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Successful treatment with tacrolimus in TAFRO syndrome: two case reports and literature review

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Abstract

Rationale: TAFRO syndrome is a systemic inflammatory disorder characterized by thrombocytopenia, anasarca, fever, reticulín fibrosis, renal dysfunction, and organomegaly. In contrast to that in multicentric Castleman disease, interleukin-6 targeting strategies seem ineffective in some TAFRO syndrome cases; however, the optimal treatment remains unclear. Here, we report 2 cases of TAFRO syndrome, where 1 with cardiomyopathy, successfully treated with tacrolimus. This is the first case report of successful treatment with tacrolimus in TAFRO syndrome.

Patient concerns: Both patients (cases 1 and 2) developed fever, anasarca, thrombocytopenia, renal dysfunction, and mild hepatosplenomegaly.

Diagnoses: In both patients, lymph node pathology revealed mixed type Castleman disease-like features, and bone marrow showed reticulín myelofibrosis. TAFRO syndrome was diagnosed based on the patients' laboratory, clinical, and pathologic findings. In case 2, we observed a rare complication of cardiomyopathy with no evidence of takotsubo cardiomyopathy or viral myocarditis.

Interventions and outcomes: In case 1, tocilizumab combined with glucocorticoids was ineffective and caused septic shock; additionally, cyclosporine A was discontinued because of hepatotoxicity. However, tacrolimus was effective in resolving TAFRO syndrome without any adverse events. In case 2, tacrolimus completely reversed TAFRO syndrome and was also effective in cardiomyopathy.

Lessons: This report suggests that tacrolimus is potentially effective and safe as an initial treatment and a glucocorticoid-sparing agent. Our literature review shows that calcineurin inhibitors, including tacrolimus, may be effective in TAFRO syndrome. Since previous studies indicate a role of Th1 inflammation in TAFRO syndrome pathogenesis, tacrolimus may, therefore, be effective in treating TAFRO syndrome.

Abbreviations: ALP = alkaline phosphatase, ANA = antinuclear antibody, ANCA = antineutrophil cytoplasmic antibody, BNP = brain natriuretic peptide, CRP = C-reactive protein, CT = computed tomography, HHV-8 = human herpesvirus 8, HIV = human immunodeficiency virus, IgG = immunoglobulin G, IL-6 = interleukin-6, IP-10 = interferon- γ -induced protein 10, LVEF = left ventricular ejection fraction, MCD = multicentric Castleman disease, sIL-2R = soluble interleukin-2 receptor, TAFRO = thrombocytopenia, anasarca, fever, reticulín fibrosis, renal dysfunction, and organomegaly, VEGF = vascular endothelial growth factor.

Keywords: calcineurin inhibitors, cardiomyopathy, cyclosporine A, multicentric Castleman disease, tacrolimus, TAFRO syndrome

1. Introduction

TAFRO syndrome was first described in Japan in 2010 as a unique variant of multicentric Castleman disease (MCD) with an aggressive clinical course and comprised thrombocytopenia, anasarca, fever, reticulín fibrosis, renal dysfunction, and organomegaly (TAFRO).^[1] MCD constitutes a heterogeneous group of

lymphoproliferative disorders characterized by excessive systemic inflammatory features, including frequent fever, generalized peripheral lymphadenopathy, hepatosplenomegaly, polyclonal hypergammaglobulinemia, and elevated levels of serum C-reactive protein (CRP), interleukin-6 (IL-6), and vascular endothelial growth factor (VEGF). These clinical manifestations of MCD are possibly driven by excessive proinflammatory hypercytokinemia, particularly in association with elevated levels of IL-6. On the contrary, MCD is strongly associated with human herpesvirus-8 (HHV-8), which infects B cells and expresses a viral homolog of IL-6; TAFRO syndrome is considered as a subgroup of HHV-8-negative MCD or idiopathic MCD group.^[2]

Although IL-6 levels in TAFRO syndrome are elevated, many of its features differ considerably from classical MCD features, including severe thrombocytopenia and absence of hypergammaglobulinemia,^[3] which is difficult to explain owing to hyper-IL-6 syndrome because IL-6 overexpression typically results in thrombocytosis and hypergammaglobulinemia. In addition, IL-6 targeting strategies seem to be ineffective for some TAFRO syndrome cases, whereas they are highly effective for MCD (91% complete response rate).^[4] These findings suggest that not only IL-6 but also other proinflammatory conditions may play roles in the pathogenesis of TAFRO syndrome.^[5] Furthermore, the

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combination of glucocorticoids and tocilizumab, an anti-IL-6 receptor antibody, increases the risk of severe infections.^[6] In terms of effectiveness and adverse events, IL-6-targeting agents may not be the best choice for TAFRO syndrome; however, the optimal treatment remains unclear.

