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Case report

Two patients with TAFRO syndrome exhibiting strikingly similar anterior mediastinal lesions with predominantly fat attenuation on chest computed tomography

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ABSTRACT

We herein report on two middle-aged men with TAFRO (thrombocytopenia, anasarca, fever, reticulin fibrosis or renal failure, and organomegaly) syndrome, a unique clinicopathological variant of multicentric Castleman's disease recently proposed in Japan. Strikingly similar anterior mediastinal fat swellings with soft tissue density were observed in the patients on chest computed tomography. In TAFRO syndrome, bilateral pleural effusion and slight lymph node swelling are common in the thoracic region; however, anterior mediastinal lesions have not been previously observed. Although the mechanisms of anterior mediastinal lesions have not been defined, these lesions seem to have a close relationship with TAFRO syndrome.

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1. Introduction

TAFRO (thrombocytopenia, anasarca, fever, reticulin fibrosis or renal failure, and organomegaly) syndrome is considered as a clinicopathological variant of multicentric Castleman's disease (MCD) that has been identified in Japan [1]. Recently, newly proposed diagnostic criteria of TAFRO syndrome were published [2]. In the thoracic part, previous reports have shown that affected patients usually had bilateral pleural effusion and slight lymph node swelling. However, mediastinal lesions in patients with TAFRO syndrome have not yet been described [1–11].

We herein report two cases of TAFRO syndrome patients who showed characteristic anterior mediastinal lesions on chest computed tomography (CT).

2. Case presentation

2.1. *Case 1*

A 46-year-old Japanese man who smoked came to our hospital with general fatigue, dyspnea, and chest discomfort. He had no remarkable medical history. Physical examination at the initial visit showed a height of 176.0 cm, body weight of 79.8 kg, arterial blood pressure of 106/58 mmHg, pulse rate of 96/min, respiratory rate of 24/min, and body temperature of 38.0 °C. Breath sounds were low in the bilateral lower lungs. Pitting edema was present in the lower extremities. No superficial lymphadenopathy was observed. His laboratory examination findings are shown in Table 1. He had a slightly increased white blood cell count, thrombocytopenia, elevation of C-reactive protein (CRP) levels, slight renal dysfunction, liver dysfunction, hypoalbuminemia, and elevated d-dimer levels. Although his antinuclear antibodies were 80x, the results of the tests for other autoantibodies were negative. The results of the tests for the antibodies of human immunodeficiency virus (HIV), human T-lymphotrophic virus type 1 (HTLV-1), human herpes virus type 8 (HHV-8), and Histoplasma were all negative. The serum immunoglobulin levels were normal. Soluble interleukin-2 receptor (sIL-2R), IL-6, and vascular endothelial growth factor (VEGF) values were high. A chest X-ray on admission showed bilateral pleural effusion and enlargement of the mediastinal shadow (Fig. 1A). Chest and abdominal CT revealed bilateral pleural effusion, hepatosplenomegaly, slight mediastinal lymph node swelling, and anterior mediastinal fat swelling with soft tissue density distributed in a patchy fashion and vascular proliferation (Fig. 1B and C). T1-weighted fat-suppressed magnetic resonance (MR) imaging of the thorax showed anterior mediastinal lesion mainly with soft tissue intensity (Fig. 1D). Although we started the patient on a regimen of antibiotics, he became increasingly ill. Biopsy of the anterior mediastinal lesions was performed using a thoracoscope on day 8 of hospitalization. The biopsy

Table 1 – Laboratory data of the two patients at the initial hospital visit.

