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TAFRO Syndrome: A Novel Systemic Inflammatory Disorder Characterized by Thrombocytopenia, Anasarca, Fever, Renal Dysfunction and Organomegaly

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Abstract

TAFRO syndrome is a systemic inflammatory disorder characterized by a constellation of symptoms; thrombocytopenia with reticulin fibrosis of bone marrow, anasarca including pleural effusion and ascites, fever, renal dysfunction, and organomegaly (hepatosplenomegaly and lymphadenopathy). Although several histopathological features of TAFRO syndrome resemble those of mixed type of multicentric Castleman disease (MCD), some cases of TAFRO syndrome don't show any significant lymphadenopathy. In addition, several clinical and laboratory findings of TAFRO syndrome are different from those of MCD. The onset and clinical course of TAFRO syndrome may be acute or subacute, sometimes fetal, but its etiology, pathogenesis and specific marker is undetermined. Some patients have been successfully treated with corticosteroids, immunesuppressants including cyclosporine A, tocilizumab or rituximab, whereas others were refractory to treatment and succumbed to the disease. For contribution to the prompt diagnosis and appropriate treatment of TAFRO syndrome, the research team has defined its preliminary diagnostic criteria, disease severity classification and treatment strategy for TAFRO syndrome. To promote the research on TAFRO syndrome, multicenter retrospective clinical study in Japan has been performed, and prospective study is being designed by a nation-wide research team on TAFRO syndrome.

Keywords: TAFRO syndrome; Thrombocytopenia; Anasarca; CD-like histopathology; Idiopathic MCD

Introduction

We first reported three patients who presented with thrombocytopenia with reticulin fibrosis of bone marrow, anasarca, high fever and hepatosplenomegaly in 2010 [1]. Histological findings of liver and spleen were non-specific and hyaline-vascular (HV)-type Castleman disease (CD)-like histology of the lymph node was obtained in only one case. The constellation of these symptoms and laboratory findings was non-specific and not compatible with any known autoimmune diseases or well-defined lymphoproliferative disorders (LPD). So we called it TAFRO syndrome tentatively, and suggested that it was a systemic inflammatory disorder with a background of immunological abnormality. Similar cases have since been reported [2-6] and multicenter retrospective study of patient registry (UMIN 000011809) has been performed by the research team. Several research meetings have evaluated the diagnosis and treatment of TAFRO syndrome [7], and they proposed diagnostic criteria, disease severity classification and treatment strategy for TAFRO syndrome, 2015 version [8]. I review the achievements of the research team and consider about the clinicopathological features of TAFRO syndrome by comparison with HHV-8-negative idiopathic MCD [9] and other diseases that can demonstrate CD-like histopathology.

Diagnostic criteria

All Japan TAFRO syndrome Research Group in the Research Program for Intractable Disease by Ministry of Health, Labor and Welfare (MHLW) Japan proposed diagnostic criteria of TAFRO syndrome, 2015 version (Table 1) [8]. A diagnosis of TAFRO syndrome requires all of the three major categories and at least two of four minor categories. Anasarca, including pleural effusion, ascites and general edema appears often from onset. Thrombocytopenia is usually progressive and sometimes life-threating bleeding needs platelet transfusions. High fever of unknown etiology refractory to antibiotics is accompanied by high concentration of serum C-reactive protein (CRP) in a typical case. CD-like feature on lymph node biopsy is not a major category, but one of minor categories, because some patients don't show any evaluable lymphadenopathy. As it is very important to exclude malignancies, especially lymphoma, lymph node biopsy, if applicable, is strongly recommended. Bone marrow aspiration often results in dry tap, and bone marrow biopsy reveals increased number of megakaryocytes and reticulin myelofibrosis in most patients. Hepatosplenomegaly in this disease is usually mild and only confirmed by CT-scan, whereas presence of huge hepatosplenomegaly may indicate lymphoma or other diseases. Lymphadenopathy in this disease is usually smaller than 1.5 cm in diameter, whereas marked lymphadenopathy may indicate lymphoma or other diseases. Renal dysfunction with proteinuria and/or microhematuria is often accompanied by progressive renal insufficiency with oliguria because of intravascular hypovolemia. The diagnosis of TAFRO syndrome requires the exclusion of various diseases listed in Table 1. Malignancies, including lymphoma, especially angioimmunoblastic T-cell lymphoma (AITL), lymphoma associated hemophagocytic syndrome (LAHS), and Hodgkin lymphoma, myeloma, mesothelioma; et cetera should be excluded by histology or cytology of lymph node, bone marrow, pleura and pleural effusion. Autoimmune disorders, including systemic lupus erythematosus (SLE), ANCA-associated vasculitis, rheumatoid arthritis (RA), et cetera can be excluded with positive reaction of disease specific autoantibodies. POEMS syndrome, *IgG4*-related

