Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9160-21
Intern Med 61: 2967-2972, 2022
http://internmed.jp

【 CASE REPORT 】

TAFRO Syndrome That Responded to Prednisolone-only Treatment: Evaluating Changes in IL-6

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Abstract:
Thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly (TAFRO) syndrome is a systemic inflammatory disorder characterized by the above-mentioned symptoms. Because of the similarity in phenotypes between TAFRO syndrome and decompensated liver cirrhosis, an accurate diagnosis is often difficult. We herein report a 62-year-old Japanese patient with TAFRO syndrome who was misdiagnosed with intractable ascites associated with liver cirrhosis. Improvement of symptoms after treatment with prednisolone was associated with interleukin-6 rather than C-reactive protein. The pathogenesis of TAFRO syndrome, which has similar clinical manifestations to liver cirrhosis, remains unclear, and our findings may help elucidate the concept of this condition.

Key words: Castleman's disease, glomeruloid hemangioma, IL-6, intractable ascites, TAFRO syndrome

(Intern Med 61: 2967-2972, 2022)
(DOI: 10.2169/internalmedicine.9160-21)

Introduction

Castleman's disease (CD), a rare lymphoproliferative disorder of unknown etiology characterized by systemic inflammation and multiple lymphadenopathies, was first described by Castleman in 1954 (1). CD comprises different variants with several common histopathological features: unicentric CD is localized to a single region of lymph nodes, whereas multicentric CD (MCD) manifests with systemic inflammatory symptoms, such as multiple regions of lymphadenopathy and organ insufficiency. MCD is further subdivided into human herpesvirus 8-associated MCD and human herpesvirus 8-negative/idiopathic MCD (iMCD). Regardless of the subtype, MCD is frequently associated with systemic symptoms, and elevated serum interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) are frequently reported to be responsible for some of its symptoms.

TAFRO syndrome, characterized by thrombocytopenia (T), anasarca (A), fever (F), reticulin fibrosis on bone marrow biopsy (R), and organomegaly (O), was first reported in 2010 (2); it is extremely rare and is categorized as a subtype of iMCD. Since its first report, many cases have been described worldwide, and guidelines, diagnostic criteria, and disease severity classification for its treatment were proposed in 2015. However, its detailed pathogenesis remains unclear, and these patients are often difficult to diagnose due to the involvement of multiple organs (3-5). Compared to unicentric CD or other subtypes of iMCD, its clinical course is particularly progressive; therefore, clinicians often experience difficulty treating patients with TAFRO syndrome (3). In some of these patients, immunosuppressive therapies, such as rituximab, tocilizumab, cyclosporine, and prednisolone, may be effective, while in others, they can be ineffective or even fatal (3, 6). A better understanding of the pathogenesis of these diseases will contribute to the establishment of the disease concept of TAFRO syndrome.