Laboratory data								
	Case 1	Case 2			Case1	Case 2		
WBC	9000	39730	/μL	CRP	23.21	22.75	mg/dL	
Net	78.6	95	%	IgG	1577	1104	mg/dL	
Mon	9.9	5	%	IgA	354	196	mg/dL	
Eos	0.2	0	%	IgM	47	243	mg/dL	
Baso	0.2	0	%	Anti-nuclear antibody	80	40		
Lym	11.1	0	%	Ferritin (<280)	467	735	ng/mL	
RBC	438×10^4	444×10^4	/μL	EBV VCA IgM	<10	<10		EBV: Epstein-Barr virus
Hb	14.5	12.4	g/dL	EBV VCA IgG	80	40		VCA: viral capsid antigen antibody
Ht	42.9	35.5	%	EBV EBNA	20	40		EBNA: EBV nuclear antigen
Plt	8.4×10^4	4.3×10^4	/μL	HIV antibody	(–)	(–)		HIV: human immunodeficiency virus
TP	6.1	5.7	g/dL	HTLV1 antibody	(–)	(–)		HTLV-1: human T-cell leukemia virus-1
ALB	2.5	2.7	g/dL	HHV-8 antibody	(–)	(–)		HHV-8: human herpesvirus-8
UN	12.9	26	mg/dL	Histoplasma antibody	(–)	Not done		
Cre	1.21	1.43	mg/dL					
Na	137	139	mmol/L	Soluble IL-2R (<421)	1735	1896	U/mL	IL-2R: interleukin-2 receptor
K	4.5	3.8	mmol/L	IL-6 (<2.41)	32.6	49.7	pg/mL	IL-6: interleukin-6
Cl	108	104	mmol/L	VEGF(plasma) (<38.3)	86.1	224	pg/mL	VEGF: vascular endothelial growth factor
AST	18	37	IU/L					
ALT	18	13	IU/L	**Urinalysis**				
γ-GTP	133	67	IU/L	PH	5.5	5.0		
T-bil	1.18	4.07	mg/dL	SG	1.019	1.015		
ALP	497	616	IU/L	Protein	+	+		
LDH (<230)	185	369	IU/L	Glucose	–	–		
				Occult blood	–	+		
PT	14.1	15.9	sec					
APTT	30.2	64.2	sec					
FIBG	695	482.5	mg/dL					
FDP-DD	5.9	42.8	μg/mL					

specimen of the patient showed fat necrosis and irregular fibrosis with lymphoplasmacytic infiltration on hematoxylin and eosin (H&E) staining (Fig. 1E). In addition, the sample of the mediastinal lymphatic tissue was compatible with mixed-type MCD. The immunohistochemical examination of the specimens showed mixed infiltration by cluster of differentiation (CD)20+, CD3+, and CD138+ cells and no expression of the latency-associated nuclear antigen-1 (LANA-1). Furthermore, the bone marrow specimen of the patient revealed fine reticulin fibrosis on H&E staining. Pulse steroid therapy for 3 days with 1000 mg of methyl-prednisolone (PSL) daily was not effective in treating the patient; therefore, plasma exchange therapy was performed. This therapy reduced the levels of CRP and icterus, but the hepatic insufficiency, thrombocytopenia, and anasarca worsened. On day 15 of hospitalization, his symptoms and laboratory results met the diagnostic criteria for TAFRO syndrome [2]. Thus, we diagnosed the patient with TAFRO syndrome and restarted pulse therapy with methyl-PSL. Resuming steroid therapy after plasma exchange was effective, and the patient began to gradually recover. He received 60 mg of oral PSL for 4 weeks after pulse therapy. The anasarca, pleural effusion, ascites, fever, and anterior mediastinal mass showed improvements, and the CRP levels decreased to a normal range. After a reduction in the PSL dose by 5 mg per week, the bilateral pleural effusions completely disappeared, and the anterior mediastinal mass was significantly decreased on a chest CT (Fig. 1F). Accordingly, the patient was discharged from our hospital after 83 days of hospitalization. He is now in remission with a small maintenance dosage of PSL.