To the best of our knowledge, this is the first report of 2 cases of TAFRO syndrome successfully treated with tacrolimus, where 1 with a rare complication of cardiomyopathy, which was also completely resolved after treatment. We also discuss the relationship between the action mechanism of tacrolimus and possible pathogenesis of TAFRO syndrome.

2. Case reports

2.1. Case 1

A 68-year-old Japanese woman without medical history was admitted to our hospital with a 4-week history of abdominal distension and fever of 38.1°C. Physical examination revealed swollen cervical and axillary lymph nodes (<1 cm in diameter) and abdominal tenderness. Laboratory studies revealed anemia (hemoglobin, 7.3 g/dL); thrombocytopenia (38,000/ μ L); reduced immunoglobulin G (IgG, 770 mg/dL); elevated levels of alkaline phosphatase (ALP, 720 U/L), soluble interleukin-2 receptor (sIL-2R, 3060 U/mL), and CRP (2.7 mg/dL); and renal dysfunction (serum creatinine 1.6 mg/dL) with microhematuria. Test results for autoantibodies, including antinuclear antibody (ANA) and antineutrophil cytoplasmic antibody (ANCA); and viruses, including HHV-8 and human immunodeficiency virus (HIV), were negative. Computed tomography (CT) revealed systemic lymphadenopathy, bilateral pleural effusion, massive ascites, and hepatosplenomegaly. IL-6 and VEGF levels in serum (24 and 390 pg/mL, respectively) and in ascitic fluid (1800 and 63 pg/mL, respectively) were elevated. Cervical lymph node biopsy revealed atrophic germinal centers, expanded mantle zones, and proliferated high endothelial venules and small number of plasma cells in the interfollicular zones (Fig. 1A, B). Bone marrow biopsy revealed hyperplasia of megakaryocytes and reticulin fibrosis. These symptoms and histopathologic findings met the diagnostic criteria for TAFRO syndrome.^[3,7]

Initial treatment with 60 mg/day (1 mg/kg/day) of oral prednisolone gradually improved renal dysfunction but failed to resolve thrombocytopenia and massive ascites, requiring frequent platelet transfusion, romiplostim administration, and ascites drainage (Fig. 2). Additional treatment with 8 mg/kg of

tocilizumab failed to improve the symptoms; moreover, the patient developed septic shock from empyema caused by methicillin-sensitive *Staphylococcus aureus*, necessitating the discontinuation of tocilizumab. Additionally, 150 mg/day (2.5 mg/kg/day) of cyclosporine A had to be discontinued within a week because of hepatotoxicity. Referring to literature demonstrating the effectiveness of calcineurin inhibitor,^[8,9] we administered 4 mg/day (0.07 mg/kg/day) of tacrolimus targeting 5 to 10 ng/mL of trough concentrations, after obtaining informed consent from the patient. Tacrolimus improved renal dysfunction and thrombocytopenia rapidly without requiring platelet transfusion or romiplostim administration. Abdominal distension gradually subsided without ascites drainage: CT showed complete ascites resolution 4 weeks after tacrolimus initiation, and glucocorticoids were tapered off rapidly. The patient has had an uneventful course without relapse for more than 3 years.

