Case Study

Complete Resolution of TAFRO Syndrome (Thrombocytopenia, Anasarca, Fever, Reticulin Fibrosis and Organomegaly) after Immunosuppressive Therapies using Corticosteroids and Cyclosporin A : A Case Report

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A 49-year-old woman with severe thrombocytopenia was admitted after an episode of syncope. She also had anemia, fever, pleural effusion and ascites, and multiple lymphadenopathies subsequently appeared. Her bone marrow showed increased megakaryocytes with mild fibrosis, whereas her lymph nodes lacked histologically specific findings. Her presentation was not consistent with multicentric Castleman's disease, angioimmunoblastic T-cell lymphoma, systemic lupus erhythematosus or any other well-recognized entities. Her clinical features were, however, thought to be compatible with TAFRO (thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly) syndrome. Corticosteroid therapy induced a partial remission of fever and systemic fluid retention, but thrombocytopenia persisted. After additional immunosuppressive therapy with cyclosporin A, her symptoms showed full resolution. 〔*J Clin Exp Hematop 53(1)* : 95-99, 2013〕

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INTRODUCTION

Castleman's disease (CD) is a rare systemic disorder,[1] and multicentric Castleman's disease (MCD) is a subtype with multiple lesions and systemic symptoms.[2] Recently, some cases, resembling MCD but with distinctive features, such as severe thrombocytopenia, massive fluid retention and myelofibrosis, have been reported and this diagnosis has been given the designation TAFRO syndrome, which stands for thrombocytopenia, anasarca, fever, reticulin fibrosis and organomegaly.[3] Herein we report a typical case.

CASE REPORT

A 49-year-old woman had initially noticed fatigue and leg edema. A few weeks later, she fainted while driving her car, resulting in a traffic accident. She was slightly injured and was admitted to a general hospital. She was transferred to our

hospital because severe thrombocytopenia and anemia were revealed by laboratory tests. Her past medical history was unremarkable except for a Caesarean section at age 30 years. She neither smoked nor drank alcohol.

On admission, she had slight tachycardia. Pale palpebral conjunctiva was consistent with anemia. Submandibular lymph nodes were swollen and elastic hard with a maximum diameter of 2 cm. Coarse crackles were heard over both lower lung fields. Pitting edema was present in the lower extremities. Neither purpural nor petechial lesions were present. As shown in Table 1, she had normocytic anemia, thrombocytopenia, elevation of C-reactive protein, slight renal dysfunction with elevated blood urea nitrogen-to-creatinine ratio and hyperuricemia, hypoalbuminemia, polyclonal hyperglobulinemia, hypocomplementemia, activated partial thromboplastin time prolongation and d-dimer elevation. Increases in ferritin, soluble interleukin-2 receptor, rheumatoid factor, platelet-associated IgG and interleukin-6 were moderate. Anti-cardiolipin β_2 glycoprotein I complex antibodies, lupus anticoagulants and antinuclear antibodies were not measured. Anti-glycoprotein IIb/IIIa (GPIIb/IIIa) IgG producing B-lymphocytes were significantly increased in number. Computed tomography revealed bilateral pleural effusions, slight ascites, hepatosplenomegaly and paraaortic lymphadenopathy (Fig. 1). Bone marrow aspirations were repeatedly attempted from both the sternum and the ilium but all were dry taps. Bone marrow biopsy revealed a normocellular marrow with increased megakaryocytes and mild hyperplasia of

Table 1. Laboratory data of the present case

Complete blood count		Biochemistry		Virologic test	
White blood cell	$5,200 \times 10^6$/L	Total protein	6.7 g/dL	HIV-Ab	(−)
Stab	5.0%	Albumin	2.8 g/dL	EBV-DNA	(−)
Segmented	76.5%	BUN	31.9 mg/dL	HHV-8-DNA	(−)
Eosinophil	0%	Creatinine	0.96 mg/dL	**Immunologic test**	
Basophil	0%	Uric acid	11.3 mg/dL	IgG	2,611 mg/dL
Monocyte	6.0%	Total bilirubin	0.6 mg/dL	IgA	204 mg/dL
Lymphocyte	12.5%	AST	16 IU/L	IgM	74 mg/dL
Red blood cell	21.9×10^{12}/L	ALT	4 IU/L	IEP	(−)
Hemoglobin	6.2 g/dL	LDH	203 IU/L	CH50	40.2/mL
Hematocrit	19.2%	ALP	179 IU/L	C3	76 mg/dL
MCV	87.8 fL	γ-GTP	12 IU/L	C4	14 mg/dL
MCH	28.4 pg	Na	134 mEq/L	ANA	×40 speckled
MCHC	32.3 g/dL	K	4.6 mEq/L	RF-IgG	81 IU/L
Platelet	17×10^9/L	Cl	104 mEq/L	IC (C1q)	< 1.5 μg/mL
Reticulocyte	3.56%	Ca	7.6 mg/dL	aCL-β_2GPI	(−)
Coagulation test		CK	79 IU/L	LC	(−)
Prothrombin time	12.7 sec	CRP	6.04 mg/dL	Coombs test	(−)
APTT	40.8 sec	Glucose	100 mg/dL	PA-IgG	488 ng/10^7 cells
Fibrinogen	350.0 mg/dL	Fe	21 μg/dL	aGPIIb/IIIa	9.6/10^5 MNC
D-dimer	10.2 μg/mL	UIBC	128 μg/dL	**Cytokines**	
Urine test		Ferittin	333 ng/mL	sIL-2R	865 U/mL
U-glucose	(−)	Vitamin B12	237 pg/mL	IL-6	11.0 pg/mL
U-protein	(1+)	Folate	4.3 ng/mL	VEGF	330 pg/mL
U-occult blood	(−)	Haptoglobin	177 mg/dL	TGF-β	2.75 ng/mL