We herein report a 62-year-old Japanese patient with TA-

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Received: December 6, 2021; Accepted: January 19, 2022; Advance Publication by J-STAGE: February 26, 2022
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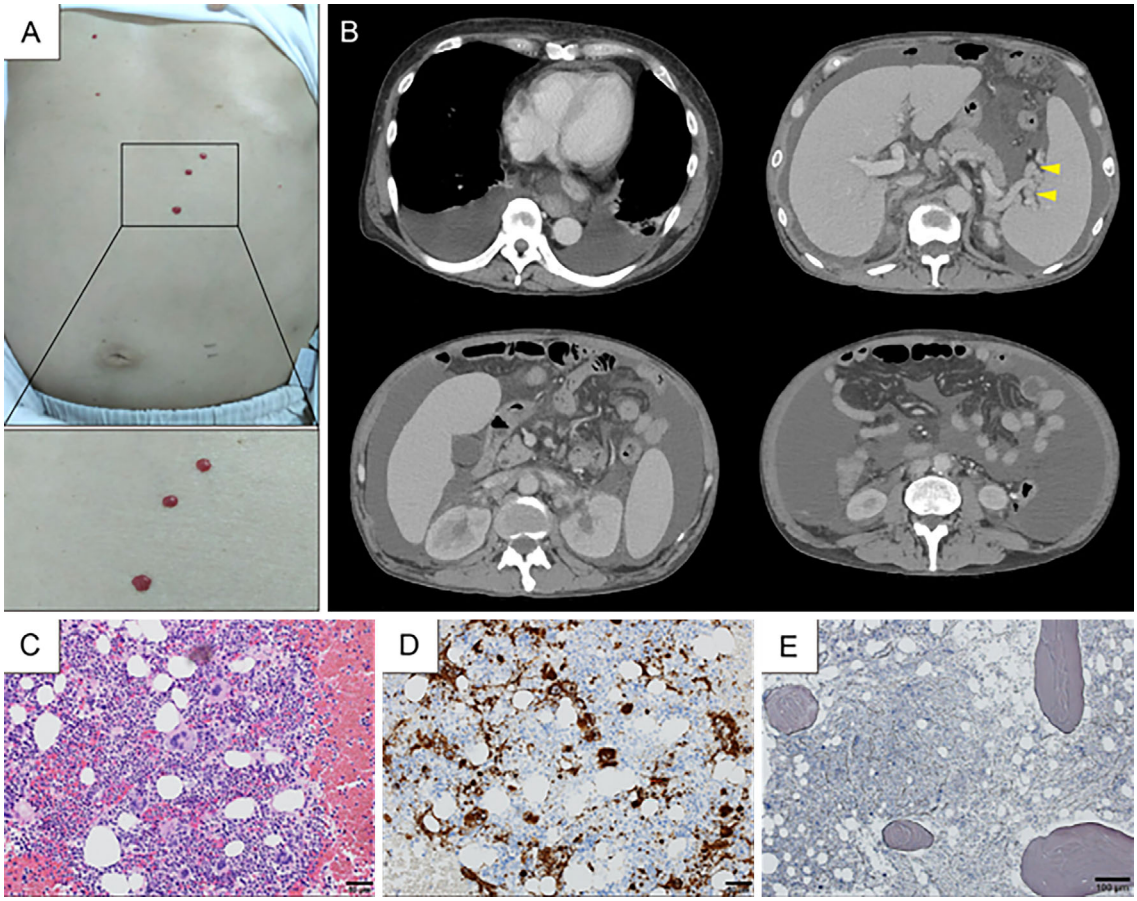

Figure 1. **Clinical, radiological, and pathological features of the patient. (A) Hemangioma of the trunk. (B) Computed tomography showing abnormal body fluid retention and lymphadenopathy at the splenic lymph nodes. Arrowheads represent the splenic lymph nodes. (C-E) Bone marrow histology revealed increased CD41-positive megakaryocytes and mild myelofibrosis (C: Hematoxylin and Eosin staining, ×400; D: CD41 staining, ×400; E: silver staining. ×200).**

FRO syndrome who was thought to have intractable ascites due to liver cirrhosis. Improvement of symptoms by treatment with prednisolone was associated with IL-6 rather than C-reactive protein (CRP).

Case Report

The patient was a 62-year-old Japanese man who was started on oral treatment for depression and temporal lobe epilepsy in X-6 (year) by his local doctor. He was also diagnosed with alcoholic liver disease in the same year but only advised to abstain from drinking. In January X, he developed a loss of appetite, abdominal bloating, and weight gain, with the appearance of hemangioma-like skin lesions on his trunk (Fig. 1A). He was diagnosed with alcoholic liver cirrhosis and hepatorenal syndrome by his local doctor due to the presence of thrombocytopenia, renal dysfunction, pleural effusion, ascites, splenomegaly, and a history of alcohol intake. He was admitted by the doctor from February to May X and treated with diuretics, albumin infusion, abdominal paracentesis, and cell-free and concentrated ascites reinfusion therapy (CART). However, since no improvement in his symptoms was observed, he was referred to our hospital in May X.

