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Original Article

ORIGINAL ARTICLE

Long-term clinicopathological characteristics of TAFRO syndrome and its relapse: a case series study

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ABSTRACT

Introduction. This study aimed to analyze the clinical course of TAFRO syndrome in patients through extended follow-up, focusing on recurrent cases and long-term remission.
Methods. This was a retrospective case series study. We assessed the clinical course of patients diagnosed with TAFRO syndrome between January 2012 and September 2022 at Toranomon Hospital or Toranomon Hospital Kajigaya, excluding those patients who died during the initial hospitalization.
Results. Twelve patients were included. Baseline characteristics, laboratory findings, treatment modalities, and outcomes were assessed. During the median follow-up period of 1474 days, two patients experienced recurrence following a reduction in tocilizumab (TCZ) dose, whereas two achieved remission for >400 days without TCZ treatment. The remaining eight patients maintained remission under the continued TCZ therapy. Recurrence diagnosis was complicated by the non-simultaneous presentation of the five manifestations of TAFRO syndrome. The patients who experienced recurrence showed milder manifestations and faster recovery than the initial onset. Glomerular endotheliopathy was evident in kidney biopsies during recurrence, which was similar to the initial presentation. In a case where only inflammation preceded other manifestation, a kidney biopsy was pivotal in distinguishing TAFRO syndrome relapse from other inflammatory conditions such as infection. Pretreatment serum IL-6 levels were within the reference range only in patients who experienced long-term remission without TCZ treatment.
Conclusions. This is the first study to perform kidney biopsies on recurrent TAFRO cases, highlighting recurrence after TCZ dosage reduction, non-simultaneous manifestation of symptoms, the utility of kidney biopsies in recurrence diagnosis, and potential non-IL-6 pathogenesis factors. Pretreatment serum IL-6 levels may help identify patients suitable for maintenance therapy without TCZ. Further investigation is warranted to identify stratified treatment approaches based on individual etiologic factors.

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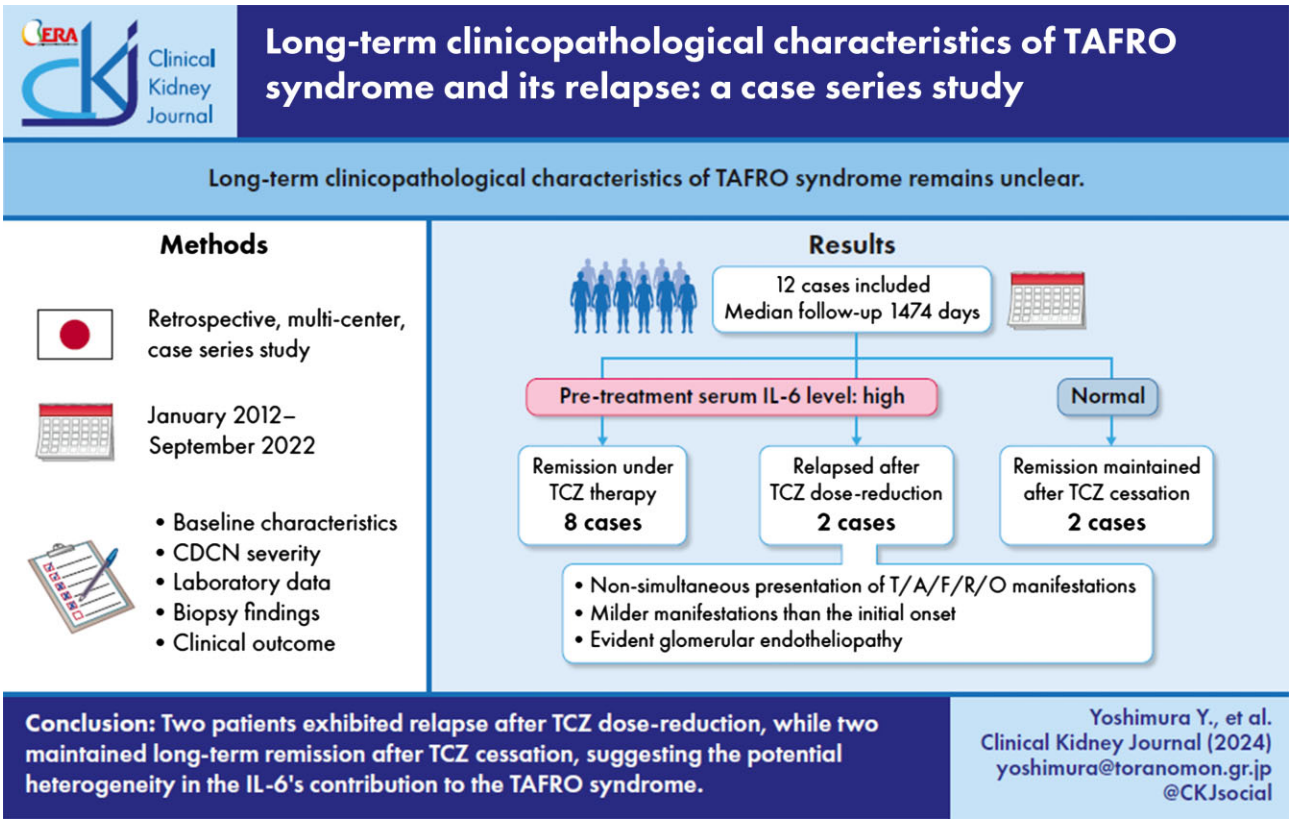
GRAPHICAL ABSTRACT



Keywords: interleukin-6, kidney biopsy, relapse, TAFRO syndrome, tocilizumab

INTRODUCTION

TAFRO syndrome is a rare systemic inflammatory disease characterized by five manifestations: thrombocytopenia (T), anasarca (A), fever/inflammation (F), renal insufficiency/reticulin fibrosis of the bone marrow (R), and organomegaly (O) [1]. TAFRO syndrome is thought to be a subtype of idiopathic multicentric Castleman disease (iMCD) [2], which has more severe manifestations and worse outcomes, such as the need for hemodialysis (HD) or death [3, 4]. Although we previously reported on the clinicopathological features of TAFRO syndrome [5], its long-term clinical course remains unclear. In addition, the current international treatment guidelines for iMCD [6] recommend IL-6 blockade therapy uniformly as frontline induction therapy. Here, we present a case series analysis of the clinical course of TAFRO syndrome in 12 patients who underwent extended follow-up.