MCV, mean corpuscular volume ; MCH, mean corpuscular hemoglobin ; MCHC, mean corpuscular hemoglobin concentration ; APTT, activated partial thromboplastin ; BUN, blood urea nitrogen ; AST, aspartate aminotransferase ; ALT, alanine aminotransferase ; LDH, lactate dehydrogenase ; ALP, alkaline phosphatase ; γ-GTP, γ-glutamyltranspeptidase ; CK, creatine kinase ; CRP, C-reactive protein ; UIBC, unsaturated iron binding capacity ; HIV, human immunodeficiency virus ; EBV, Epstein-Barr virus ; HHV-8, human herpesvirus-8 ; IEP, serum immunoelectrophoresis ; ANA, anti-nuclear antibody test ; RF-IgG, IgG type rheumatoid factor ; IC (C1q), C1q-binding immune complex ; aCL-β_2 GPI, anti-cardiolipin-β_2 glycoprotein I complex antibodies ; LC, lupus anticoagulants ; PA-IgG, platelet-associated IgG ; aGPIIb/IIIa, anti-glycoprotein IIb/IIIa-IgG producing B-cells ; sIL-2 R, soluble interleukin-2 receptor ; IL-6, interleukin-6 ; VEGF, vascular endothelial growth factor ; TGF-β : transforming growth factor-β ; MNC, mononuclear cell
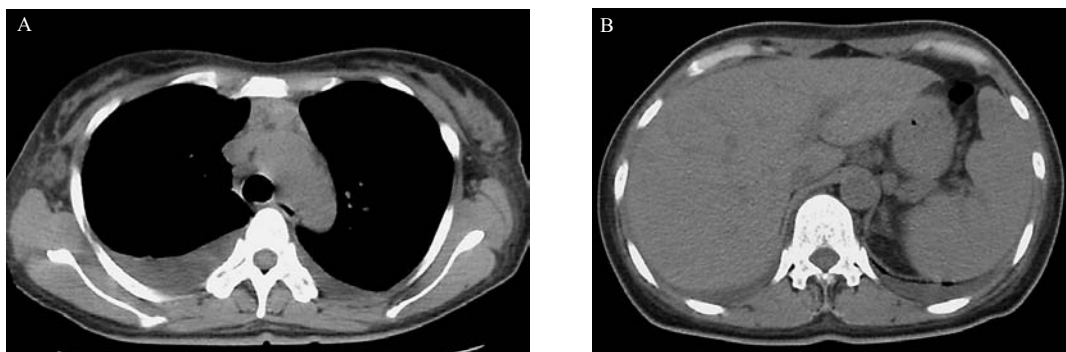

Fig. 1. Computed tomography at the admission revealed bilateral pleural effusions (*1A*) and mild hepato-splenomegaly (*1B*).

reticulin fibers, but no infiltration of atypical lymphocytes (Fig. 2).

After admission, her anasarca and ascites showed exacerbation with a 12 kg weight gain together with elevated temperature and multiple sites of superficial lymphadenopathy. Despite platelet transfusions, there was no improvement in her platelet counts, and purpural and pathechial lesions appeared on her extremities.

Based on these findings, she was suspected to have a lymphoproliferative disorder such as angioimmunoblastic T-cell lymphoma (AITL) or an autoimmune disorder such as systemic lupus erythematosus (SLE). On the 18th hospital day, a cervical lymph node biopsy was performed. As shown in Fig. 3, lymph follicles were atrophic and dysplastic follicular dendritic cells were present in the atrophic germinal center. Some of the follicles showed tight concentric layering of lymphocytes in the mantle zone.