On a physical examination, he showed the following clinical features: blood pressure, 110/68 mmHg; heart rate, 67 beats/min; respiratory rate, 15 breaths/min; and body temperature, 36.3°C. He was alert and conscious, with a soft and distended abdomen and no pitting edema or signs of polyneuropathy. A laboratory examination (Table) revealed a white blood cell count of 6,600/μL, hemoglobin of 9.1 g/dL, mean corpuscular volume of 94.5 fL, platelet count of 81,000/μL, prothrombin time international normalized ratio of 1.17, fibrin degradation products, 29 mg/mL, total protein of 5.7 g/dL, albumin of 3.1 g/dL, total bilirubin of 0.4 mg/dL, aspartate aminotransferase of 41 IU/L, alanine transaminase of 18 IU/L, lactate dehydrogenase of 88 IU/L, alkaline phosphatase of 718 IU/L, γ-glutamyl transferase of 391 IU/L, blood urea nitrogen of 70 mg/dL, creatinine of 1.60 mg/dL, IgG of 777 mg/dL (normal range: 861-1,747), IgM of 49 mg/dL (33-183), IgA of 98 mg/dL (93-393), procalcitonin of 2.73 ng/mL, and CRP level of 6.58 mg/dL. Serum protein electrophoresis/immunofixation did not reveal any M-protein. Antinuclear, antineutrophil cytoplasmic, and antimitochondrial antibodies were negative. Chronic liver diseases, such as hepatitis B, hepatitis C, autoimmune hepatitis,

Table. Laboratory Data on Admission.

Biochemistry		**Peripheral blood**	
TP	5.7 g/dL	WBC	6,600 /μL
Albumin	3.1 g/dL	Neutrophil	81.2 %
T-Bil	0.4 mg/dL	Lymphocyte	13.5 %
D-Bil	0.2 mg/dL	Monocyte	4.7 %
AST	41 IU/L	Eosinophil	0.3 %
ALT	18 IU/L	Basophil	0.3 %
LDH	88 IU/L	RBC	307×10^4 /μL
ALP	718 IU/L	Hb	9.1 g/dL
γ-GTP	391 IU/L	Ht	29.0 %
BUN	70 mg/dL	MCV	94.5 fL
Cr	1.60 mg/dL	Ret%	2.10 %
UA	9.5 mg/L	Ret	50,200 /μL
Na	137 mEq/L	Plt	8.1×10^4 /μL
K	5.2 mEq/L	**Serology**	
Cl	109 mEq/L	RF	(-)
CRP	6.58 mg/dL	ANA	(-)
TSH	0.786 μIU/L	AMA-M2	(-)
FT4	1.20 ng/dL	Anti-SS-A/SS-B	(-)/(-)
IgA	98 mg/dL	MPO/PR3-ANCA	(-)/(-)
IgM	49 mg/dL	Anti-Tg/TPO	(-)/(-)
IgG	777 mg/dL	Anti-ds-DNA Ab	(-)
IgE	28 IU/dL	C3/C4	93/34 mg/dL
Ferritin	317.0 ng/dL	M protein	(-)
Cu	151 μg/dL	M2BPGi	1.34 C.O.I
Ceruloplasmin	37 mg/dL	Type IV collagen	273.0 ng/mL
Mg	2.66 mg/dL	**Viral markers**	
Zn	67 μg/dL	HBsAg	(-)
NH_3	92 μg/dL	Anti-HBc Ab	(-)
Vit B1	14 ng/mL	Anti-HCV Ab	(-)
Vit B12	362 pg/mL	IgM/IgG anti-CMV Ab	(-)/(+)
Folate	5.0 ng/mL	Human herpes virus 8	(-)
β-D-glucan	<6.0 pg/mL	**Tumor markers**	
Endotoxin	<2.0 pg/mL	AFP	1.2 ng/mL
IL-2R	1,893 U/mL	DCP	33 mAU/mL
VEGF	3,500 pg/mL	CEA	0.6 ng/mL
PCT	2.73 ng/mL	CA19-9	<2.0 U/mL
Coagulation		PSA	0.786 ng/mL
PT%	75 %	**Urinalysis**	
PT-INR	1.17	NAG	25.0 IU/L
APTT	53.6 s	β2MG	<50 μg/L
D-dimer	2.3 μg/mL	BJ protein	(-)
FDP	18.8 μg/dL	**Ascitic fluid**	
TAT	1.6 ng/mL	Color	Pale yellow
		Total protein	2.5 g/dL
		Alb	1.4 g/dL
		LDH	32 U/L
		Cell count	32 /μL