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Major categories	Minor categories	Disease to be excluded
Anasarca , including pleural effusion, ascites and general edema	Castleman's disease-like features on lymph node biopsy	Malignancies, including lymphoma, myeloma, mesothelioma, et cetera
Thrombocytopenia; defined as a pre-treatment platelet count ≤ 100,000/μl	Reticulin myelofibrosis and/or increased number of megakaryocytes in bone marrow	Autoimmune disorders, including systemic lupus erythematosus (SLE), ANCA-associated vasculitis, et cetera
Systemic inflammation, defined as fever of unknown etiology above 37.5℃ and/or serum C-reactive protein concentration ≥ 2mg/dl	Mild organomegaly, including hepatomegaly, splenomegaly and lymphadenopathy	Infectious disorders, including acid fast bacterial infection, rickettsial infection, lyme disease, severe fever with thrombocytopenia syndrome (SFTS), et cetera
	Progressive renal insufficiency	POEMS syndrome
		IgG4-related disease
		Hepatic cirrhosis
		Thrombotic thrombocytopenic purpura (TTP)/ hemolytic uremic syndrome (HUS)

Table 1: The 2015 diagnostic criteria for TAFRO syndrome [8].

disease, and thrombotic thrombocytopenic purpura (TTP) each has its own diagnostic criteria and disease specific markers.

Clinical features

TAFRO syndrome typically affects individuals in the fourth to sixth decades of life, but it can occur at any age [2,7,10]. It occurs in men and women equally. The initial symptoms are usually peripheral edema, fever, general fatigue, sometimes epigastric pain, but these symptoms and laboratory findings on disease onset are non-specific. General condition of the patients rapidly deteriorates during the symptomatic treatment or the examinations for diagnosis. Persistent fever refractory to antibiotic therapy, dyspnea due to marked pleural effusion, ascites and general edema (anasarca) are most critical suffering for patients (Figure 1A and 1B). Anasarca is always refractory to diuretics and one third of the patients need hemodialysis for acute renal failure and extravascular volume overload. Hepatosplenomegaly is usually mild and only confirmed by CT-scan (Figure 1A and 1D). Lymphadenopathy is usually smaller than 1.5cm in diameter, and some patients don't show any detectable lymphadenopathy by CT-scan. On the other hand, some patients show anterior mediastinal infiltrative lesion [11] (Figure 1C).

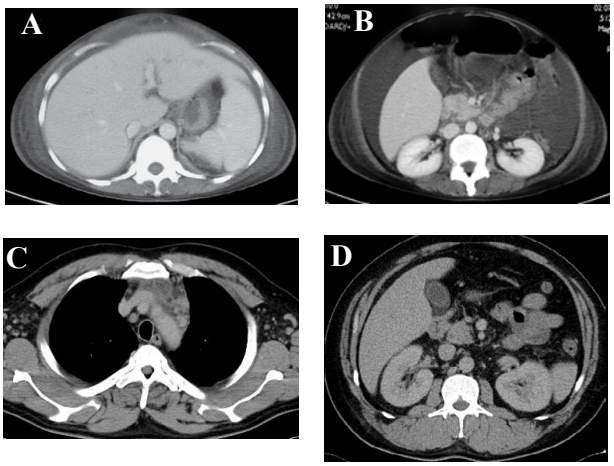

Figure 1: Contrast-enhanced CT in a 47-yeay-old woman (A and B) and in a 39-year-old man (C and D) with TAFRO syndrome. (A): Hepatosplenomegaly and marked subcutaneous edema. (B): Massive ascites and edema, but no para-aortic lymphadenopathy. (C): Bilateral axillary and mediastinal mild lymphadenopathy, anterior mediastinal infiltrative lesion, and subcutaneous edema. (D): Gallbladder wall edema and very mild retroperitoneal lymphadenopathy.

