

TAFRO syndrome with a rapid fatal course despite corticosteroid and tocilizumab therapy

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Abstract TAFRO syndrome is a recently proposed subtype of multicentric Castleman's disease. Some patients have a refractory and aggressively fatal course. Here we report a case of TAFRO syndrome with a rapid fatal course despite corticosteroid and tocilizumab therapy. A 68-year-old Japanese male suffered from abdominal pain, watery diarrhea, fever, and general fatigue. On the 12th hospital day, severe thrombocytopenia, anasarca, and renal failure developed. The histopathological findings of lymph node biopsy were indicative of MCD. Although corticosteroid and tocilizumab were administered, the patient died of multiple organ failure on the 30th hospital day. Autopsy findings revealed that inflammation due to TAFRO syndrome was suppressed but multiple infarctions progressed and became the direct cause of death. Our case suggested that TAFRO syndrome should not be excluded even if clinical findings are insufficient for the diagnostic criteria at the onset and that in patients with TAFRO syndrome who are at a high risk of thrombosis, multiple infarctions may become a direct cause of death.

Keywords TAFRO syndrome · Castleman's disease · Tocilizumab · Multiple infarctions · Abdominal pain

Introduction

Castleman's disease (CD) is a rare form of lymphoproliferative disorder that is diagnosed by pathological findings. Histologically, the affected lymph tissues are classified as hyaline-vascular (HV) type, plasma-cell (PC) type, and a mixed-type variant of the two [1]. High interleukin (IL)-6 levels are closely related to this disease. In addition, CD is divided into two clinical subtypes: unicentric variant CD and systematic or multicentric variant CD (MCD) [2].

TAFRO syndrome is a recently proposed subtype of MCD [3–5], which is characterized by various symptoms, namely thrombocytopenia; anasarca, including pleural effusion and ascites; fever; reticulin fibrosis (myelofibrosis); renal insufficiency; and organomegaly, including hepatosplenomegaly and lymphadenopathy. Lymph node histology in most patients reveals mixed-type CD, with few patients having HV-type MCD histology. However, compared with patients with MCD, patients with TAFRO syndrome present with atypical findings such as normal immunoglobulin levels, thrombocytopenia, relatively small lymphadenopathy, marked pleural effusion, ascites, and edema, in addition to an acute or subacute onset and clinical course [5]. These clinicopathologic discrepancies suggested that TAFRO syndrome is a distinct new entity rather than a subtype of MCD [6]. Similar to patients with MCD, some patients with TAFRO syndrome are sensitive to corticosteroids and anti-IL-6 receptor antibody (tocilizumab, TCZ) [6–8]; however, other patients are refractory to these treatments and exhibit an aggressively fatal course [9–13].

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Here we report a case of a patient with TAFRO syndrome who died of multiple organ failure on the 30th hospital day despite prednisolone and TCZ treatment.

Clinical history

A 68-year-old Japanese male who was noted to have hypertension, diabetes mellitus, and dyslipidemia by periodic medical examinations visited the emergency department of our hospital for upper abdominal pain. Treatment for peptic ulcer did not resolve his symptoms. Upper gastrointestinal endoscopy and abdominal ultrasonography were performed; however, only mild splenomegaly was observed and there were no signs of dilatation or increased wall thickness in the intestinal tract as well as ascites. Whole-body enhanced computed tomography (CT) showed no findings regarding the cause of abdominal pain, except for mild cervical lymphadenopathy. Abdominal pain improved soon after the initiation of antibiotic therapy; however, watery diarrhea, fever, and general fatigue developed and were exacerbated. On January 2013, the patient was emergently hospitalized.

On admission, his height and weight were 167.6 cm and 81.7 kg (body mass index, 28.9), respectively. His vital signs were as follows: temperature, 37.5 °C; heart rate, 104 bpm; blood pressure, 194/112 mmHg; and respiratory rate, 20–24 breaths/min. His oxygen saturation was 100% while breathing ambient air. Breathing rate and heart beats were normal. His abdomen was soft but distended due to obesity. Liver and spleen were not palpable. Bowel sounds were normal. His superficial lymph nodes were not palpable. Lower extremities were not edematous. There were no skin lesions. No particular abnormalities were detected by neurological examination.