2.2. *Case 2*

A 43-year-old Japanese man who smoked presented at our hospital with general fatigue, fever, and anasarca. He had no remarkable medical history. Physical examination at the initial visit showed a height of 172.0 cm, body weight of 85.0 kg, arterial blood pressure of 152/96 mmHg, pulse rate of 116/min, respiratory rate of 40/min, and body temperature of 38.6 °C. Breath sounds were low in the bilateral lower lungs. Pitting edema was present in the lower extremities. Superficial lymphadenopathies were found in the neck, submandibular, and axillary regions. His laboratory examination findings are shown in Table 1. He had an increased white blood cell count, thrombocytopenia, hypoalbuminemia, renal dysfunction, liver dysfunction, elevation of CRP, and elevated d-dimer. Although his antinuclear antibodies were 40x, the other autoantibodies were absent. Antibodies of HIV, HTLV-1, and HHV-8 were all negative. The serum immunoglobulin

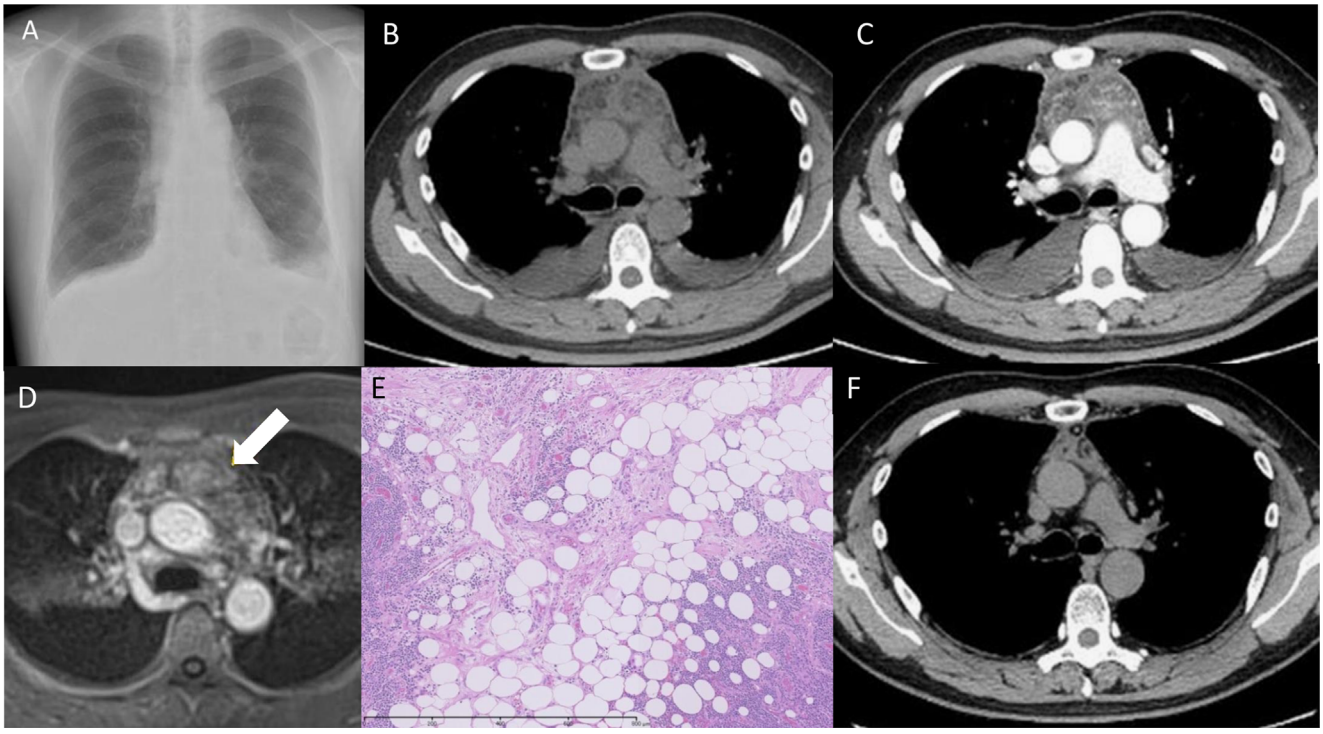

Fig. 1 – A 46-year-old man (case 1). A chest radiograph (A) and noncontrast computed tomography (CT) (B) at the initial visit revealed bilateral pleural effusions and anterior mediastinal fat swelling with soft tissue density distributed in a patchy fashion. The anterior mediastinal lesion was inhomogeneously enhanced on contrast-enhanced CT (C). T1-weighted fat-suppressed magnetic resonance (MR) imaging of the thorax showed anterior mediastinal lesion mainly with soft tissue intensity (white arrow) (D). The mediastinal biopsy specimen obtained by thoracoscopy showed irregular fibrosis with lymphoplasmacytic infiltration on hematoxylin and eosin (H&E) staining (E). Scale bar = 800 μm. After therapy, his bilateral pleural effusions completely disappeared, and the anterior mediastinal lesion was significantly decreased on noncontrast CT (F).

levels were almost normal. The sIL-2R, IL-6, and VEGF values were high. A chest X-ray on admission showed bilateral pleural effusion and enlargement of the mediastinal shadow (Fig. 2A). Chest and abdominal CT performed at the time of admission revealed bilateral pleural effusion and ascites, hepatosplenomegaly, systemic lymphadenopathy of less than 15 mm in diameter, and an anterior mediastinal lesion predominantly with fat attenuation (Fig. 2B). An axillary lymph node specimen of the patient obtained by surgical