TP: total protein, T-Bil: total bilirubin, D-Bil: direct bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, BUN: blood urea nitrogen, Cr: creatinine, CRP: C-reactive protein, TSH: tyrosine-stimulating hormone, FT4: free T4 (thyroxine), IL-2R: interleukin 2 receptor, VEGF: vascular endothelial growth factor, PCT: procalcitonin, PT: prothrombin time, INR: international normalized ratio, APTT: activated partial thromboplastin time, FDP: fibrin/fibrinogen degradation products, TAT: thrombin-antithrombin complex, WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, MCV: mean corpuscular volume, Ret: reticulocyte, Plt: platelet count, RF: rheumatoid factor, ANA: antinuclear antibody, AMA: anti-mitochondria antibody, AMA-M2: anti-mitochondrial M2 antibody, M2BPGi: mac-2 binding protein glycosylation isomer, HB: hepatitis B, Ag: antigen, Ab: antibody, HCV: hepatitis C virus, CMV: cytomegalovirus, AFP: α-fetoprotein, DCP: des-γ-carboxy prothrombin, PSA: prostate specific antigen, NAG: N-acetyl-β-D-glucosaminidase, β2MG: β2 microglobulin, BJ: Bence Jones

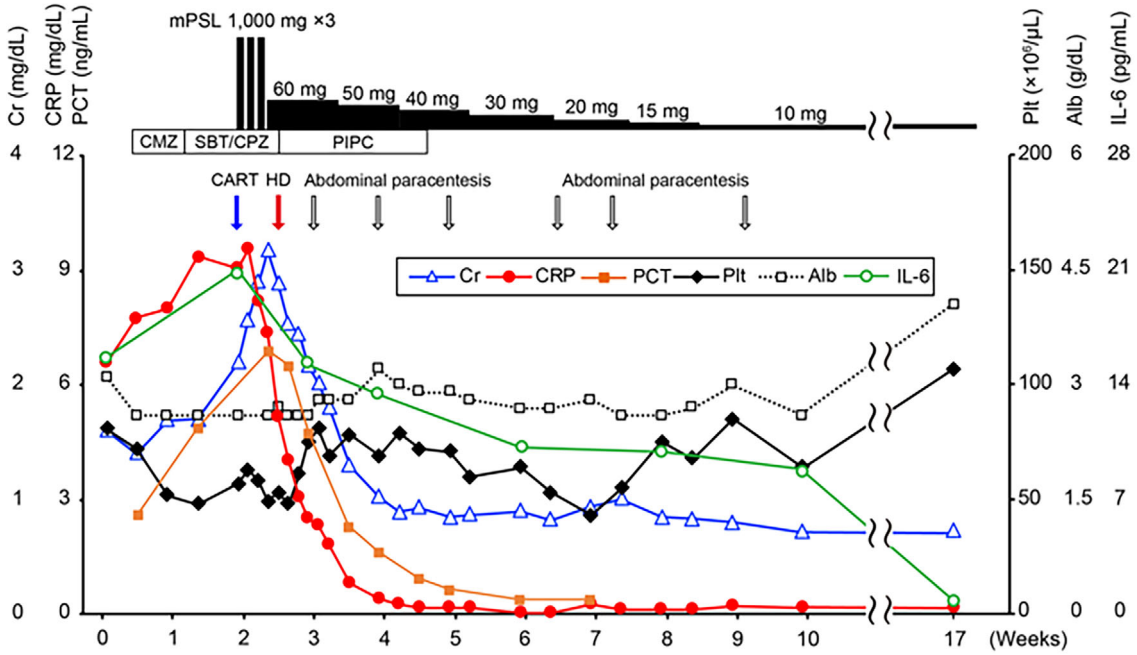

Figure 2. **Clinical course of the patient. Cr: creatinine, CRP: C-reactive protein, PCT: procalcitonin, mPSL: methylprednisolone, CMZ: cefmetazole, SBT/CPZ: sulbactam/cefoperazone, PIPC: piperacillin, CART: cell-free and concentrated ascites reinfusion therapy, HD: hemodialysis, Plt: platelet, Alb: albumin, IL-6: interleukin-6**

and primary biliary cholangitis, were excluded. Serum IL-6 was 14.7 pg/mL (reference range, 0-2.4), and VEGF was 3,500 pg/mL (reference range, 0-38.3). A urinalysis showed proteinuria of 0.1 g/gCr. Blood and ascites cultures were negative. The cytopathology of the ascites was negative.

Chest and abdominal computed tomography showed bilateral pleural effusion, ascites, and hepatosplenomegaly (Fig. 1B). Abdominal ultrasonography showed an enlarged liver and spleen (splenic length, 142 mm) with a smooth surface, and Doppler ultrasound did not detect any blood flow obstruction. An ascitic fluid analysis showed transdutative ascites (Table). To evaluate the pathological condition, we attempted to perform a percutaneous liver biopsy; however, this was difficult due to the high risk of bleeding and uncontrolled ascites. In addition, a transjugular liver biopsy was not feasible at our facility. Bone marrow histology revealed increased