MATERIALS AND METHODS

Study design

This was a case series study. We retrospectively analyzed the clinical course of patients who were diagnosed with TAFRO syndrome at Toranomon Hospital or Toranomon Hospital Kajigaya between January 2012 and September 2022. Diagnosis was made according to the criteria proposed by Nishimura *et al.* [7] Cases in which the patient died during the initial hospitalization were excluded.

Relapse was defined as the condition in which at least one of the five manifestations was observed after discharge. However, cases in which the manifestation appeared to be due to causes other than TAFRO syndrome, such as infection, were excluded.

In the clinical course analysis, Day 1 was defined as the day of diagnosis of TAFRO syndrome at the initial onset.

The internal ethics review board approved this study design and protocol (approval number 2458-B), which were performed in accordance with the principles of the Declaration of Helsinki.

Data collection

Clinicopathological data were retrieved from medical records. They included baseline patient demographics (sex, age at diagnosis, follow-up period, comorbidities, initial symptoms, Eastern Cooperative Oncology Group Performance Status, and the Castleman Disease Collaborative Network severity), blood examination findings [platelets (minimum value), alkaline phosphatase (measured by the International Federation of Clinical Chemistry method), lactate dehydrogenase, creatinine (Cr) (maximum value), C-reactive protein (CRP), fibrinogen, immunoglobulin G, IgA, IgM, IgE, interleukin-6 (IL-6), vascular

endothelial growth factor, and soluble IL-2 receptor], urine examination findings (gravity, red blood cells, white blood cells, and protein), biopsy findings (kidney and bone marrow), treatment [corticosteroid, tocilizumab (TCZ), rituximab (RTX), cyclosporin A (CyA), thrombopoietin-receptor agonist (TPO-RA), and platelet concentrate (PC) transfusion], and outcome.

Statistical analysis

Charts were drawn using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

We identified 14 patients who met the diagnostic criteria for TAFRO syndrome during the study period. However, two patients were excluded due to death during the initial hospitalization. Consequently, a total of 12 patients were included in the analysis. The clinicopathological characteristics at the time of the initial attack in Cases 1–6 [5] and 8 [8] have been previously reported. The median follow-up period was 1474 days. The baseline characteristics of the patients are summarized in Table 1. All patients were Japanese. Complement levels (C3, C4, and C1q) and ADAMTS13 activity were within the reference range. Screening of autoantibodies were negative, including anti-nuclear antibody, anti-SS-A antibody, myeloperoxidase-antineutrophil cytoplasmic antibody, proteinase3-antineutrophil cytoplasmic antibody, lupus anticoagulant, and anti-cardiolipin antibody. Human immunodeficiency virus antigen and antibody and human herpesvirus 8-polymerase chain reaction results were negative.

Induction therapy

In our study, all 12 patients underwent corticosteroid treatment, and all except the patient in Case 3 were administered TCZ therapy. Additional treatment with RTX was introduced in Cases 5, 7, 8, and 9, and CyA was added in Cases 9 and 12, and in these patients, thrombocytopenia did not respond sufficiently to corticosteroids and TCZ therapy. TPO-RA and/or PC transfusions were temporarily utilized in most cases.

Long-term clinical courses

Among the 12 patients, the recurrence of TAFRO syndrome was observed in two (Cases 6 and 9), while long-term remission without immunosuppressants was achieved in two patients (Cases 4 and 5). The remaining eight patients maintained remission under the continued TCZ therapy. No patients died during the observational period.

Prognosis of renal dysfunction

All cases demonstrated the manifestation of renal dysfunction and seven patients (Cases 2, 4, 6, 7, 8, 9, and 11) required HD temporally. In all cases except Case 8, renal function recovered to within reference range, with a median time from onset of TAFRO syndrome to normalization of serum Cr levels of 54 days (range 10–146 days). Case 8 exhibited an irreversible deterioration in renal function accompanied by marked hypertension, and a kidney biopsy demonstrated malignant nephrosclerosis-like lesions, as previously reported [8].

Clinical course of relapsing cases

The patients in Cases 6 and 9 experienced recurrences. Figure 1 visualizes the detailed clinical course of Cases 6 and 9.

The patient in Case 6 relapsed ~2.5 years after the initial onset. Following successful induction therapy, prednisolone (PSL) treatment was tapered and ceased on day 866, and remission was maintained with 8 mg/kg intravenous TCZ (TCZ-IV) every 4 weeks. TCZ was switched to a 162 mg subcutaneous injection of TCZ (TCZ-SC) every 2 weeks on day 966 to reduce the burden of frequent hospital visits. After the patient started receiving TCZ-SC, her CRP levels increased, which raised suspicion of an infection at that time. She was readmitted to our hospital on day 1104 and started receiving broad antibiotics. However, inflammation worsened, and then thrombocytopenia manifested on day 1110, leading to the suspicion of a TAFRO syndrome flare-up. Anasarca, renal insufficiency, and organomegaly also appeared later. Following methylprednisolone (mPSL) pulse therapy, the administration route of TCZ was changed from SC to IV, and each manifestation resolved. While she required intratracheal intubation and HD at the time of the initial onset, she did not at the time of the recurrence. Pretreatment serum IL-6 levels were high both at the time of the initial onset and the time of recurrence. The maximum serum creatinine levels reached 5.64 mg/dL (day 17) during the initial onset, necessitating HD. In the case of recurrent onset, the maximum serum creatinine level was 1.77 mg/dL (day 1118). However, by the end of the observation period, the serum creatinine level had completely normalized to 0.71 mg/dL. The duration of hospitalization during the initial attack and the recurrence were 163 and 74 days, respectively.