The laboratory findings were showed in Table 1. Lower intestinal endoscopy did not reveal any finding suggestive of pseudomembranous enterocolitis. Despite broad spectrum antibiotic therapy, fever and elevated C-reactive protein levels did not improve. Exacerbation of abdominal distention, general edema, and oliguria were observed. Hypoalbuminemia and renal dysfunction gradually deteriorated. Positron emission tomography (PET)-CT revealed abnormal accumulation in the bilateral cervical and supraclavicular lymph nodes and left subclavian lymph nodes (Fig. 1). Whole-body enhanced CT performed on the 11th hospital day revealed massive pleural effusion and ascites. Considering the possibility of sarcoidosis, malignant lymphoma, or vasculitis syndrome, 1 mg/kg of prednisolone was initiated after cervical lymph node biopsy.

Lymph node biopsy showed blurred follicles with atrophic germinal centers. The peripheries of the follicles were surrounded by small lymphocytes that were tightly layered in a concentric manner, resulting in an onion-skin appearance (Fig. 2a, b). The inter-follicular area had increased plasma cell proliferation and vascularity, partially radiating from the germinal center (Fig. 2c, d). These histopathological findings

were indicative of mixed-type CD. CD21 was positive for germinal center, but rarely stained inter-follicular area, excluding angioimmunoblastic T-cell lymphoma.

Because acute renal failure, pulmonary edema, and hyperkalemia were observed, emergency dialysis was started on the 15th hospital day. The laboratory data at that time were as follows: white blood cell count, $24.6 \times 10^9/L$; hemoglobin, 10.1 g/dL; platelet count, $20.0 \times 10^9/L$; total protein, 5.0 g/dL; albumin, 1.5 g/dL; and serum creatinine, 5.48 mg/dL. Based on the pathological diagnosis of mixed-type CD, 8 mg/kg of TCZ was administered on the 22nd hospital day. However, the clinical status of the patient did not improve, and he died of heart and respiratory failure on the 30th hospital day.

Materials and methods

Autopsy was performed with the consent of his family. Hematoxylin and eosin staining sections and immunohistochemistry sections were prepared from formalin-fixed, paraffin-embedded tissue. Commercially available antibodies were used for immunohistochemistry.

Results

Anasarca was prominent with increased body weight (101.2 kg). Pleural effusion (right lung, 600 mL; left lung, 1000 mL), ascites (3000 mL), and pericardial effusion (15 mL) were found with mild fibrinous serositis. Multiple lymphadenopathies (diameter, 0.5–3.0 cm) in cervical, mediastinal, para-aortic abdominal, and mesenteric lymph nodes were confirmed. Microscopic findings revealed the disappearance of lymphoid follicles and significant decrease in the number of plasma cells compared with the lymph node biopsy specimen (Fig. 3a–c). The bone marrow was hyperplastic with increased megakaryocytes and reticulin fibers (Fig. 3d, e). Infarctions of the kidney, liver, spleen, and digestive tract were found without finding suggesting vasculitis (Fig. 3f–j). On autopsy, it was identified that renal and hepatic infarctions due to circulation failure were the direct causes of death.

Discussion

At the time of admission, our case did not meet the diagnostic criteria for TAFRO syndrome proposed by Masaki et al. in 2015 [5]. However, severe thrombocytopenia, anasarca, and renal failure developed on the 12th hospital day. The histopathological findings of lymph node biopsy were indicative of MCD. The autopsy finally revealed myelofibrosis. Our case suggested that TAFRO syndrome should not be excluded even if clinical findings are insufficient for the diagnostic criteria at

