

[ CASE REPORT ]

## Successful Treatment of TAFRO Syndrome with Tocilizumab, Prednisone, and Cyclophosphamide

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### Abstract:

TAFRO syndrome is a rare systemic inflammatory disease characterized by thrombocytopenia, pleural effusion, fever, renal dysfunction, reticulin fibrosis of the bone marrow, and organomegaly. The clinical course varies significantly among patients. However, the prognosis is usually dismal in patients with severe TAFRO syndrome, and no optimal treatment has yet been established. We herein describe the first case of TAFRO syndrome, which was successfully treated with combination therapy consisting of tocilizumab, prednisone, and cyclophosphamide.

**Key words:** TAFRO syndrome, tocilizumab, cyclophosphamide

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### Introduction

TAFRO syndrome is a systemic inflammatory disease characterized by thrombocytopenia, anasarca including pleural effusion and ascites, fever, renal dysfunction, and organomegaly (1, 2). This syndrome sometimes mimics the mixed type of multicentric Castelman disease (MCD), but the clinical characteristics and courses are different between TAFRO syndrome and MCD. The etiology remains largely unknown, leading to the lack of any standard treatments for TAFRO syndrome. While a majority of patients with this syndrome are refractory to treatment and tend to demonstrate a fatal outcome, other patients responding to immunosuppressive drugs, such as glucocorticoids, cyclosporine A, tocilizumab and rituximab have also been reported (3-15). However, there have been no reported case of TAFRO syndrome that were successfully treated with tocilizumab, prednisone, and cyclophosphamide. We herein report a case of TAFRO syndrome, which was successfully treated with tocilizumab, prednisone, and cyclophosphamide, together with a review of the pertinent literature.

### Case Report

A 72-year-old man was admitted to the hospital for the

evaluation of bilateral pleural effusion. He had been well until 4 weeks before this admission when he started complaining of fatigue, appetite loss and dyspnea. Three weeks later, he was pointed out to have bilateral pleural effusion by computed tomography (CT) of the lung. On admission, the patient was alert and oriented. His temperature was 37.1°C, blood pressure 153/90 mmHg, pulse 89 beats per minute, and oxygen saturation 96% while he was breathing ambient air. There were coarse crackles at the lung bases. Pitting edema was present in the both lower extremities. His superficial lymph nodes were not palpable. Neither purpural nor petechial lesions were not seen. The results of a laboratory examination are shown in Table 1. A complete blood count for peripheral blood showed anemia, lymphopenia, and marked thrombocytopenia. Coagulation tests revealed an elevation of fibrinogen together with fibrinogen degradation product (FDP) and D-dimer. The blood chemistry findings were remarkable for C-reactive protein (CRP), mild renal impairment, hypoalbuminemia and an elevation of soluble IL-2 receptor. Immunoglobulin (Ig) G level elevated, but IgG-4 remained normal. Although anti-Sjögren syndrome (SS)-A antibody was positive, all other antibodies were negative, which were indicative of Sjögren syndrome and other collagen disease. However, the patient denied any symptoms related to dry mouth or dry eye. A whole body CT showed the swelling of bilateral axillary, mediastinal,





**Figure 1.** CT of the chest and abdomen on admission showing axillary, mediastinum, paraaortic lymph node swelling, bilateral pleural effusion and ascites.

methylprednisolone, the patient developed temporary cardiac arrest due to severe lactic acidosis, which was immediately reversed by the rapid infusion of sodium bicarbonate. However, his renal function rapidly deteriorated during these episodes, and he was thus placed on continuous hemodiafiltration (CHDF), which was performed intermittently because of his unstable hemodynamic status. The patient subsequently received biweekly injections of tocilizumab (8 mg/kg) on day 16 and a single dose of cyclophosphamide (1,000 mg) on day 20, respectively. After the administration of cyclophosphamide, his hemodynamic status started to stabilize, and CHDF was performed as scheduled. CHDF was eventually stopped after 18 days and hemodialysis was stopped about 3 months after starting tocilizumab. During this period, corynebacterium sepsis and pneumonia developed on day 57, which were all successfully treated with antibiotics. The platelet count started increasing gradually on day 82 and the patient became platelet transfusion independent at 3 months after the administration of cyclophosphamide. Repeated CT scans confirmed a decrease of pleural effusion and ascites, and also a decrease in the size of the lymph nodes on day 228 (Fig. 2). Currently, he is being followed as an outpatient and is free from fever, ascites, pleural effusion, and thrombocytopenia with tocilizumab (8 mg/kg) infusion every 2 weeks and prednisone (8 mg). The clinical course of patient is shown in Fig. 3.