The patient in Case 9 relapsed ~2 years after the initial onset. After the induction therapy succeeded, PSL was tapered and ceased on day 596, and remission was maintained with 8 mg/kg TCZ-IV once every 5 weeks. From day 701, the frequency of TCZ-IV was reduced to once every 6 weeks. Then, the patient developed recurrence with thrombocytopenia, inflammation, and renal insufficiency on day 743, followed by anasarca and organomegaly. The patient recovered faster than during the initial onset and did not require massive blood transfusions or CyA, which were required during the initial onset. Pretreatment serum IL-6 levels were high both at the time of the initial onset and the time of recurrence. The maximum serum creatinine levels reached 4.65 mg/dL (day 26) during the initial onset, while 2.29 mg/dL (day 779) in the recurrent onset. By the end of the observation period, it had normalized to 0.75 mg/dL. The durations of hospitalization during the initial attack and the recurrence were 318 and 40 days, respectively.

Kidney biopsy findings

Kidney biopsy findings at the time of recurrence are compared to those at the initial onset in Fig. 2. For the patient in Case 6, kidney biopsies were performed both at the initial onset and at the relapse. At the initial onset, typical glomerular endotheliopathy was observed (Fig. 2a–c) as we previously reported [5]. At the recurrent onset in Case 6, a kidney biopsy was performed on day 1118 after mPSL pulse therapy but revealed marked glomerular endotheliopathy. Endothelial cell swelling, mesangiolysis, and double contour of the glomerular basement membrane were observed (Fig. 2d and e). Electron microscopy revealed prominent subendothelial edema and mesangiolysis, as well as a thickened capillary wall (Fig. 2f). Overall, renal pathology showed glomerular endotheliopathy typical of TAFRO syndrome, as well as findings related to concomitant diabetes mellitus. These findings were similar between the biopsies obtained during the initial

Table 1: Baseline characteristics of the patients.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Median	Case 6 relapse	Case 9 relapse	Reference range
Demographics																
Sex	Female	Male	Female	Male	Male	Female	Male	Female	Male	Male	Male	Male		Female	Male	
Age at diagnosis, years	80	53	60	34	50	38	78	18	67	51	84	39	52	41	69	
Follow-up period, days	3566	1932	2023	1756	1606	1665	1341	532	782	380	93	224	1474			
Comorbidities	HT	HT		UC	T2DM	T1DM, UC	HT, T2DM, PTC	HT			Glaucoma (blind)			T1DM, UC		
Initial symptoms	Anasarca	Anasarca, lowering urine output	Anasarca, body weight gain	Anasarca, dyspnea	Anasarca, anorexia, abdominal swelling	Anasarca, fever, abdominal pain		Fever, fatigue	Anasarca, anorexia, abdominal swelling	Fever, diarrhea	Dyspnea	Fatigue		Fatigue, anorexia, back pain	Fatigue, anorexia	
ECOG PS	2	2	1	3	1	4	1	1	3	1	1	1		1	1	
CDCN severity	Severe	Severe	Not Severe	Severe	Not Severe	Severe	Not Severe	Severe	Severe	Not Severe	Severe	Not Severe		Not Severe	Not Severe	
Blood examination																
Plt (minimum), x$10^3/\mu$L	2.9	13	46	4.1	18	2.4	16	16	4	36	1.3	43	15	40	23	158–348
ALP (IFCC), IU/L	1438	570	534	641	1181	1179	180	220	713	214	183	196	552	558	184	38–113
LDH (IFCC), IU/L	173	195	194	259	235	407	301	258	198	216	172	253	226	480	194	124–222
Cr (maximum), mg/dL	2.01	4.98	1.85	6.28	2.68	5.64	3.66	5.49	4.65	2.24	5.89	1.70	4.16	1.77	2.29	Male 0.65–1.07, Female 0.46–0.79
CRP, mg/dL	7.3	14.3	2.1	12.5	11.9	21.5	2.4	9.0	15.7	20.5	20.4	34.4	13.4	19.1	26.2	<0.14
Fibrinogen, mg/dL	357	512	389	408	631	1031	426	471	590	642	325	111	448	770.7	559.2	150–300
Immunoglobulin G, mg/dL	893	685	1449	1221	685	835	1297	621	2249	1147	1184	886	1020	848	965	870–1700
IL-6, ng/L	21.3	17.5	1.9	6.2	3.0	103	17.3	NA	16.9	27.3	25.3	16.4	17.3	524	101	<7.0
VEGF, pg/mL	454.0	58.3	48.8	552.0	133.0	288.0	116.0	NA	NA	255.0	NA	169.0	169.0	163.0	1932	<38.3
sIL-2R, U/mL	803	724	256	1026	1094	2306	1489	1991	2050	475	1021	338	1024	1782	NA	157–475
Urine examination																
RBC/HPF	5–10	5–10	Many	Many	5–10	<1	5–10	<1	<1	1–4	Many	<1		<1	1–4	<4
Protein, g/gCr	0.86	0.30	3.71	0.45	0.43	0.59	3.27	0.10	0.22	0.50	0.27	0.13	0.44	0.56	0.09	
Biopsy																
Kidney	Glomerular endothe-liopathy	Glomerular endothe-liopathy	Glomerular endothe-liopathy	Glomerular endothe-liopathy	Glomerular endothe-liopathy	Glomerular endothe-liopathy	Glomerular endothe-liopathy	Glomerular endothe-liopathy	NA	Glomerular endothe-liopathy	NA	Glomerular endothe-liopathy		Glomerular endothe-liopathy	Glomerular endothe-liopathy	
Bone marrow	Reticulin fibrosis	Reticulin fibrosis	Reticulin fibrosis	Reticulin fibrosis	Reticulin fibrosis	Reticulin fibrosis	Reticulin fibrosis	Reticulin fibrosis	Reticulin fibrosis	Reticulin fibrosis	Reticulin fibrosis	Reticulin fibrosis		NA	NA	
Treatment																
Corticosteroid	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y	
mPSL pulse	N	Y	N	N	N	Y	N	Y	Y	N	Y	Y		Y	Y	
TCZ (induction therapy)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y	
TCZ (maintenance therapy)	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y		Y	Y	
RTX	N	N	N	N	Y	N	Y	Y	Y	N	N	N		N	N	
CyA	N	N	N	N	N	N	N	N	Y	N	N	Y		N	N	
TPO-RA	Y	N	N	Y	Y	N	Y	Y	Y	N	Y	Y		Y	Y	
PC	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y		Y	N	
Temporal HD	N	Y	N	Y	N	Y	Y	Y	Y	N	Y	N		N	N	
Outcome	Improved	Improved	Improved	Improved	Improved	Relapsed	Improved	Improved	Relapsed	Improved	Improved	Improved		Improved	Improved	