Table 1 Laboratory data on admission

Complete blood cell count		Blood chemistry		Serological test	
White blood cell	10.2 × 10 ⁹ /L	Total protein	5.8 g/dl	C-reactive protein	24.92 mg/dl
Neutrophil	79.6%	Albumin	2.6 g/dl	IgG	958 mg/dl
Lymphocyte	12.3%	GOT	27 U/l	IgA	207 mg/dl
Monocyte	7.2%	GPT	20 U/l	IgM	31 mg/dl
Basophil	0.1%	LDH	157 U/L	IgG4	<3.0 mg/dl
Eosinophil	0.8%	ALP	545 U/L	M-protein	(-)
Hemoglobin	12.9 g/dl	Total bilirubin	0.9 mg/dl	C3	69 mg/dl
Hematocrit	40.1%	Blood urea nitrogen	22 mg/dl	C4	16 mg/dl
Platelet count	186.0 × 10 ⁹ /L	Creatinine	1.07 mg/ml	Antinuclear antibody	(-)
		Ferritin	346 ng/ml	Rheumatoid factor	<5.0 IU/ml
		ACE	5.1 U/L	PR3-ANCA	<1.0 U/ml
Coagulation test		Lysozyme	16.3 µg/ml	MPO-ANCA	<1.0 U/ml
PT	14.0 s	IL-6	80.3 pg/ml	Soluble IL-2 receptor	1020 U/ml
PT-INR	1.25	HbA1c	6.8%	Hepatitis B surface antigen	(-)
APTT	44.3 s	VEGF	127 pg/ml	Hepatitis C virus antibody	(-)
Fibrinogen	519 mg/dl			HIV antibody	(-)
D-dimer	11.1 µg/ml				
Infection-associated test					
Gaffky scale		0	Aspergillus antigen	(-)	
TB-specific IFN-γ release assay		Negative	Candida antigen	(-)	
PCR assay of TB/MAC DNA		Negative	<i>Cryptococcus neoformans</i> antigen	(-)	
β-D-glucan		<4.0 pg/ml	Blood culture (2 sets)	Negative	

PT-INR international normalized ratio, *APTT* activated partial thromboplastin, *ACE* angiotensin-converting enzyme, *VEGF* vascular endothelial growth factor, *ANCA* anti-neutrophil cytoplasmic antibody, *HIV* human immunodeficiency virus, *TB* mycobacterium tuberculosis, *IFN* interferon, *PCR* polymerase chain reaction analysis, *MAC* mycobacterium avium complex

the admission. Because myelofibrosis is a relatively specific finding of TAFRO syndrome, and bone marrow biopsy should always be performed.

A review of 12 patients with TAFRO syndrome treated with TCZ revealed that all patients, except one, were alive despite short observation periods [7]. Although our patient