## Discussion

TAFRO syndrome was first described by Takai et al. (12).

The three reported cases had fever, anasarca, organomegaly, thrombocytopenia, and reticulin fibrosis of the bone marrow. The histological features of lymph nodes are mixed type MCD so that TAFRO syndrome thus appears to be a clinicopathologic variant of MCD (1, 2).

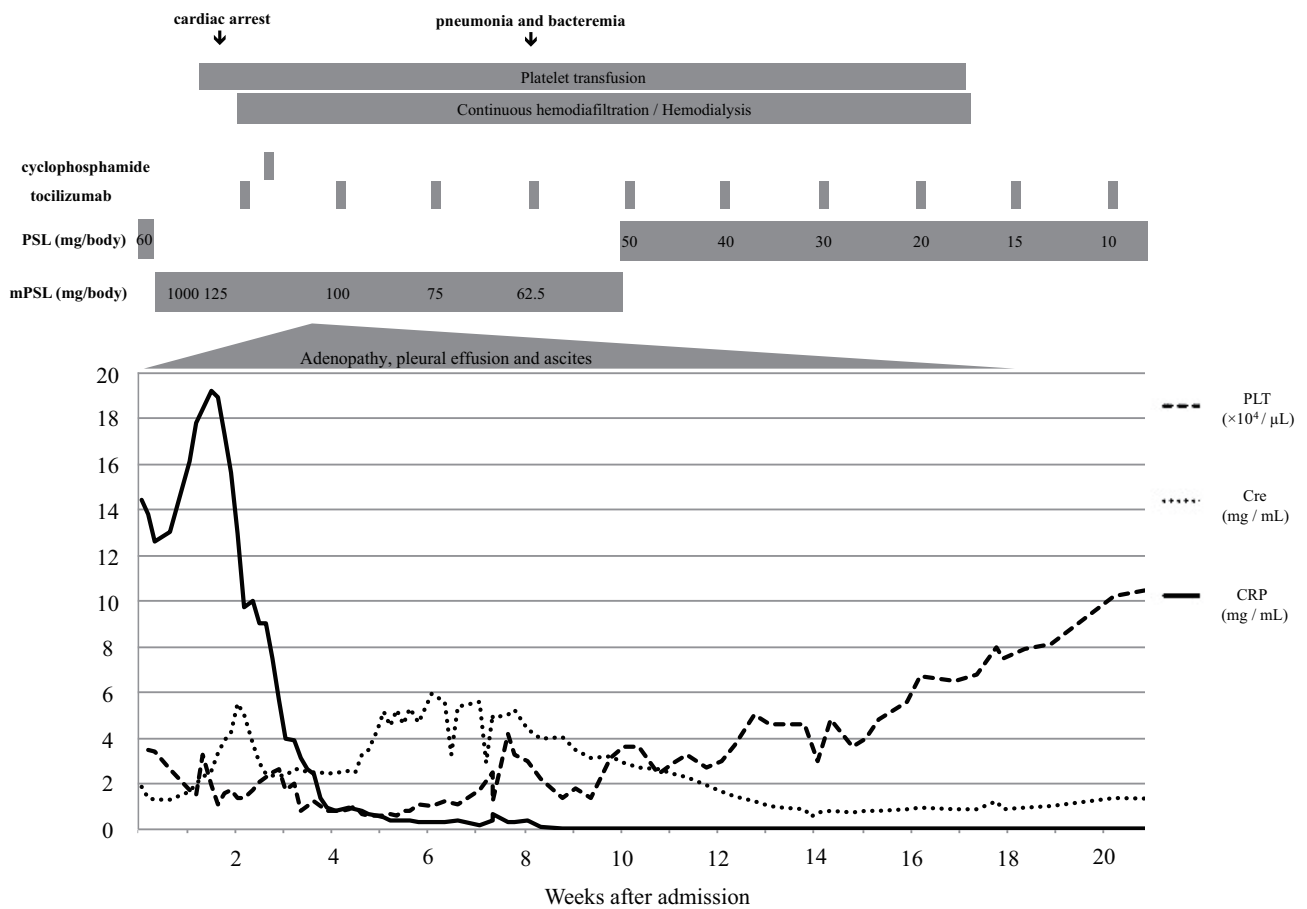
Our patient presented with an elevation of CRP, bilateral pleural effusion, ascites, thrombocytopenia, myelofibrosis, and renal dysfunction. He possessed five specific signs and symptoms in TAFRO syndrome. Recently, Masaki et al. proposed the diagnostic criteria, disease severity classification and treatment strategy for TAFRO syndrome (2). Although a lymph node biopsy is strongly recommended, the histological findings are not required for diagnosing this syndrome and classified thus there are considered to only be a minor criterion. Our patient fulfilled all the major criteria. In some cases TAFRO syndrome progresses rapidly so that the adequate samples may not be obtained. Both an early diagnosis and early intervention are crucial to obtain a better treatment outcome. As a result, we think that these diagnostic criteria are simple and in line with good clinical practice.