ALP, alkaline phosphatase; CDCN, Castleman Disease Collaborative Network; Cr, creatinine; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HD, hemodialysis; HT, hypertension; IFCC, International Federation of Clinical Chemistry; Ig, immunoglobulin; LDH, lactate dehydrogenase; N, no; NA, not available; Plt, platelets; PTC, papillary thyroid cancer; RBC, red blood cell; sIL-2R, soluble IL-2 receptor; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus; UC, ulcerative colitis; VEGF, vascular endothelial growth factor; Y, yes.

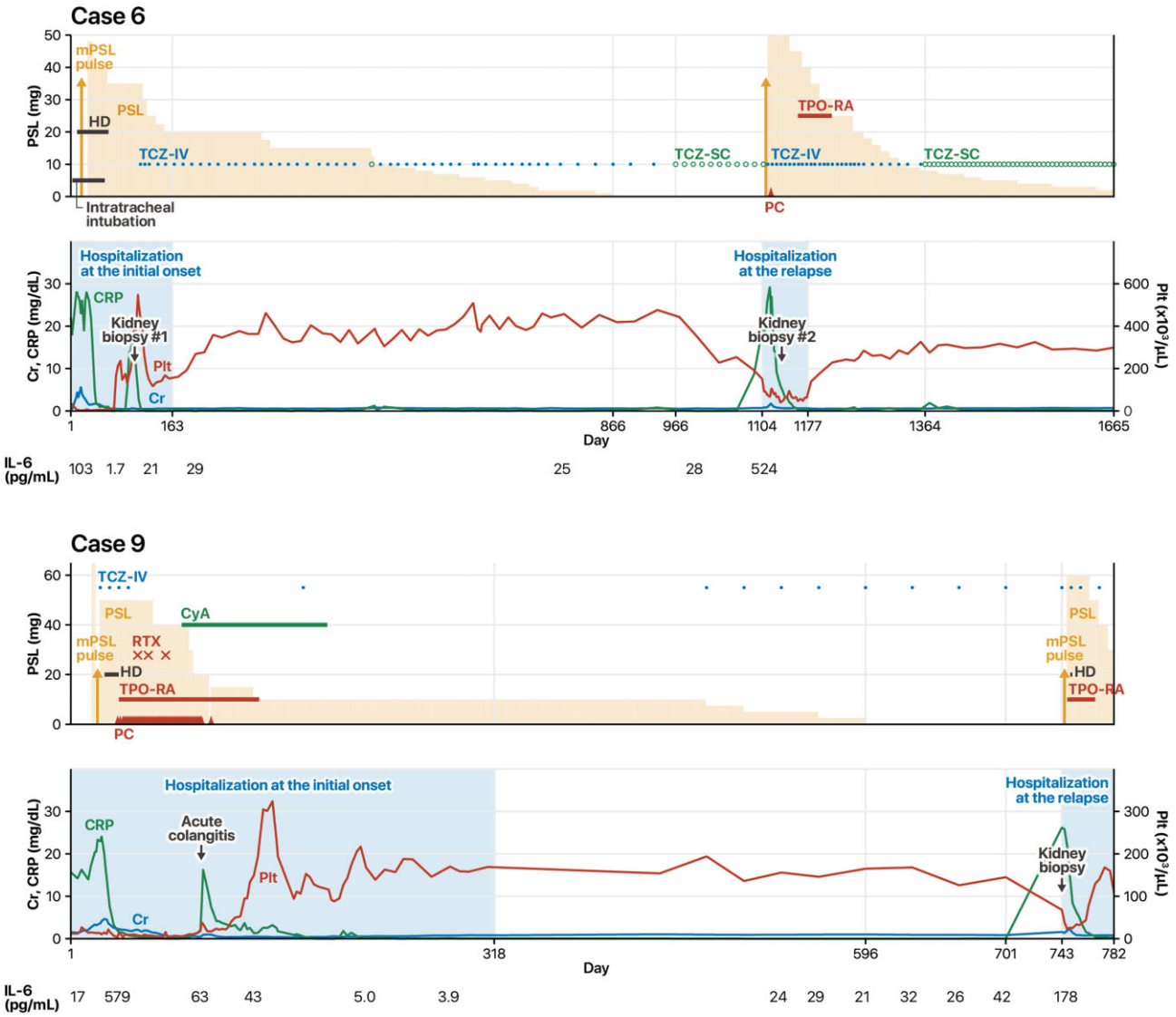


Figure 1: Clinical course of Cases 6 and 9. Cr, creatinine; HD, hemodialysis; Plt, platelets; TCZ-SC, subcutaneous injection of TCZ; TCZ-IV, intravenous injection of TCZ.

and recurrent onset. In this case, the kidney biopsy played a crucial role in diagnosing TAFRO syndrome relapse, because the only systemic inflammation preceded other manifestations and the other inflammatory conditions such as infections could not be clinically ruled out in acute phase.