Laboratory findings

Thrombocytopenia may be absent or mild on the onset, but platelet count decreases progressively during the clinical course in almost all patients [2,7]. Increased platelet-associated *IgG* (PAIgG) and proliferation of megakaryocytes in the bone marrow may suggest immunological destruction of platelets similar to idiopathic thrombocytopenic purpura (ITP). But severe thrombocytopenia of TAFRO syndrome is usually refractory to corticosteroids, high dose immunoglobulin or splenectomy. Serum immunoglobulin levels are always normal, and neither monoclonal gammopathy nor polyclonal hypergammaglobulinemia is shown. Although some patients show positive anti-nuclear antibody (ANA), SS-A or Coomb's test, any of the autoimmune disease-specific autoantibody is negative. Marked hypoalbuminemia with or without proteinuria is associated with marked anasarca refractory to diuretics. Pleural effusion or ascites is usually exudative, which may suggest the serositis of body cavities. C-reactive protein (CRP) is usually high level associated with the degree of systemic inflammation. Serum interleukin-6 (IL-6) level is slightly to moderately elevated, and IL-6 level of effusion is markedly elevated [4]. Serum or plasma VEGF level is normal or mildly elevated [2,4,7]. Renal function may be normal or slightly disturbed with proteinuria and/or microscopic hematuria, but that of many patients will be deteriorated progressively associated with severe anasarca and oliguria. Liver function is almost normal except serum alkaline phosphatase (ALP) level, which is elevated in most patients whereas lactate dehydrogenase (LDH) level is within normal limits. Coagulation factors are almost normal except high level of fibrinogen. The level of FDP is slightly or moderately elevated, which may reflect the presence of ascites, whereas small number of patients may complicate thrombosis or disseminated intravascular coagulation (DIC) [6].

Histopathological features

Iwaki et al. have reported several common histopathological findings from clinicopathological analysis of 44 patients of TAFRO syndrome [12]. The characteristic histopathological findings include atrophic germinal centers, expansion of the interfollicular zone, proliferation of highly dense endothelial venules, and relatively few mature plasma cells (Figure 2A). Hyaline vascular (HV) features such as penetrating blood vessels are present but not as prominent as usually seen in HV or mixed-type MCD (Figure 2B). Immunohistochemical studies show that the follicular dendritic cell (FDC) networks tend to be expanded or disrupted in the interfollicular zone of TAFRO syndrome [12]. Bone marrow aspiration often results in dry tap, and bone marrow biopsy reveals increased number of megakaryocyte with slight atypia (Figure 2C). Reticulin fibrosis with a loose network of reticulin fibers are observed in more than 80% of biopsied bone marrow (Figure 2D). Myelofibrosis is rarely associated with autoimmune diseases especially systemic lupus erythematosus [13]. The response to steroid therapy in

most patients with autoimmune myelofibrosis suggests the background of systemic immunological abnormality [14]. Abnormal lymphoid cell proliferation, hemophagocytic histiocytosis or significant plasmacytosis is not observed in the bone marrow. Histological examination of the kidney, which has been performed in only limited cases, has shown the membranoproliferative glomerulonephritis with proliferation of mesangial cell and matrix. Histological examination of the liver in our cases showed mild infiltration of lymphocytes and mild fibrosis in the portal areas, which were non-specific findings. Histology of the spleen was also non-specific [2].