CD41-positive megakaryocytes and mild myelofibrosis (Fig. 1C-E). Gallium scintigraphy showed no findings other than a physiological accumulation. Cirrhosis from his drinking habit could have caused the thrombocytopenia, elevated FIB-4 index (7.40), and splenomegaly; however, alcoholic liver cirrhosis and hepatorenal syndrome were excluded using a blood test by the initial doctor in X-1 (year), which showed no liver and kidney dysfunction, and a family interview confirmed that he had abstained for over three years.

In summary, he had thrombocytopenia, pleural effusion, ascites, unexplained inflammatory response, organomegaly (hepatosplenomegaly), and renal dysfunction. He was finally diagnosed with TAFRO syndrome after carefully ruling out possible causative infections, cirrhosis, and malignant tumors. The severity at the diagnosis was moderate (pleural effusion/ascites, 2 points; thrombocytopenia, 1 point; inflammatory response, 1 point; estimated glomerular filtration rate decrease, 1 point; total, 6 points) (7).

A summary of the hospitalization progress is shown in Fig. 2. He had been treated with antibiotics since admission due to the positive serum procalcitonin value, but treatment was discontinued by day 34 following de-escalation after the diagnosis of TAFRO syndrome. He was administered steroids on day 14, namely intravenous methylprednisolone at 1,000 mg/day for 3 days, followed by oral prednisolone at 60 mg/day (gradually reduced by 5-10 mg every week and maintained at 10 mg/day). He developed uremia and underwent hemodialysis once on day 18. Subsequently, his symptoms and renal function improved. By day 25, despite maintaining CRP negativity, he developed a poor appetite, general fatigue, and repeated ascites retention and was treated with abdominal paracentesis and albumin infusion. He was discharged on day 74 when his symptoms were finally controlled, and sufficient prednisolone tapering was completed. No other immunosuppressive agents were administered during the hospitalization. On the final day of the observation (day 118), abdominal ultrasonography showed shrinkage of the spleen and no ascites (splenic length, 115 mm), and a laboratory examination showed improvement in the platelet count (127,000/μL) and serum albumin level (4.0 g/dL), whereas the cutaneous lesion did not show obvious changes during the observation period.