2.2. Case 2

A 17-year-old Japanese man without medical history was admitted to our hospital with a 4-week history of abdominal pain, nausea, and fever of 38.8°C. Physical examination revealed swollen axillary lymph nodes (<1 cm in diameter) and abdominal tenderness. Laboratory studies revealed anemia (hemoglobin, 6.7 g/dL); thrombocytopenia (68,000/ μ L); reduced IgG (810 mg/dL); elevated levels of ALP (870 U/L), sIL-2R (1250 U/mL), and CRP (23.0 mg/dL); and renal dysfunction (serum creatinine 1.6 mg/dL) with microhematuria. Test results for autoantibodies, including ANA and ANCA; and viruses, including HHV-8 and HIV, were negative. Electrocardiogram and echocardiography were normal. CT showed bilateral pleural effusion, ascites, and mild hepatosplenomegaly. Serum IL-6 and VEGF levels (70 and 730 pg/mL, respectively) and IL-6 and VEGF levels in the pleural effusion (370 and 88 pg/mL) and ascitic fluid (460 and 100 pg/mL) were elevated. Axillary lymph node biopsy revealed expanded mantle zones and proliferated high endothelial venules in atrophic germinal centers and interfollicular zones with small number of plasma cells. Bone marrow biopsy revealed normoplasia of megakaryocytes and reticulin fibrosis. The patient was diagnosed with TAFRO syndrome.^[3,7]

The CRP level and fever improved spontaneously, but thrombocytopenia, creatinine level, pleural effusion, and ascites deteriorated (Fig. 3). Four weeks after admission, the patient suddenly developed cardiogenic shock without obvious causes; evidence of myocardial infarction, takotsubo cardiomyopathy, or

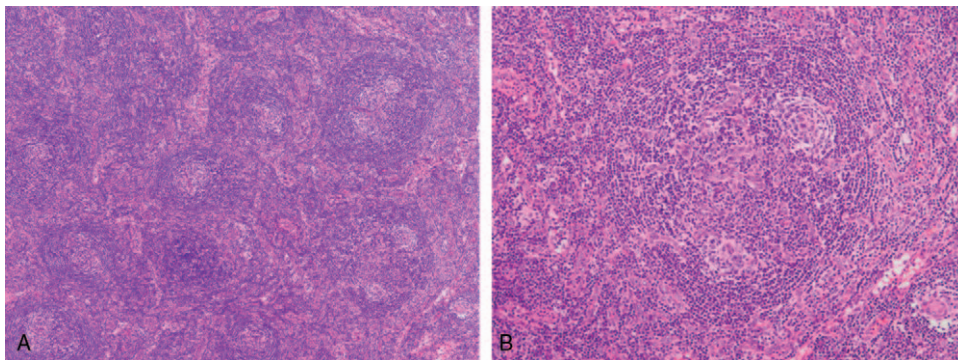


Figure 1. Histologic findings of the cervical lymph node. (A) Lymph node with proliferated high endothelial venules and small number of plasma cells in the interfollicular zone. Hematoxylin and eosin staining (40 $\times$ magnification). (B) Atrophic germinal centers with enlarged nuclei of high endothelial cells and expanded mantle zones. Hematoxylin and eosin staining (100 $\times$ magnification).

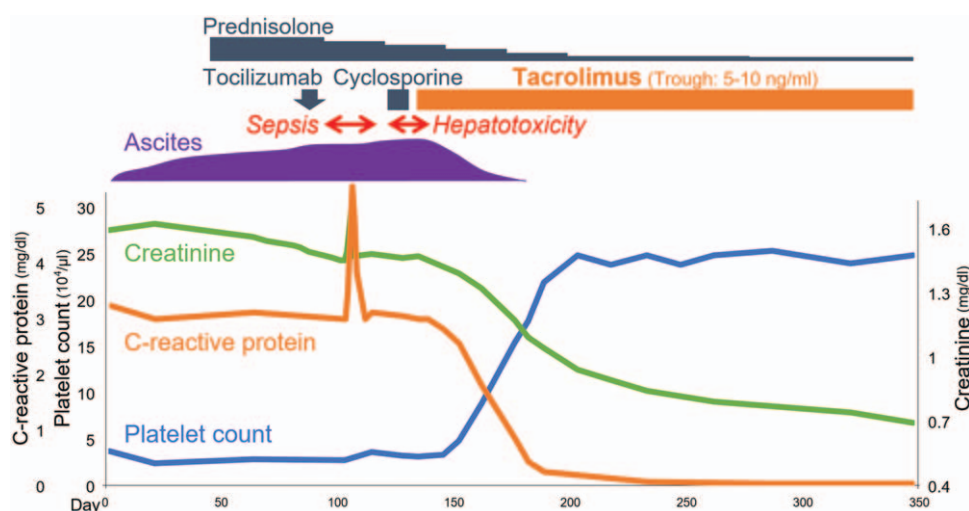


Figure 2. Clinical course of case 1.