The day after the lymph node biopsy, corticosteroid therapy with 40 mg of dexamethasone for 4 days was started, followed by 15 mg of prednisolone daily. Anasarca, pleural effusion, ascites, fever and the superficial lymphadenopathy showed immediate improvement and C-reactive protein was decreased to within normal range. In contrast, her anemia and thrombocytopenia persisted and a hematoma appeared on her right elbow. On the 36th day, she was treated with 250 mg of cyclosporin A (for a dose of 5 mg/kg of body weight). Her hemoglobin concentration and platelet counts gradually increased, and the prednisolone was stopped on the 53rd day after tapering. She was discharged on the 57th day. Two weeks later, her platelet count had increased to within normal range. Bone marrow biopsy was performed again, and demonstrated normal marrow with no evidence of fibrosis.

DISCUSSION

CD is a non-neoplastic lymphoproliferative disorder first reported in 1956 by Castleman.[1] CD cases are pathologically classified into 2 subtypes, hyaline vascular (HV) and plasma cell (PC).[2] MCD is a clinical subtype of CD with systemic lymphadenopathy, usually associated with PC type histology.[4]
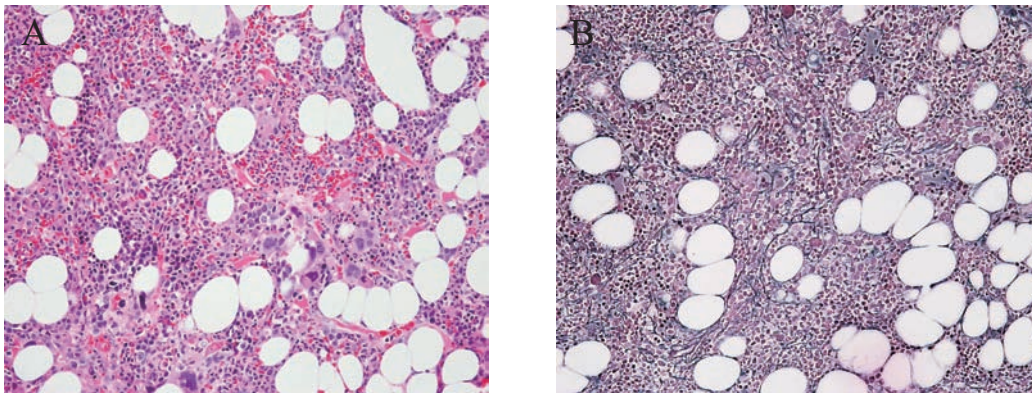

Fig. 2. Histological findings of the bone marrow. (**2A**) A high-power field of the bone marrow showed normocellular marrow with increased megakaryocytes. There was no infiltration of atypical lymphoid cells. H&E stain, ×100. (**2B**) Silver stain showed mild hyperplasia of reticulin fibers. ×100.
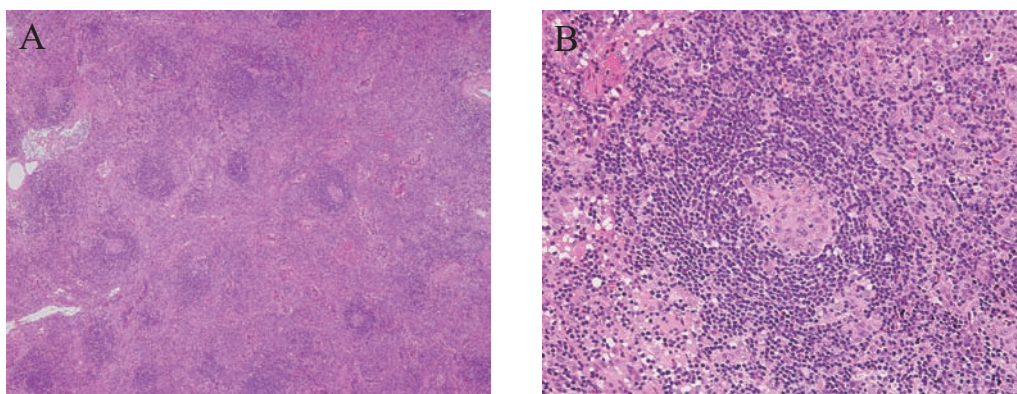

