastinum (b), and ascites (c)

Fig. 2 Gallium scintigraphy

Fig. 3 Clinical course until the diagnosis was established. *mPSL* methylprednisolone, *PSL* prednisolone

Table 2 Laboratory data when platelet count began to fall

PLT	$2.8 \times 10^4/\mu\text{l}$	FDP	87.7 $\mu\text{g/ml}$
PT	16.7 s	HIT IgG	(–)
APTT	41.4 s	ADAMTS-13 activity	31%
Fib	$\geq 600 \text{ mg/dl}$	PA IgG	600 $\text{ng}/10^7 \text{ cells}$

HIT heparin-induced thrombocytopenia, *PA IgG* platelet-associated IgG

platelet count increased without transfusion. Hemodialysis was discontinued on hospital day 251 and he was discharged on hospital day 356.

Discussion

Masaki et al. proposed diagnostic criteria, disease severity classification and treatment strategy for TAFRO syndrome [1]. Our case fulfilled all the major criteria (anasarca, thrombocytopenia, and systemic inflammation (fever of unknown etiology and/or elevation of CRP)) and three of the four minor criteria (reticulon myelofibrosis and/or increased number of megakaryocytes in bone marrow, mild lymphadenopathy, and progressive renal insufficiency). One minor criterion (Castleman's disease (CD)-like features in lymph node biopsy) was not able to be determined owing to a lack of lymph node biopsy. In our case, platelet

count at admission was very close to normal range but his platelet count decreased gradually and dropped to $81,000/\mu\text{l}$ before treatment. And compared the result of a medical check 6 months before admission ($>200,000/\mu\text{l}$), his platelet count at admission decreased significantly. So we thought that thrombocytopenia started before treatment. According to the severity classification for TAFRO syndrome, the full score in our case reflected a grade 5 (very severe) condition. Masaki et al. reported 28 cases, none of which were grade 5. Our case thus represented a very rare case of successful treatment for grade 5 TAFRO syndrome.

Some patients with TAFRO syndrome have been successfully treated with steroid, immunosuppressants, including cyclosporine A (CyA), TCZ and rituximab, and/or immunomodulatory drugs like thalidomide [2–6]. According to the 2015 treatment strategy for TAFRO syndrome, steroid is the first-line treatment, with CyA as the second-line therapy. TCZ and rituximab are recommended in patients with renal insufficiency, because CyA is contraindicated. In our case, steroid showed limited efficacy and had to be stopped due to severe duodenal ulcers. The patient was treated by hemodialysis and was unable to take medicine orally, so we chose TCZ as a second-line treatment about 40 days after stopping steroid. In previous cases of successful TCZ treatment, steroid were used with TCZ [2, 7]. This is thus the first report of successful treatment of TAFRO syndrome using only TCZ.

IL-6 and VEGF are elevated in serum, pleural effusion, and ascites of patients with TAFRO syndrome as with our

Fig. 4 Clinical course until discharge. CHDF, continuous hemodiafiltration; HDF, hemodiafiltration; ALB, albumin transfusion; PC, platelet transfusion; A, *Pseudomonas aeruginosa* pneumonia; B,

Pneumocystis pneumonia; C, *Stenotrophomonas maltophilia* pneumonia; D, *Cytomegalovirus* infection; E, *Candida* bacteremia; F, *Clostridium difficile* enteritis; G, *Escherichia coli* pyelonephritis

case. These cytokines may be involved in the pathogenesis of TAFRO syndrome. On the other hand, some cases were resistant to TCZ, an anti-IL-6 receptor antibody [8]. Although thrombocytopenia is one of the major diagnostic criteria in TAFRO syndrome, IL-6 stimulates megakaryocyte maturation, which typically results in thrombocytosis under normal circumstances [9]. Konishi et al. suggested that IL-2-related immunological abnormality plays a role in the pathogenesis of TAFRO syndrome, in addition to IL-6 [4]. Their case achieved remission with CyA and CyA interferes in T cell activity via inhibition of calcineurin which is responsible for activating IL-2 encoding gene transcription [10]. Moreover, IL-2 administration induces capillary leak syndrome, elevated Cr levels and thrombocytopenia [11, 12], so they discussed that IL-2-dependent pathway should be considered in the etiology of TAFRO syndrome. These findings suggested that IL-6 may not be the primary pathological driver of hypercytokinemia.

Although progressive renal insufficiency is one of the main characteristics in TAFRO syndrome, the association between kidney disease and TAFRO syndrome remains unclear and no studies have focused on the renal histopathology. In most previous case reports, the common etiology of renal failure due to CD reported is amyloidosis [13–15]. Morita-Hoshino et al. reported that autopsy showed the deposition of AA amyloid in multiple organs such as kidney, liver, spleen, and gastrointestinal tract [15]. And they discussed that the overproduction of serum amyloid A protein (SAA) due to IL-6 stimulation of hepatocytes can lead some patients to develop AA amyloidosis. But in our case, gastric biopsy did not show the deposition of amyloid. Two cohort studies have described renal histopathology in CD patients, reporting thrombotic microangiopathy (TMA)-like lesions as the most common [13, 14]. Other than that, CD patients show membranous proliferative glomerulonephritis (MPGN), crescentic

glomerulonephritis, or interstitial nephritis [13, 14]. Damin et al. suggested that VEGF is likely involved in renal insufficiency, considering that small-vessel lesions (TMA-like lesions or MPGN) are common in CD patients [14]. However, 95% of patients in that report had proteinuria, unlike our case. Kubokawa et al. noted that urinalysis showed mild proteinuria and mildly elevated urinary NAG and β 2MG without fractured red blood cells in peripheral blood, and these findings suggested that the kidney pathophysiology in their case was interstitial nephritis [16]. e. Unfortunately, we couldn't do renal biopsy, so the cause of renal failure was unclear. Case reports with descriptions of renal histopathology are necessary to clarify the mechanisms underlying renal insufficiency in TAFRO syndrome.

In this case, the patient's son had died 2 years before he was admitted. The son had also shown fever of unknown origin, elevation of CRP, thrombocytopenia, acute renal failure, mild lymphadenopathy and anasarca. Blood, sputum and urine culture tests for the son all yielded negative results, treatment with antibiotics had shown no efficacy, and negative results were seen for autoantibodies. Exact diagnosis could not be made in the absence of bone marrow biopsy, lymph node biopsy or autopsy, and we thus could not completely exclude malignancy. However, the son had only been 28 years old when he died, with no significant medical history, so the possibility of malignancy seems extremely low. In the absence of malignancy, that patient would have met the diagnostic criteria for TAFRO syndrome. Although no previous articles appear to have reported a family history of TAFRO syndrome, we suspected a family history for the present patient.

Conclusions

Successful treatment for very severe TAFRO syndrome was achieved by TCZ without steroid. More cases need to be accumulated to reveal the mechanisms of TAFRO syndrome.

Compliance with ethical standards

Disclosure All the authors have declared no competing interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee at which the studies were conducted (IRB approved Number 27063) and the 1954 Helsinki declaration and its later amendments or comparable ethical standards.

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