For the patient in Case 9, a kidney biopsy was performed only at the time of recurrence after mPSL pulse therapy, which also showed glomerular endotheliopathy (Fig. 2g and h). Electron microscopy revealed marked subendothelial swelling and effacement of foot process (Fig. 2i).

Cases of long-term remission after the cessation of maintenance therapy

In contrast to recurrent cases (Cases 6 and 9), Cases 4 and 5 showed long-term remission after the termination of medication, including TCZ. In Case 4, PSL and TCZ were discontinued on days 1314 and 1364, respectively, although the patient received tofacitinib and filgotinib for coexisting ulcerative colitis. Remission was sustained until the last follow-up on day 1765. In Case 5, PSL and TCZ were discontinued on days 1220 and 141, respectively, and remission was maintained without any medication until the last follow-up on day 1606.

DISCUSSION

TAFRO syndrome is a rare systemic inflammatory disease characterized by a constellation of manifestations, including thrombocytopenia, anasarca, fever/inflammation, renal insufficiency/reticulin fibrosis of the bone marrow, and organomegaly [1]. In this study, we evaluated its long-term clinical course and encountered two cases of recurrence (Cases 6 and 9). Reports of recurrent TAFRO syndrome cases are extremely rare [9]. This represents the first study on such recurrent cases in which kidney biopsies in the recurrent onsets were performed. The following four clinical features were shared between the recurrent cases.

First, all recurrence occurred following a reduction in TCZ dose, and none of our patients experienced relapse on PSL discontinuation, suggesting that TCZ could play a crucial role in