Fig. 3. Histological findings of the lymph node. (**3A**) A medium-power field of the lymph node showed atrophic lymphoid follicles. There were dysplastic follicular dendritic cells in the atrophic germinal center. H&E stain, ×20. (**3B**) A high-power field of the lymph node showed the follicles with tight concentric layering of lymphocytes in the mantle zone. H&E stain, ×100.
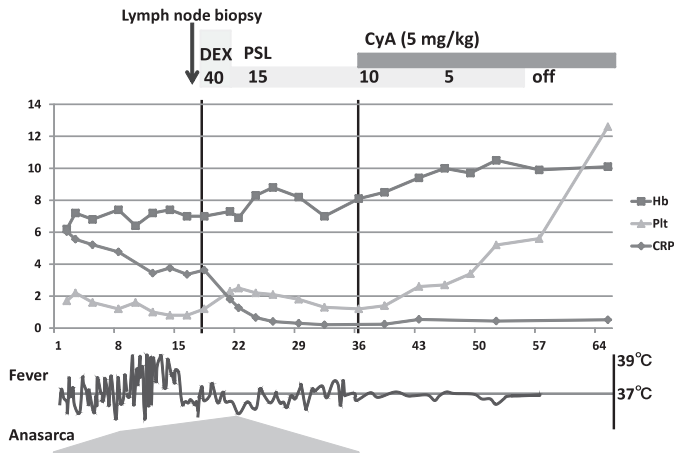
Fig. 4. Clinical course of the present case. DEX, dexamethasone ; PSL, predonisolone ; CyA, cyclosporin A ; Hb, hemoglobin ; Plt, platelet ; CRP, C-reactive protein

Localized CD often shows HV type histology, but some localized CD cases with systemic symptoms have PC type.[2,4] Symptoms such as fever are thought to be the result of hypercytokinemia, especially interleukin-6 produced by proliferating plasmacytoid B cells.[5] In western countries, MCD is reported to be strongly associated with human immunodeficiency virus (HIV) infection,[6] and most HIV-positive MCD and nearly half of HIV-negative MCD cases are also human herpesvirus-8 positive.[7,8] In Japan, however, HIV negative MCD cases have been reported to be unrelated to human herpesvirus-8 and demonstrate a rather chronic course.[9,10] Kojima *et al*. classified Japanese MCD into 2 subtypes. One is typical MCD which is the idiopathic plasmacytic lymphadenopathy with polyclonal hyperimmunoglobulinemia (IPL) type and the other is atypical MCD which is the non-IPL type.[11] Histologically, a majority of non-IPL MCD cases have HV type. In our case, the lymph node histology mimicked the findings of MCD, showing atrophic follicles and hyperplasia of follicular dendritic cells in the germinal center, but specific findings for MCD, neither HV nor PC type, were lacking.

In 2009, Takai reported a series of 3 cases showing thrombocytopenia with mild myelofibrosis and systemic symptoms such as fever, effusion, hepatosplenomegaly and lymphadenopathy, and proposed a distinct entity which they gave the name TAFRO syndrome.[3] These cases were responsive to corticosteroid therapy, but amelioration thrombocytopenia and anasarca were not consistently achieved. Cyclosporin A induced complete remissions in 2 of their 3 cases. Only one case had lymphadenopathy sufficient to allow a biopsy, and the pathological findings revealed limited similarities to HV type MCD. Although clinically and histologically TAFRO syndrome is similar to non-IPL type MCD, differences include the severity of thrombopenia and marrow fibrosis. The clinical features of our case were compatible with TAFRO syndrome.

The effectiveness of immunosuppressive therapies suggests an immunological disorder. If thrombocytopenia is autoimmune-mediated, i.e. occurs via autoantibodies against GPIIb/IIIa, it may be difficult to distinguish TAFRO syndrome from other forms of immune thrombocytopenia. Collagen diseases including SLE often show the secondary immune thrombocytopenia associated with systemic symptoms such as fever, effusion and lymphadenopathy. Pathological findings of lymph nodes in collagen diseases are difficult to distinguish from those of MCD,[12] making identification of the presence of autoantibodies important for diagnosis. Reticulin fibrosis of bone marrow has also been reported in SLE.[13,14] In our case, most of the symptoms and pathologic findings could have been explained by SLE, but no specific autoantibodies were detected. SLE was thus ruled out as only two (serositis, hematologic disorder) of the 11 classification criteria were satisfied.

AITL is a mature T-cell neoplasm, a subtype of peripheral T-cell lymphoma. Clinically, affected individuals often have systemic symptoms such as fever and effusion, as well as having immunological abnormalities such as immune thrombocytopenia, autoimmune hemolytic anemia and a variety of autoantibodies.[15] Pathological features of the involved lymph nodes in AITL show some similarity to those of MCD,[16] most notably vascular hyperplasia and plasmacytic infiltration, while the germinal center differs in appearance. Southern blotting tests may prove T-cell receptor clonality in some AITL cases,[17] but this does not provide a definitive diagnosis. The pathological findings of the present case were not compatible with AITL, and the southern blotting test revealed no clonal rearrangement of T-cell receptor.

We experienced a case with clinical features that were highly consistent with TAFRO syndrome. The question is whether TAFRO syndrome is really a distinct entity, or instead an atypical subtype of MCD, or an as yet unrecognized manifestation of a known autoimmune disorder such as SLE. Collection of similar cases and further studies are warranted to answer these questions.

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