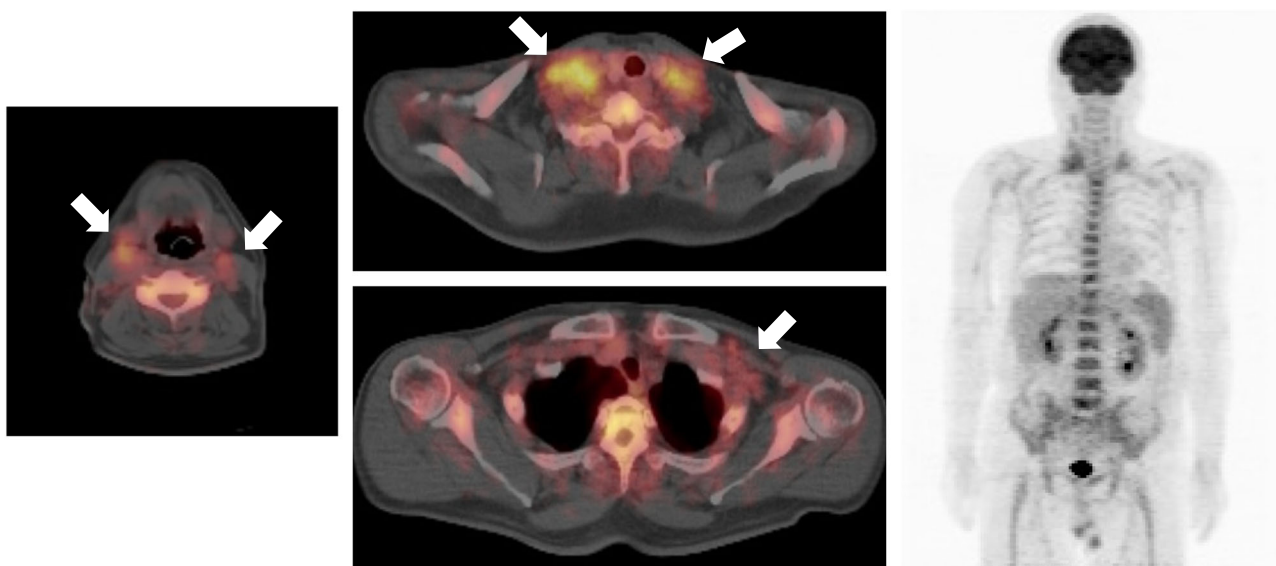
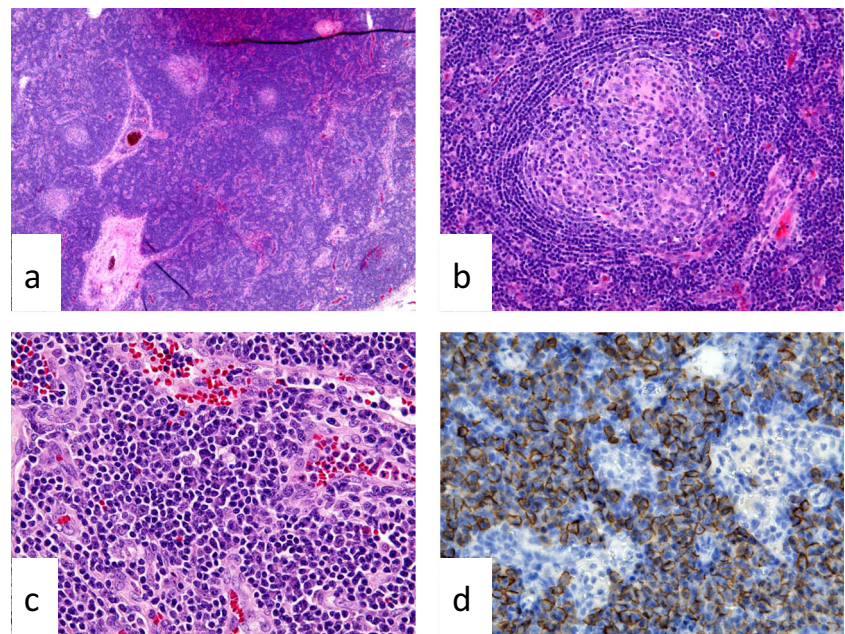


Fig. 1 Positron emission tomography-computed tomography showing abnormal accumulations in bilateral cervical and supraclavicular lymph nodes and left subclavian lymph nodes (arrows)

Fig. 2 Pathological findings of the cervical lymph node biopsy. **a** Lymph node biopsy showing blurred follicles with atrophic germinal center (hematoxylin and eosin staining, $\times 100$). **b** Peripheries of the follicles are surrounded by small lymphocytes that are tightly layered in a concentric manner, resulting in an onion-skin appearance ($\times 400$). **c**, **d** Inter-follicular area with increased plasma cells and hyper-vascularity (**c**, $\times 400$; **d**, CD138 staining, $\times 400$)



died of multiple organ failure despite TCZ treatment, autopsy findings suggested that inflammation due to TAFRO syndrome was suppressed by corticosteroid and TCZ treatment. The direct cause of his death was considered renal and hepatic infarction due to circulation failure. Tadokoro et al. reported a case of a patient with TAFRO syndrome who died of multiple organ failure 2 weeks after the initiation of TCZ therapy. Autopsy revealed infarction of the brain and ascending colon, suggesting that TAFRO caused excessive vascular permeability, leading to severe hypovolemia and subsequent organ failure and death [12]. This patient had a 4-year history of hypertension and dyslipidemia. Our patient also had risk factors of arteriosclerosis, such as hypertension, diabetes mellitus, dyslipidemia, and a long history of smoking. In patients with TAFRO syndrome who are at a high risk of thrombosis, multiple infarctions may become a direct cause of death. In a case

report, Fujiwara et al. suggested that hypercytokinemia in TAFRO syndrome inhibits a disintegrin and a metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity, thereby inducing thrombotic microangiopathy [7]. In our case, because inflammation due to TAFRO syndrome had improved at the time of autopsy, it could not be known whether hypercytokinemia in TAFRO syndrome influenced his multiple infarctions.