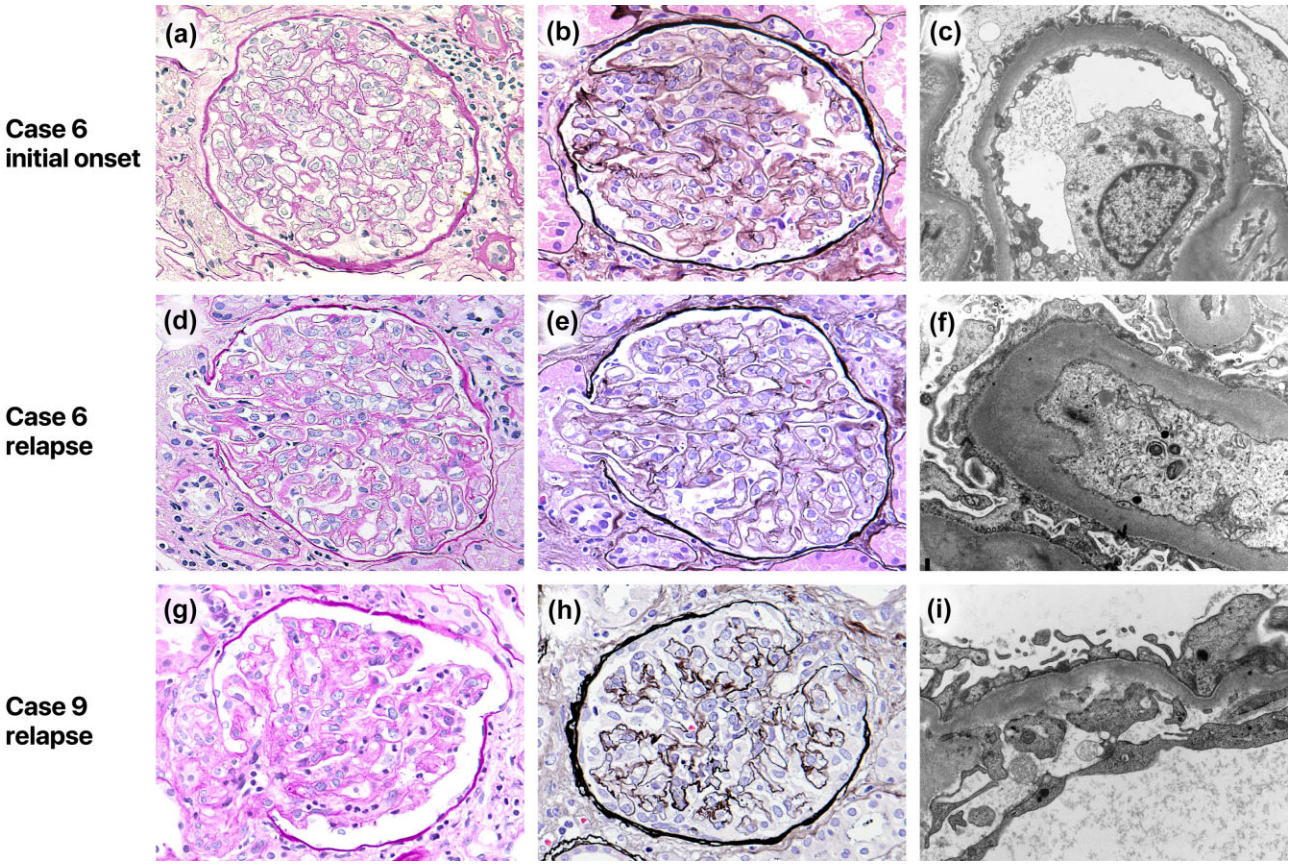


Figure 2: Kidney biopsy findings. (**a**) Light microscopy demonstrated glomerular endotheliopathy characterized by edematous endothelial swelling. Case 6 initial onset, Periodic acid-Schiff (PAS) staining, ×400. (**b**) Double contour of the glomerular basement membrane and mesangiolysis. Periodic acid-methenamine silver (PAM) staining, ×400. (**c**) Electron microscopy (EM) showed endothelial cell swelling with the subendothelial space expansion. Glomerular basement membrane was thickened, consistent with the concomitant diabetes mellitus. (**d**)–(**f**): Similar pathological findings were identified in Case 6 relapse. PAS staining ×400, PAM staining ×400, and EM, respectively. (**g**), (**h**): Case 9 relapse. PAS staining ×400 and PAM staining ×400, respectively. (I) EM demonstrated marked subendothelial swelling and effacement of the foot process.

maintaining remission in these cases. In Case 6, the recurrence followed the switch of TCZ from IV (8 mg/kg every 4 weeks) to SC (162 mg every 2 weeks). In Case 9, the recurrence followed the reduction in TCZ dose. Considering these facts, the activity of TAFRO syndrome might persist long after the initial onset of the disease and could be appropriately controlled by a sufficient dose of TCZ in the range in which remission is clinically achieved. In the MRA229JP study, which was a study evaluating the efficacy and safety of TCZ-SC (162 mg every 2 weeks) versus TCZ-IV (8 mg/kg every 4 weeks) in patients with rheumatoid arthritis, it was suggested that serum TCZ trough concentrations tended to decrease with increasing body weight, body surface area, and body mass index (BMI). American College of Rheumatology 20 responses were consistently lower in patients treated with TCZ-SC than in patients treated with TCZ-IV in patients with body weight ≥70 kg or BMI ≥25 kg/m^2 [10]. In fact, the BMI of the patient in Case 6 was 32.3 kg/m^2. Therefore, the switch from TCZ-IV to TCZ-SC was considered a substantial reduction in TCZ dose for the patient, which might have triggered recurrence in this case. After day 1 364, TCZ-IV was switched to TCZ-SC (162 mg every week), and the patient experienced no recurrence.

Second, five manifestations did not appear simultaneously in patients who experienced recurrence, which could make diagnosing recurrence difficult and delayed. Moreover, the order in which five manifestations appeared was different between cases. During the relapse of the disease in Case 6, inflammation manifested first, followed by thrombocytopenia and later by anasarca, renal insufficiency, and organomegaly. In the recurrence of the disease in Case 9, thrombocytopenia, inflammation, and renal insufficiency occurred first, followed by anasarca and organomegaly. Particularly in Case 6, only systemic inflammation preceded before the other manifestations appeared, which required us to exclude infection. A kidney biopsy provided critical evidence of TAFRO syndrome relapse.

Third, the five manifestations observed in the patients who experienced recurrence were milder than those observed during the initial onset. They could successfully recover with more modest treatment, and the duration of hospitalization was no longer than that during the initial onset. Table 2 illustrates the comparison between the initial onset and relapse in terms of disease severity, laboratory findings, treatment needed, and duration of hospitalization. Although insufficient immunosuppression might trigger recurrence as mentioned before, the reason recurrences were not as severe as the initial attacks could have been that the patients were on immunosuppressive treatment at the time of recurrence. The biopsy in the recurrence in Case 6 showed that the endothelial damage had worsened

Table 2: Comparison of initial onset and relapse.

		Initial onset	Relapse
CDCN severity	Case 6	Severe	Not severe
	Case 9	Severe	Not severe
Plt (minimum), $\times 10^3/\mu$L	Case 6	2.4 (day 17)	40 (day 1133)
	Case 9	4 (day 36)	23 (day 747)
CRP, mg/dL	Case 6	21.5	19.1
	Case 9	15.7	26.2
Cr (maximum), mg/dL	Case 6	5.64 (day 17)	1.77 (day 1118)
	Case 9	4.65 (day 26)	2.29 (day 779)
Treatment	Case 6	mPSL pulse, PSL, TCZ, HD (51 days), intratracheal intubation	mPSL pulse, PSL, TCZ
	Case 9	mPSL pulse, PSL, TCZ, RTX, CyA, massive PC transfusion, HD (10 days)	mPSL pulse, PSL, TCZ, HD (2 days)
Hospitalization duration, days	Case 6	163	74
	Case 9	318	40

CDCN, Castleman Disease Collaborative Network; HD, hemodialysis; Plt, platelets.

compared to the first biopsy, but we think it is not sound to directly compare the severity of renal pathology because the timing of kidney biopsy was disparate between the initial and recurrent episodes. On initial presentation of Case 6, the patient exhibited severe manifestations of TAFRO syndrome, including tracheal intubation and ventilator, and severe thrombocytopenia. Consequently, a kidney biopsy was feasible only on the 99th day following the onset of renal dysfunction. By contrast, during the recurrence episode, a kidney biopsy was performed on the third day after the reemergence of renal dysfunction.