Discussion

Liver cirrhosis, especially the decompensated type, is often associated with anasarca (ascites, pleural effusion, or general edema), thrombocytopenia, splenomegaly, an immunocompromised state (cirrhosis-associated immune dysfunction), and renal dysfunction due to hepatorenal syndrome (8, 9). The diagnostic criteria for TAFRO syndrome include the following 3 major criteria: anasarca (pleural effusion, ascites, or general edema), thrombocytopenia (≤ 100,000/μL), and systemic inflammation (fever above 37.5°C and/or serum CRP ≥2 mg/dL); and the following 4 minor criteria: MCD-like findings on a lymph node biopsy, reticulin myelofibrosis, and/or increased megakaryocytes in bone marrow, organomegaly, and renal insufficiency (4). The presence of all three major and at least two minor criteria is necessary for the diagnosis of TAFRO syndrome.

As mentioned above, decompensated cirrhosis and TAFRO syndrome have similar phenotypes, which can make an accurate diagnosis difficult. In this report, the patient had a history of alcohol consumption, was diagnosed with intractable ascites associated with liver cirrhosis, and underwent repeated abdominal paracentesis and CART. In a previous study, CART and hemodialysis were reported to be partially effective for TAFRO syndrome, and more than 80% (16/19) of patients with TAFRO syndrome required hemodialysis within 3 weeks of admission (10). Even if TAFRO syndrome has not been diagnosed, CART and hemodialysis may improve the symptoms. We should be mindful of misdiagnosing TAFRO syndrome as liver cirrhosis.

The important points that our clinical team emphasized in distinguishing liver cirrhosis were as follows: (i) no chronic liver disease that clearly causes liver cirrhosis, (ii) the presence of a fever and high inflammatory response that cannot be explained by liver disease, (iii) serum lactate dehydrogenase level has not increased (4), and (iv) a sufficient therapeutic effect has not been obtained by treatment for liver cirrhosis.

Consistent with a previous report that patients with TAFRO syndrome have a more aggressive clinical course with poor prognoses than other types of iMCD (11), our patient showed a rapid deterioration of symptoms, including ascites and renal dysfunction. The severity of TAFRO syndrome at the diagnosis was moderate (7), and according to a recent study for predicting the prognosis in patients with TAFRO syndrome, our patient was classified into the intermediate-risk group (age ≥60 years old) (12). After commencing treatment with prednisolone, a good response was obtained, and the CRP level markedly decreased to the normal range; however, general fatigue, poor appetite, and repeated ascites retention persisted. Interestingly, the serum IL-6 levels remained high even when the CRP level normalized. We considered using tocilizumab, an IL-6 antibody; however, we decided to follow up with continued PSL monotherapy to avoid over-immunosuppression, which can result in miserable outcomes (13). Thereafter, the patient's appetite improved with a decrease in the IL-6 level. IL-6 affects the appetite and eating behavior (14); therefore, serum IL-6 might be a better indicator of appetite in TAFRO syndrome than CRP.

Although the pathogenesis of TAFRO syndrome is not well understood, excessive activation of inflammatory pathways and pro-inflammatory cytokines, such as IL-6 and VEGF, is considered to result in this histopathological change. The increased expression of VEGF and its receptor Fms-like tyrosine kinase 1 is considered to be one of the causes of glomeruloid hemangioma (15), so it is not specific to TAFRO syndrome and may appear in diseases with high VEGF levels. Similar to several reports, glomeruloid hemangioma on the patient's trunk appeared at the same time as the onset of symptoms in this study (16-18). Given that the lesion appeared with the onset of the disease, it is important to recognize this lesion as an early sign of TAFRO syndrome. Unfortunately, since the observation period was relatively short at roughly three months in this report, the relationship between the long-term changes in VEGF levels and hemangioma should be explored in greater detail. Glomeruloid hemangiomas appear as small erythematous papules on the forehead and trunk and can easily be overlooked or misdiagnosed as cherry (senile) hemangiomas (16-18). A careful physical examination is thus required to detect these lesions.

Conclusion

We encountered a case of TAFRO syndrome that presented with similar manifestations to liver cirrhosis. Our findings are important in recognizing the concept of TAFRO syndrome and understanding its pathogenesis.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

The authors thank the patient and his family for their involvement in this study.

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