According to the disease severity classification, the present case was classified as a very severe (grade 5) (2). In our case, the FDP and D-dimer levels were both increased, which might be due to pleural effusion and ascites. An elevation of the FDP and D-dimer levels has also been described in other case reports (3-6, 8, 10-15). We also speculate that these data may indicate the severity of TAFRO syndrome. In fact, the administration of steroids, including pulse therapy, was only partially effective in lowering the CRP level and renal dysfunction did not improve. Some cases reported the successful treatment with cyclosporine A (CsA) in steroid-refractory TAFRO syndrome (3-5). However, we considered cyclophosphamide to be the more appropriate choice due to the renal dysfunction observed in our case. The administration of single-dose cyclophosphamide in combination with the tocilizumab and steroid was successful to control disease activity and it also improved the patient's quality of life. Although anti-SS-A antibody was positive, the patient did not have the symptoms of SS. Edahiro et al. also reported a case of TAFRO syndrome with a positive finding for anti-SS-A/B antibody (16). On the other hand, Takasawa et al. reported a case of TAFRO syndrome complicated with SS (17). These phenomena may indicated that immunologic dysregulation is involved in the pathogenesis of TAFRO syndrome.

Twenty-nine case reports on TAFRO syndrome were identified by a PubMed search from 2010 to 2016 (3-25). The clinical characteristics and courses of those cases are summarized in Table 2 together with our case. Their median age of was 49 years of age (range 15 to 77). Pleural effusion was observed in 27 cases and ascites in 25. The median platelet count was 30,000/ $\mu$ L (range 8,000 to 214,000). Median value of CRP and serum creatinine were 13.43 mg/dL (range 1.74 to 31.6) and 1.25 mg/dL (range 0.51 to 2.59), respectively. Initial treatment with steroids alone was performed in 22 cases, but a response was obtained in only 9



**Figure 2.** CT of the chest and abdomen 228 days after the treatment showing a marked improvement in lymphadenopathy, pleural effusion and ascites.