Fourth, glomerular endotheliopathy was the renal pathological finding observed in patients who experienced the recurrence of TAFRO syndrome, which was similar to the onset of TAFRO syndrome. Notably, in Cases 6 and 9, glomerular endotheliopathy was evident despite the biopsy being performed after mPSL pulse therapy. As the kidney pathology during recurrence mirrors that at the initial presentation, a kidney biopsy can provide valuable assistance in diagnosing recurrent cases. The reproducible demonstration of glomerular endotheliopathy in TAFRO syndrome may be attributed to the cytokine storm characteristic of the syndrome's acute phase. In TAFRO syndrome, there is an unfettered production of inflammatory cytokines such as IL-6 [11]. Similarly, in patients with coronavirus disease 2019 (COVID-19), thrombotic microangiopathy-like systemic dysfunctions, including renal glomerular endotheliopathy, have been observed. Dysregulated complement activation and cytokine storms in COVID-19 thought to play a central role to these multi-organ thrombotic complications [12]. Additionally, cases of glomerular endothelial cell injury have been reported in patients experiencing cytokine release syndrome following chimeric antigen receptor T-cell therapy [13]. Notably, TCZ has gained approval for the treatment of cytokine release syndrome induced by cancer therapy [14].

While Cases 6 and 9 developed relapse after TCZ withdrawal, Cases 4 and 5 maintained long-term remission after TCZ was discontinued. Interestingly, among the 11 cases treated with TCZ, only Cases 4 and 5 had serum IL-6 levels within the reference range at the time of diagnosis, as shown in Table 1. (Serum IL-6 levels were elevated during TCZ therapy and returned to within the normal range after the discontinuation of TCZ therapy. We attributed this phenomenon to the IL-6 receptor blockade by TCZ.) Furthermore, recent studies have revealed that three patients with IL-6 blockade-refractory TAFRO syndrome exhibited increased mammalian target of rapamycin (mTOR) signaling activity driven by type I interferon signaling and sirolimus-induced remission [9, 15]. These facts suggest that factors other than IL-6 might also have been involved in Cases 4 and 5. This new perspective challenges the prevailing paradigm that uniformly advocates for the use of IL-6 inhibitors as first-line therapy [16–18], and implies the prospect of stratified treatment strategy according to the individual pathogenic factors and their degree of contribution to the disease in each patient (Fig. 3). mTOR inhibitors and RTX may serve as potential agents for personalized therapeutic intervention. Moreover, pretreatment serum IL-6 levels might be a clue to determine the modality of maintenance immunosuppressants. Although it is known that TCZ can prolong the half-life of inactive or circulating IL-6, thereby complicating the interpretation of serum IL-6 levels post-TCZ administration [19]. Nevertheless, in the relapse episodes of both Cases 6 and 9, we observed a significant increase in serum IL-6 levels—on the order of magnitude—compared to their baseline levels during the remission maintenance phase. This led us to hypothesize that IL-6 levels could serve as a useful guide for therapeutic intervention. The remission of TAFRO syndrome in Cases 4 and 5 might also have been influenced by the use of Janus kinase inhibitors for ulcerative colitis. Further investigation is warranted.

Limitations

This study has several limitations. First, this was a case series with a small number of patients, resulting in limited generalizability. Especially, only in Case 6 was a renal biopsy able to be conducted, both at the time of initial onset and at the time of recurrence. Second, the potential for referral bias should be acknowledged, as all the cases in this report were referred from other hospitals. This could mean that our cases might have exhibited greater diagnostic and/or treatment challenges than typical TAFRO syndrome cases. In addition, some information was missing regarding the patient's course at the previous hospital. Furthermore, the treatment strategy we employed was not uniform across patients, because the pathophysiology and

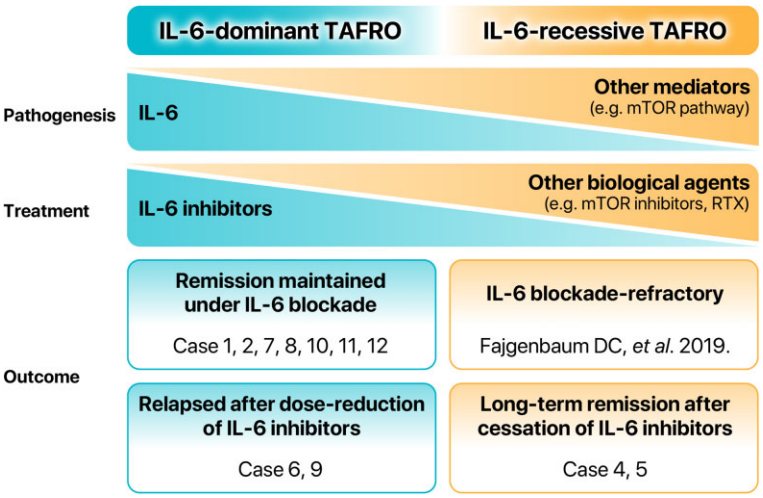


Figure 3: A schematic diagram that delineates the correlation between pretreatment serum IL-6 levels and clinical trajectories.

therapeutic options for TAFRO syndrome are not fully elucidated. We endeavored to adhere to the consensus recommendations delineated in guidelines [1, 6], but needed a trial-and-error approach to managing the acute and severe clinical presentations in individual cases. However, it is difficult to conduct a large-scale study on TAFRO syndrome due to its rarity, and our study provided numerous valuable insights.

CONCLUSION

In this study, we analyzed the long-term clinical course of TAFRO syndrome in 12 patients through extended follow-up, revealing that two experienced recurrences, while two maintained long-term remission even after the cessation of TCZ. Recurrences were observed after a reduction in the TCZ dose and exhibited milder manifestations. The kidney biopsy findings in recurrent cases were characterized by marked glomerular endotheliopathy, which was similar to the findings during the initial onset. A kidney biopsy could provide valuable assistance in diagnosing recurrent cases, especially in cases where clinical differentiation of conditions other than TAFRO syndrome is difficult. The renal dysfunction was severe, requiring temporary HD in most patients, but renal function normalized in all cases except one. Furthermore, our data imply that TAFRO syndrome may involve multiple mediators, not only IL-6, with varying degrees of contribution depending on the patient, and pretreatment serum IL-6 levels could potentially serve as a biomarker to identify candidates for maintenance therapy without TCZ. Further investigation is warranted to identify stratified treatment approaches based on individual etiologic factors.