Another notable finding in the present case is abdominal pain as the initial symptom. Extensive evaluation by enhanced CT, abdominal ultrasonography, and upper gastrointestinal endoscopy did not reveal any findings suggestive of gastrointestinal ulceration, ischemic bowel disease, or ascites. In a review of 25 patients with TAFRO syndrome, eight patients were reported to have abdominal pain [14]. Additionally, Hiramatsu et al. described several patients with TAFRO syndrome who had

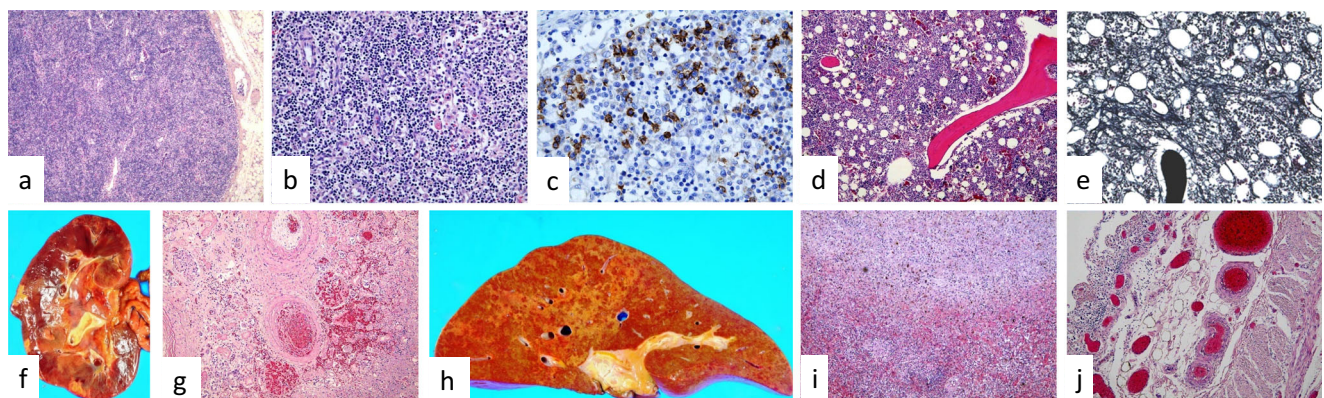


Fig. 3 **a–c** Pathological findings of autopsy. Disappearance of lymphoid follicle structures and significant decrease in the number of plasma cells compared with the lymph node biopsy specimen (**a**, $\times 100$; **b**, $\times 400$; **c**, CD138 staining, $\times 400$). **d** and **e** Bone marrow is hyperplastic with

increased megakaryocytes and reticulin fibers (**d**, $\times 100$; **e**, silver impregnation staining). **f–j**. Infarctions of the kidney (**f**; **g**, $\times 100$), liver (**h**), spleen (**i**, $\times 100$), and digestive tract (**j**, $\times 100$) were found

abdominal pain as the initial symptom, with a few ascites [15]. Thus, abdominal pain may be a symptom to be noted as the initial symptom of TAFRO syndrome, even if there are few ascites.

In conclusion, we report a case of TAFRO syndrome with a rapid fatal course despite corticosteroid and TCZ treatment. Autopsy findings revealed that inflammation due to TAFRO syndrome was suppressed with these therapeutics; however, multiple infarctions due to circulation failure become the direct cause of death. Our case suggested that TAFRO syndrome should not be excluded even if clinical findings are insufficient for the diagnostic criteria at the onset and that in patients with TAFRO syndrome who are at a high risk of thrombosis, multiple infarctions may become a direct cause of death.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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