**Figure 3.**

**Table 2. Characteristics of Previous Reported Cases with TAFRO Syndrome.**

Reference	Age (years)	Sex	Anasarca	Platelet ( $\times 10^4/\mu\text{L}$ )	CRP (mg/dL)	Creatinine (mg/dL)	1st		2nd / 3rd / 4th		Outcome
							Treatment	Response	Treatment	Treatment	
3	61	M	PE, ascites, edema	1.3	17.22	2.15	mPSL	PD	TCZ / CyA	Alive	
4	49	F	PE, ascites, edema	1.7	6.04	0.96	Dex	PR	CyA	Alive	
5,12	47	F	PE, ascites, edema	1.5	18.27	0.7	CHOP	PR but relapse	PSL *	Alive	
5,12	56	M	PE, ascites	1.9	16.35	1.9	IvIG, mPSL	PD	CyA	Alive	
5,12	49	M	PE, ascites, edema	1	16.42	0.9	IvIG, mPSL	PD	-	Dead	
5,12	53	F	Ascites	3.8	31.6	0.7	PSL	PR	Splenectomy, PSL / Cyclophosphamide	Alive	
5,12	56	F	PE, ascites, edema	4.4	6.35	1.53	PSL, CyA	CR	-	Alive	
6	49	F	Ascites	2	21.9	2.2	mPSL	PD	TCZ	Alive	
7	15	M	PE, ascites	3	17.8	N.D	mPSL	PD	TCZ	Alive	
8	50	M	PE, ascites, edema	6.7	17.19	2.26	mPSL	PD	TCZ	Alive	
9	48	F	PE, edema	2.3	1.74	0.72	IvIG	PD	PSL / Rituximab	Alive	
10	48	M	PE, ascites, edema	1.6	2.5	1.5	mPSL	PD	TCZ, IvIG / Rituximab, TPOR agonist	Alive	
15	77	F	Edema	4.4	9.6	0.93	TCZ	PD	PSL / Rituximab / CyA	Alive	
11	29	F	PE, ascites	1.9	18.9	1.94	mPSL	PD	CHOP**	Alive	
11	21	F	PE, ascites	5.9	28.87	0.82	mPSL	PD	TCZ / CyA / R-CHOP**	Alive	
13	72	M	PE, edema	5	22.26	0.88	PSL	PD	TCZ	Dead	
14	57	F	PE, ascites	1.3	17.73	1.34	IvIG, mPSL	PD	CHOPEP	Dead***	
14	73	M	PE, ascites	2.4	4.17	1.45	PSL	PD	-	Dead	
16	46	F	PE, ascites	1.9	3.2	0.51	mPSL	CR	-	Alive	
17	46	F	PE, ascites	21.2	13.43	0.89	mPSL	PR	CyA	Alive	
18	57	M	PE, ascites, edema	N.D	N.D	N.D	Glucocorticoid	PR	TCZ	Alive	
19	66	M	PE, ascites	0.8	N.D	1.2	Glucocorticoid	PR	CyA / Glucocorticoid, CyA	Dead	
20	56	M	PE, ascites	7.6	11.7	1.43	PSL	PD	TCZ / Thalidomide	Alive	
21	39	M	PE, ascites	3.6	4.49	1.18	mPSL	CR	-	Alive	
21	38	M	PE, ascites	20.2	11.18	2.59	PSL	CR	-	Alive	
22	28	M	PE	7.5	N.D	2.5	PSL	PR	Rituximab	Alive	
23	21	F	PE, ascites, edema	2.9	22.2	0.8	mPSL	PD	TCZ / R-CVP	Alive	
24	47	F	PE, ascites, edema	3.9	12.4	1.4	PSL	PD	TCZ	Alive	
25	43	F	PE	13.5	20.1	0.86	PSL, TCZ, Rituximab	CR	-	Alive	
Presented case	72	M	PE, ascites, edema	3.4	12.59	1.3	mPSL	Not improved	TCZ, Cyclophosphamide	Alive	

M: male, F: female, PE: pleural effusion, mPSL: methylprednisone, PSL: prednisone, IvIG: intravenous immunoglobulin, CyA: cyclosporine A, TCZ: tocilizumab, PD: progression disease, PR: partial response, CR: complete response, R-CHOP: rituximab, cyclophosphamide, adriamycin, vincristine and prednisone, R-CVP: rituximab, cyclophosphamide, vincristine and prednisone

\* The patient relapsed four times with tapering of PSL, but responded to PSL.

\*\*Cardiomyopathy due to adriamycin was suspected, and CEPP was performed as the alternative regimen.

\*\*\*The patient died due to septic shock.

cases, suggesting that the efficacy of steroids alone as initial therapy for TAFRO syndrome is limited. Regarding the second treatment, treatments with tocilizumab were performed in 12 out of 18 patients and a complete response was obtained in 6 cases (50% of patients) and a partial response in 1 case. Regarding the subsequent therapies after the second line treatment, cyclophosphamide was used in 6 cases including those who received CHOP chemotherapy, and all achieved either a complete response (n=4) or a partial response (n=2).

In our case, the administration of cyclophosphamide soon after commencing tocilizumab was able to stabilize his hemodynamic status with acceptable toxicities, such as mild myelosuppression. The reported cases together with our case suggested that intensive immunosuppression early in the course of TAFRO syndrome results in a better control of the disease activity. To this end, the use of cyclosporine is another treatment of choice. In fact, cyclosporine was given in 9 cases and 7 cases achieved a complete remission. However, its use may be limited due to preexisting renal impairment. Although the number of cases is small, rituximab seems to be effective as six out of seven cases treated with rituximab achieved a complete response.

Based upon the literature review and our experience, it is plausible that the administration of steroids alone is not effective for severe TAFRO syndrome and an earlier introduction of agents other than steroids may improve the transplant outcome. The optimal combination of drugs for each patient remains to be elucidated, and further study is clearly warranted.

In conclusion, this is the first case of TAFRO syndrome which was successfully treated with tocilizumab, prednisone, and cyclophosphamide. Adding cyclophosphamide to tocilizumab may therefore be of value to control the disease activity and it may lead to remission in cases of steroid-refractory TAFRO syndrome, especially in cases of very severe disease. This may also result in a reduction of the steroid dose and thereby allows such patients to avoid the adverse events associated with steroids.

**The authors state that they have no Conflict of Interest (COI).**

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