Relationship to MCD and diseases with CD-like histopathology

MCD is a heterogeneous group of disorders characterized by proliferation of polyclonal lymphocytes and plasma cells due to hypercytokinemia, most notably IL-6 [15] (Table 2). Human herpes virus-8 (HHV-8) is the well-established cause of the hypercytokinemia in HHV-8-associated MCD cases [16]. There is also a group of HHV-8-negative MCD patients with unknown etiology and pathophysiology, which Fajgenbaum et al. has proposed referring to as idiopathic MCD (iMCD) [9]. Almost all cases of Japan are HHV-8-negative MCD (iMCD) [17]. Kojima et al. indicated that iMCD in Japan consists of two variants with distinct clinicopathological findings, that is, idiopathic plasmacytic lymphadenopathy with polyclonal hyper immunoglobulinemia (IPL) type and non-IPL type [17]. IPL-type MCD resembles the plasma cell-type MCD in Western countries characterized by prominent polyclonal hyperimmunoglobulinemia, systemic manifestations such as malaise, fever and weight loss, and a high level of serum IL-6. Non-IPL type MCD is characterized by mixed-type or HV-type CD histology, a high incidence of pleural effusion and ascites, and is frequently associated with autoimmune diseases during the course of the disease. Therefore, it was described that a portion of non-IPL-type cases may be secondary MCD, that is, autoimmune disease-associated lymphoproliferative disorders (LPD) [17]. Although non-IPL type MCD with effusion and thrombocytopenia [18] may overlap with TAFRO syndrome, some cases of TAFRO syndrome can't show CD-like histopathology because of an absence of obvious lymphadenopathy. POEMS (polyneulopathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome involving VEGF and other cytokine secretion by monoclonal plasma cells can demonstrate clinical and histopathological overlap with not only iMCD [9] but also TAFRO syndrome. About 60% of biopsied lymph nodes of POEMS patients showed CD-like histopathology, mainly HV type [19,20]. The frequent association between POEMS and iMCD may suggest that POEMS-driving plasma cells secrete cytokines that also cause iMCD-like reactive lymph node change [9]. IgG4-related diseases are characterized by mass-forming lesions in mainly exocrine tissue that consist of lymphplasmacytic infiltrates and sclerosis. Lymph node lesions can be subdivided into five histological subtypes, and systemic IgG4-related lymphadenopathy should be distinguished from MCD [21]. Especially type I lesions show similar clinicopathological findings to MCD including IPL, but serum IL-6 and CRP levels are normal in the majority of IgG4-related diseases [21]. Adult onset Still's disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology, frequently accompanying multiple lymphadenopathies. Despite the constellation of characteristic clinical manifestations, the absence of specific serological and pathological findings often makes this disease difficult to diagnose. Although AOSD lymphadenopathy represents a wide spectrum of histopathological features, basically characterized by paracortical hyperplasia with vascular proliferation [22], which can mimic mixed type CD. Notably, histopathological features of mixed or HV type CD are non-specific, reactive to hypercytokinemia, and can be found in several inflammatory, autoimmune, infectious, and neoplastic diseases [9]. TAFRO syndrome may be one of the systemic inflammatory disorders that can demonstrate iMCD-like histopathology by undetermined cytokines and pathogenesis.

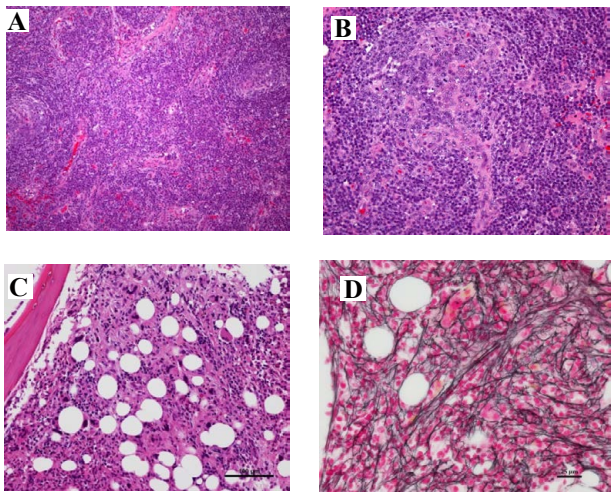

Figure 2: Histological findings of lymph node (A,B) and bone marrow (C,D) of a 39-year-old man with TAFRO syndrome. (A): Atrophic germinal centers (arrow) and expansion of the interfollicular zone with vascular proliferation. (B): Penetrating blood vessels is not as prominent as seen in HV type MCD. (C): Increased number of megakaryocytes with mild atypia. (2D): Reticulin fibrosis of bone marrow (silver stain).

Treatment strategy

Corticosteroids have been used as the first line treatment in almost all patients for the progressively deteriorated general condition

Diseases with CD-like histopathology	Histologic subtype	In Japan [17]
Primary MCD	Plasmablastic type	Very rare
HHV-8-associated [16]	Plasma cell type	IPL type
HHV-8-negative (Idiopathic MCD) [9]	HV or Mixed type	Non-IPL type
Secondary		
Autoimmune diseases (ex: SLE, RA)	HV or Mixed type	Non-IPL
POEMS syndrome [20]	HV > Mixed type	Non-IPL
IgG4-related disease [21]	Type I* ~Type V	
TAFRO syndrome	HV or Mixed type	Non-IPL
Adult onset Still's disease [22]	Mixed type	
Malignant lymphoma	AITL, etc	
Infection (ex: HIV, EBV)		

*Type I: Castleman disease-like morphology [21]

HV: Hyaline Vascular; IPL: Idiopathic Plasmacytic Lymphadenopathy with polyclonal hyperimmunoglobulinemia; AITL: Angioimmunoblastic T-cell Lymphoma.