viral myocarditis was not detected. Echocardiography revealed severe and diffuse hypokinesis of both ventricles (left ventricular ejection fraction, LVEF 20%) and moderate pericardial effusion (Fig. 4A). The brain natriuretic peptide (BNP) level was 1230 pg/mL (reference range, <18.4 pg/mL). We initiated methylprednisolone pulse therapy at 1000 mg/day for 3 consecutive days, followed by 60 mg/day (1 mg/kg/day) of oral prednisolone and 4 mg/day (0.07 mg/kg/day) of tacrolimus targeting 5 to 10 ng/mL of trough concentrations, with informed consent. One week after treatment initiation, repeat echocardiography revealed improved wall motion (LVEF 45%) and pericardial effusion. Four weeks later, serial echocardiography showed normal wall motion (LVEF 60%) without pericardial effusion (Fig. 4B), and a decrease in BNP level (8.0 pg/mL). Late gadolinium-enhanced cardiac magnetic resonance imaging showed no myocardial scarring. Thrombocytopenia, renal dysfunction, and anasarca had also improved since tacrolimus treatment initiation, and glucocorticoids were tapered off rapidly. The patient has had an uneventful course without relapse for more than 2 years.

This case report did not involve any human trials, and ethical review board approval was not necessary. Written informed consent was obtained from both the patients (cases 1 and 2) for the publication of their clinical data.

3. Discussion

This is the first case report of TAFRO syndrome successfully treated with tacrolimus. Although a standard treatment strategy for TAFRO syndrome is not yet established, our cases suggest that tacrolimus is potentially effective and safe as an initial treatment and a glucocorticoid-sparing agent.

First, tacrolimus was shown to be effective in our TAFRO syndrome cases. We reviewed the treatments of previous and current TAFRO syndrome cases to assess treatments and their responses; remission was defined as the absence of abnormalities on physical examinations and laboratory or imaging studies. Patients were treated with glucocorticoids alone or with combination therapy, including IL-6-targeting agents (tocilizumab, siltuximab);

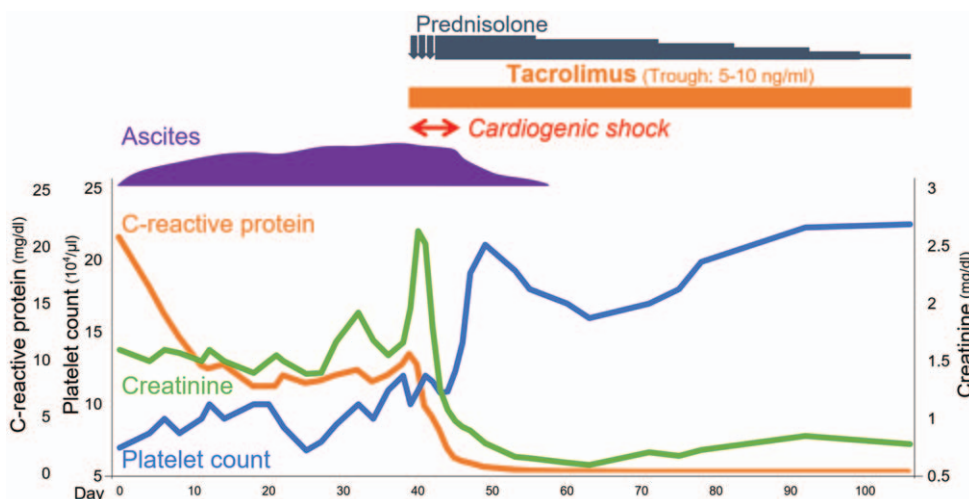


Figure 3. Clinical course of case 2.