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AUTHORS' CONTRIBUTIONS

Y.Y., H.M., and N.S. conceptualized and designed the study. Y.Y. was responsible for analyzing the data and drafting the manuscript. N.S. provided supervision throughout the study. All authors were involved in the acquisition of data. Additionally, they critically revised the manuscript for essential intellectual content and gave final approval for the version to be published.

STATEMENT OF ETHICS

The internal ethics review board approved this study design and protocol (approval number 2458-B), which were performed in accordance with the principles of the Declaration of Helsinki.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing or conflicts of interest.

REFERENCES

1. Masaki Y, Kawabata H, Takai K *et al.* Proposed diagnostic criteria, disease severity classification and treatment strategy for TAFRO syndrome, 2015 version. *Int J Hematol* 2016;**103**:686–92. https://doi.org/10.1007/s12185-016-1979-1
2. Fajgenbaum DC, Uldrick TS, Bagg A *et al.* International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. *Blood* 2017;**129**:1646–57. https://doi.org/10.1182/blood-2016-10-746933
3. Iwaki N, Fajgenbaum DC, Nabel CS *et al.* Clinicopathologic analysis of TAFRO syndrome demonstrates a distinct subtype of HHV-8-negative multicentric Castleman disease. *Am J Hematol* 2016;**91**:220–6. https://doi.org/10.1002/ajh.24242
4. Igawa T, Sato Y. TAFRO syndrome. *Hematol Oncol Clin North Am* 2018;**32**:107–18. https://doi.org/10.1016/j.hoc.2017.09.009

5. Mizuno H, Sawa N, Watanabe S *et al*. The clinical and histopathological feature of renal manifestation of TAFRO syndrome. *Kidney International Reports* 2020;**5**:1172–9. https://doi.org/10.1016/j.ekir.2020.05.004
6. Van Rhee F, Voorhees P, Dispenzieri A *et al*. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. *Blood* 2018;**132**:2115–24. https://doi.org/10.1182/blood-2018-07-862334
7. Nishimura Y, Fajgenbaum DC, Pierson SK *et al*. Validated international definition of the thrombocytopenia, anasarca, fever, reticulin fibrosis, renal insufficiency, and organomegaly clinical subtype (TAFRO) of idiopathic multicentric Castleman disease. *Am J Hematol* 2021;**96**:1241–52. https://doi.org/10.1002/ajh.26292
8. Nakayama Y, Mizuno H, Sawa N *et al*. A case of adolescent-onset TAFRO syndrome with malignant nephrosclerosis-like lesions. *Intern Med* 2022;**62**:2223–9. https://doi.org/10.2169/internalmedicine.0529-22
9. Fajgenbaum DC, Langan RA, Japp AS *et al*. Identifying and targeting pathogenic PI3K/AKT/mTOR signaling in IL-6-blockade-refractory idiopathic multicentric Castleman disease. *J Clin Invest* 2019;**129**:4451–63. https://doi.org/10.1172/JCI126091
10. Ogata A, Tanaka Y, Ishii T *et al*. Long-term safety and efficacy of weekly subcutaneous tocilizumab monotherapy in patients with rheumatoid arthritis who had an inadequate response to subcutaneous tocilizumab every other week: results from the open-label extension of the SHINOBI study. *Mod Rheumatol* 2019;**29**:767–74. https://doi.org/10.1080/14397595.2018.1533514
11. Yoshizaki K, Matsuda T, Nishimoto N *et al*. Pathogenic significance of interleukin-6 (IL-6/BSF-2) in Castleman's disease. *Blood* 1989;**74**:1360–7. https://doi.org/10.1182/blood.V74.4.1360.1360
12. Tiwari NR, Phatak S, Sharma VR *et al*. COVID-19 and thrombotic microangiopathies. *Thromb Res* 2021;**202**:191–8. https://doi.org/10.1016/j.thromres.2021.04.012
13. Wu MS, Koirala A. Thrombotic microangiopathy following chimeric antigen receptor T-cell therapy. *Clin Nephrol Case Stud* 2023;**11**:17–21. https://doi.org/10.5414/CNCS111045
14. Le RQ, Li L, Yuan W *et al*. FDA approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. *Oncologist* 2018;**23**:943–7. https://doi.org/10.1634/theoncologist.2018-0028
15. Pai RL, Japp AS, Gonzalez M *et al*. Type I IFN response associated with mTOR activation in the TAFRO subtype of idiopathic multicentric Castleman disease. *JCI Insight* 2020;**5**. https://doi.org/10.1172/jci.insight.135031
16. Casper C, Chaturvedi S, Munshi N *et al*. Analysis of inflammatory and anemia-related biomarkers in a randomized, double-blind, placebo-controlled study of Siltuximab (Anti-IL6 Monoclonal Antibody) in patients with multicentric Castleman disease. *Clin Cancer Res* 2015;**21**:4294–304. https://doi.org/10.1158/1078-0432.CCR-15-0134
17. Nishimoto N, Kanakura Y, Aozasa K *et al*. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. *Blood* 2005;**106**:2627–32. https://doi.org/10.1182/blood-2004-12-4602
18. Nishimoto N, Sasai M, Shima Y *et al*. Improvement in Castleman's disease by humanized anti-interleukin-6 receptor antibody therapy. *Blood* 2000;**95**:56–61. https://doi.org/10.1182/blood.V95.1.56
19. Dispenzieri A, Fajgenbaum DC. Overview of Castleman disease. *Blood* 2020;**135**:1353–64. https://doi.org/10.1182/blood.2019000931

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