Table 2: Diseases that can demonstrate Castleman Disease-like histopathology.

due to persistent high fever, severe thrombocytopenia, and marked anasarca (Table 3) [8]. Although prednisolone (PSL) 1 mg/kg/day is usually started in the same way as autoimmune diseases, methyl-PSL pulse therapy with 500-1000 mg/day for three days may be needed in an emergency case. Corticosteroids are usually effective for fever and elevated level of CRP, but severe thrombocytopenia, life-threating pleural effusion and ascites with renal insufficiency may need hemodialysis and the second line treatments. Immunosupressive therapy with cyclosporin-A (CsA) is recommended for patients refractory or dependent on corticosteroids [2,5]. The starting dose of oral CsA is 3-5 mg/kg/day, and the target trough level of serum CsA is 150-250 ng/mL. If serum creatinine level increase >150%, CsA dose should be decreased 50-75% [8]. If CsA is contraindicated, as in patients with renal insufficiency, tocilizumab or rituximab is recommended. Treatment with tocilizumab, anti-IL-6 receptor antibody, consistently alleviates lymphadenopathy and chronic inflammatory symptoms in MCD patients [23]. In TAFRO syndrome, tosilizumab has been used mainly in the cases with CD-like histopathology and high level of serum IL-6. Successful treatment with tocilizumab has been reported [4,6,24], but the effect of tocilizumab in TAFRO syndrome is not yet established. Rituximab, anti-CD20 antibody has been reported to be effective in a few cases [25]. Plasma exchange, cyclophosphamide, combination chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine, and PSL) [26], thalidomide [27] and lenalidomide [28], have been successful in the treatment of selected patients. Splenectomy and high-dose immunoglobulin have not been shown effective for thrombocytopenia [2]. Thrombopoietin receptor agonist romiplostim and eltrombopag has been shown effective for patients with persistent thrombocytopenia.

Future Prospects

Because of the absence of specific serological and pathological findings, TAFRO syndrome is currently diagnosed by combination of clinical and laboratory findings, and exclusion of other similar diseases. To elucidate the clinicopathological features of TAFRO syndrome and to clarify the association between TAFRO syndrome and iMCD, the multicenter retrospective clinical study has been contributed. Proposed diagnostic criteria and treatment strategy for TAFRO syndrome, 2015 version should be used to promote multicenter prospective clinical study by the Japanese research group. Analysis of collected clinical data and materials is expected to elucidate the pathophysiology, responsible cytokines, and etiology of TAFRO syndrome. Recently Iwaki, et al. has reported that elevated serum interferon γ-induced protein 10kDa (IP-10) is associated with TAFRO syndrome [29]. IP-10 is a cytokine belonging to the CXC chemokine family, and its expression has been associated not only with autoimmune diseases, but also with inflammatory diseases including infection, immune dysfunction, and tumorigenesis. They have suggested that IP-10 might be involved in the pathogenesis of TAFRO syndrome, and this hyercytokine syndrome could be triggered by an undetectable infection in the hepatobiliary system. Further researches would be expected to establish the clinicopathological entity of TAFRO syndrome by defined with specific biomarker, pathophysiology, etiology, and treatment strategy based on evidence.

(1) High-dose glucocorticoid: prednisolone 1mg/kg/day for 2 weeks, followed by tapering; or Methyl-prednisolone pulse therapy with 500-1000mg/day for 3 days if an emergency.
(2) CyclosporinA (CsA): may be added for patients refractory or dependent on glucocorticoids.
(3) Tocilizumab (anti-IL-6 receptor antibody): for patients with TAFRO syndrome complicated by Castleman's disease.
(4) Rituximab (anti-CD20 antibody).
(5) Thrombopoietin receptor agonists romiplostim and eltrombopag: for patients with persistent thrombocytopenia.

Table 3: The 2015 treatment strategy for TAFRO syndrome [8].

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