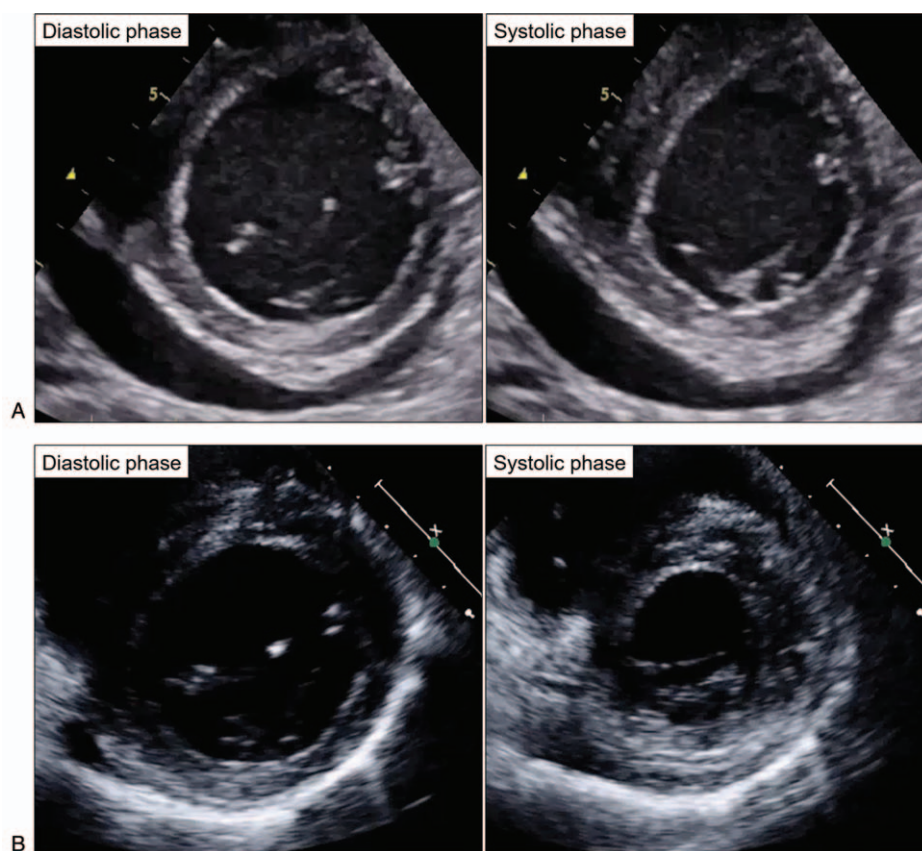


Figure 4. Clinical course of cardiomyopathy (echocardiography). (A) Severe and diffuse hypokinesis (LVEF 20%) and moderate pericardial effusion were detected. (B) Four weeks after treatment initiation, wall motion improved (LVEF 60%), and pericardial effusion disappeared. LVEF, left ventricular ejection fraction.

calcineurin inhibitors (tacrolimus, cyclosporine A); rituximab; and cytotoxic chemotherapy (Table 1). Treatment effectiveness greatly varied. Our literature review showed that calcineurin inhibitors, including tacrolimus, were effective for TAFRO syndrome, with 71% of patients attaining remission. Although the effectiveness of tacrolimus has not been compared with that of cyclosporine A, the superiority of tacrolimus over cyclosporine A has been extensively reported for kidney or liver transplant rejection, particularly in cases of glucocorticoid-resistant rejection.^[10,11] While IL-6-targeting agents were frequently used for TAFRO syndrome, only 45% of patients attained remission.

Second, tacrolimus was safe in our TAFRO syndrome cases. Literature review revealed that the frequency of severe infections in patients treated with calcineurin inhibitors was low (Table 1). Hepatotoxicity was an adverse drug reaction of cyclosporine A in some cases, including case 1, which was successfully treated by replacing cyclosporine A with tacrolimus. In fact, hepatotoxicity occurs less frequently with tacrolimus than with cyclosporine A.^[12] The frequency of severe infections, including septic shock, was high for treatment with tocilizumab, particularly in combination with high-dose glucocorticoids, as shown in case 1. In fact, in a survey of tocilizumab for rheumatoid arthritis, the

Table 1

Responses and adverse events associated with treatments of TAFRO syndrome.