biopsy on day 5 of hospitalization showed atrophic follicles and expanding interfollicular regions on H&E staining (Fig. 2C). In these interfollicular regions, endothelial venules and plasmacytic infiltration were conspicuous on H&E staining (Fig. 2C). However, the immunohistochemistry demonstrated no expression of the LANA-1 in the lesion. These findings were compatible with plasma cell type MCD. Thus, we diagnosed the patient with TAFRO syndrome based on the diagnostic criteria [2].

Neither antibiotic therapy nor pulse therapy with methyl-PSL was effective; only plasma exchange therapy was slightly effective. Thus, plasma exchange therapy was performed a total of 35 times as treatment. Although the size of the anterior mediastinal lesion significantly decreased on chest CT after therapy (Fig. 2D), the bilateral pleural effusion remained, and he died of multiple organ failure after 155 days of hospitalization.

3. Discussion

We herein reported on two middle-aged men diagnosed with TAFRO syndrome who showed anterior mediastinal lesions mainly with fat attenuation on chest CT. Of note, the anterior mediastinal lesions in the patients revealed strikingly similar clinico-radiological features. Although we tried to obtain biopsy specimens of the anterior mediastinal lesions, we were unable to perform biopsy on patient 2 because of severe general condition.

The normal contents of the anterior mediastinum include the thymus, lymph node, adipose tissue, nerves, vessels, and occasionally downward extension of the thyroid from the neck; therefore, anterior mediastinal masses generally arise from these structures [12,13]. Although typical thoracic Castleman's disease usually occurs in the mediastinum and hilum and manifests as a rounded solitary mediastinal or hilar mass with soft-tissue attenuation on CT [12,14], the anterior mediastinal mass-like lesions in the present two patients showed predominantly fat attenuation. It is reported that anterior mediastinal masses with fat attenuation include lipoma, liposarcoma, mediastinal lipomatosis, hernia, thymolipoma, and teratoma [12,13]. However, the anterior mediastinal lesions in the present two cases did not seem to conform closely to any of these conditions. Although the cause was not identified, we believe that the lesions were the inflammation and/or immune reaction of mediastinal fat and