	Treatments (N)	Remission (%) [*]		Adverse events (N)	
		First line	Total	Infections	Adverse drug reactions
Glucocorticoid monotherapy	36	11/35 (31%)	11/36 (31%)	3 (sepsis: 1)	0
IL-6 targeting agents [†]	29	7/15 (47%)	13/29 (45%)	8 (sepsis: 5)	0
Calcineurin inhibitors	14	3/4 (75%)	10/14 (71%)	3	2
Tacrolimus (case 1, 2)	2	1/1 (100%)	2/2 (100%)	0	0
Cyclosporine A	12	2/3 (67%)	8/12 (67%)	3	2 (hepatotoxicity: 2)
Cytotoxic chemotherapy [‡]	12	1/2 (50%)	7/12 (58%)	2 (sepsis: 2)	2 (cardiomyopathy: 2 [§])
Rituximab (without cytotoxic agents)	9	2/2 (100%)	5/9 (56%)	1 (sepsis: 1)	0
Other (thalidomide)	1	-	1/1 (100%)	0	0

IL-6, interleukin-6.

^{*} The percentage of those attaining remission was calculated from the number of cases with remission divided by the number of cases in which response to treatment could be assessed.

[†] Tocilizumab (n = 27) and siltuximab (n = 2).

[‡] Cyclophosphamide-based regimen (n = 11) and noncyclophosphamide-based regimen (n = 1).

[§] Cardiomyopathy was considered to be triggered by adriamycin^[18].

most frequent adverse events were severe infections; the significant risk factor was identified as a glucocorticoid dosage of ≥ 5 mg/day (prednisolone equivalent).^[6] In terms of safety, tacrolimus may be useful in treating TAFRO syndrome.

Third, the mechanism of action of tacrolimus and possible pathogenesis of TAFRO syndrome indicate that tacrolimus may be a rational treatment choice. Tacrolimus suppresses Th1 cell responses and impairs transcription of IL-2 and several other proinflammatory cytokines.^[13] In accordance with previous studies, we consider that Th1 inflammation may play a role in TAFRO syndrome pathogenesis. Increased IL-2 levels in the ascitic fluid in patients with TAFRO syndrome may suggest the contribution of endogenous IL-2 to disease pathogenesis.^[14] Additionally, high serum levels of interferon- γ -induced protein 10 (IP-10) are strongly correlated with TAFRO syndrome but not classical MCD.^[15] Overexpression of IP-10 is common in Th1-type inflammatory diseases and is critical for Th1-mediated immune responses.^[16] Tacrolimus suppresses Th1-cell responses, which may be one of the underlying mechanisms for the effectiveness of tacrolimus in TAFRO syndrome. Notably, in case 1, treatment with tacrolimus was successful for tocilizumab-resistant TAFRO syndrome; cyclosporine A has also been shown to be effective in tocilizumab-resistant cases,^[8,9] suggesting that in addition to IL-6, Th1 inflammation may play a role in TAFRO syndrome pathogenesis.

For case 2, we reported a complete reversal of cardiomyopathy, a rare complication of TAFRO syndrome, using tacrolimus and glucocorticoids. Few cases of TAFRO syndrome with cardiomyopathy have been reported,^[17,18] one of which was refractory to tocilizumab, suggesting that some proinflammatory cytokines other than IL-6 may be involved.^[17] In fact, in addition to IL-6, Th1 cytokines, such as IL-2 and tumor necrosis factor- α , have direct negative inotropic effect in a concentration-dependent, reversible manner, even after short-term exposure.^[19] Tacrolimus may therefore be effective, although the exact mechanism of cardiomyopathy has been poorly understood.

Our 2 cases suggested that tacrolimus is potentially effective and safe for TAFRO syndrome. However, with only 2 cases, it is early to conclude that tacrolimus is truly effective for TAFRO syndrome. The optimal treatment and precise pathogenesis of TAFRO syndrome remain unclear, and further research is needed to validate our findings and conclusions.

Author contributions

Validation: Daisuke Waki, Jun Saegusa, Akio Morinobu.

Writing – original draft: Taiichiro Shirai.

Writing – review & editing: Taiichiro Shirai, Akira Onishi.

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