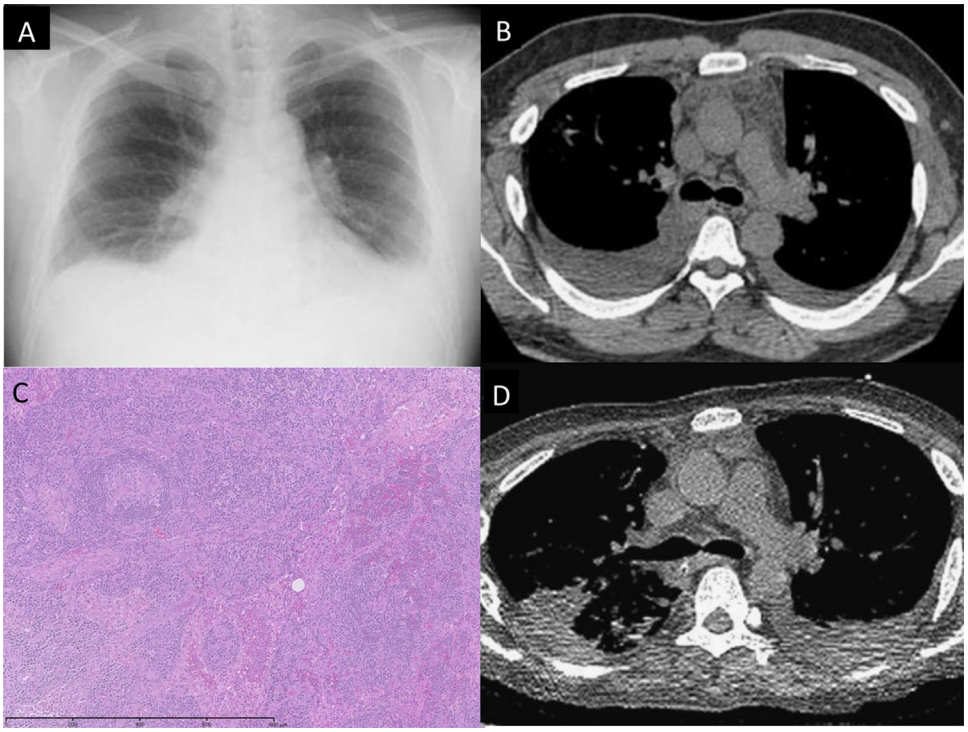

Fig. 2 – A 43-year-old man (case 2). A chest radiograph (A) and computed tomography (CT) (B) at the initial visit revealed bilateral pleural effusions, and anterior mediastinal lesion with predominantly fat attenuation and slight mediastinal lymph node swelling were observed on a noncontrast CT. An axillary lymph node biopsy specimen showed atrophic follicles and expanding interfollicular regions on hematoxylin and eosin (H&E) staining (C). In the interfollicular regions, endothelial venules and plasmacytic infiltration were conspicuous. Scale bar=800 μm. After therapy, his bilateral pleural effusions remained, but the anterior mediastinal lesion was significantly improved on noncontrast CT (D).

soft tissues induced by TAFRO syndrome based on the radiological and pathological findings.

Recently, an interesting report described that patients with multisystem inflammatory illness such as Behcet's disease had significantly greater attenuation of anterior mediastinal fat than normal subjects on chest CT [15]. The chest CT findings described in the report are comparable with those of our cases, and were attributed to either inflammatory neovascularization or minimal thymic hyperplasia induced by Behcet's disease. Multilocular thymic cysts are acquired lesions of the thymus and are most likely caused by an inflammatory process such as Sjögren's syndrome and systemic lupus erythematosus [16], however, the radiological features are different from the lesions of our patients. We therefore speculate that the mediastinal lesions of the present two patients might be inflammation of the thymus and/or peripheral adipose tissues caused by systemic inflammatory responses of TAFRO syndrome. Although we could not definitively establish relationships between TAFRO syndrome and the anterior mediastinal lesions in these two cases, we think that these mediastinal lesions might play a causal role in TAFRO syndrome.

We presented two patients with TAFRO syndrome who showed characteristic anterior mediastinal lesions. To our knowledge, this is the first report of anterior mediastinal lesions in patients with TAFRO syndrome. Further studies are needed in order to establish causal relationships between anterior mediastinal lesions and TAFRO syndrome.

Conflict of interest

The authors have no conflicts of interest.

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