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【 CASE REPORT 】

Severe TAFRO Syndrome Mimicking Hepatorenal Syndrome Successfully Treated with a Multidisciplinary Approach: A Case Report and Literature Review

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Abstract:

Finding the ideal balance between efficacy and safety of immunosuppression is challenging, particularly in cases of severe TAFRO syndrome. We herein report a 60-year-old man diagnosed with grade 5 TAFRO syndrome mimicking hepatorenal syndrome that was successfully treated by glucocorticoid, tocilizumab, and cyclosporin despite virus infection. Furthermore, by examining 14 peer-reviewed remission cases, we revealed that the recovery periods among inflammation, renal dysfunction, and thrombocytopenia were quite different, with recovery from thrombocytopenia notably slow. All patients requiring dialysis were successfully withdrawn from dialysis, and the reversibility from kidney injury was good. This clinical information will help clinicians plan treatments and tailor the intensity of immunosuppression.

Key words: TAFRO syndrome, thrombocytopenia, dialysis, kidney injury, immunosuppression

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Introduction

TAFRO syndrome, characterized by Thrombocytopenia, Anasarca, Fever, Reticulin myelofibrosis (or Renal insufficiency), and Organomegaly, is a rare systemic inflammatory disorder first proposed in Japan in 2010 (1, 2). Because of its variety of symptoms, it is important for not only hematologists and gastroenterologists but also nephrologists to be aware of TAFRO syndrome. TAFRO syndrome has been categorized as a subtype of idiopathic multicentric Castleman disease, but its clinical features differ markedly from those of classical Castleman disease.

Most patients with TAFRO syndrome have a sub-acute onset and progressive clinical courses. Therefore, the prompt initiation of treatments and multiple immunosuppressants are required (3). However, striking the appropriate balance between efficacy and safety of immunosuppression is challenging. While insufficient immunosuppression leads to fatal conditions, such as hemorrhaging and multi-organ failure, over-immunosuppression triggers severe infection and drug-associated adverse events (4).

The present case suggests that the time required for recovery from various symptoms, such as systemic inflammation, renal dysfunction, thrombocytopenia, anasarca, and organomegaly, is different. An awareness of temporal lags in the recovery periods for various symptoms can aid clinicians in deciding the proper amounts and duration of immunosup-

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Table 1. Laboratory Data.

Laboratory tests		Laboratory tests		Laboratory tests	
Urinalysis		Immunology		Infection	
Specific gravity	1.019	Immunoglobulin G (mg/dL)	2,239	HBsAg	-
pH	5	Immunoglobulin G4 (mg/dL)	44	HBsAb	-
Protein	1+	Immunoglobulin A (mg/dL)	654	HbcAb	-
Occult blood	±	Immunoglobulin M (mg/dL)	62	HCVAb	-
Glucose	-	Complement 3 (mg/dL)	97	TP Ab	-
NAG (IU/L)	53.2	Complement 4 (mg/dL)	11	T-SPOT	-
β2-microglobulin (μg/mL)	0.015	Rheumatoid factor (IU/mL)	11	HIV	-
Urin sediment		Antistreptolysin-O (IU/mL)	298	EB IgG	+
Erythrocytes (dysmorphic)/HPF	1-4	Cryoglobulin	-	EB IgM	-
Leukocytes/HPF	1-4	Antinuclear antibody	160	Varicella IgG	-
Complete blood count		Anti-GBM antibody (U/mL)	<2.0	Varicella IgM	-
White blood cell ($\times10^3$/μL)	7.28	MPO-ANCA (U/mL)	<1.0	Herpes simplex virus IgG	-
Neutrophils (%)	70.4	PR3-ANCA (U/mL)	<1.0	Herpes simplex virus IgM	-
Hematocrit (%)	40.6	Anti-SS-A/Ro antibody (IU/mL)	299	Human herpesvirus 8 DNA	-
Platelets ($\times10^3$/μL)	54	Anti-SS-B/La antibody (IU/mL)	59.1	Cytomegalovirus antigenemia assay	-
Chemistry		ADAMTS13 activity (IU/mL)	0.51	Plasma cytokine	
Aspartate aminotransferase (IU/L)	42	PAIgG (ng/10^7 cells)	249.7	Interleukin 6 (pg/mL)	22
Alanine aminotransferase (IU/L)	23	Lupus anticoagulant (U/mL)	1.01	Vascular endothelial growth factor (pg/mL)	98.8
γ-GTP (IU/L)	72	Cardiolipin β2 glicoprotein (U/mL)	0.9	Ascites tests	
Alkaline phosphatase (IU/L)	263	Cardiolipin Ab (U/mL)	8.7	White blood cell (/μL)	200
Lactate dehydrogenase (IU/L)	227	Coagulation system		Lymphocyte (%)	21
Choline esterase (IU/L)	89	PT (%)	60	Monocyte (%)	79
Total bilirubin (mg/dL)	1.3	PT-INR	1.34	Lactate dehydrogenase (IU/L)	227
Total protein (g/dL)	6.7	APTT (s)	46.8	Total protein (g/dL)	2.7
Albumin (g/dL)	2.5	Fibrinogen (mg/dL)	279	Albumin (g/dL)	1.2
Blood urea nitrogen (mg/dL)	65	D-dimer (μg/mL)	31.3	Choline esterase (IU/L)	89
Creatinine (mg/dL)	2.8	AT-III (%)	43	Total cholesterol (mg/dL)	26
Sodium (mEq/L)	137	TAT (ng/dL)	35	Triglyceride (mg/dL)	22
Potassium (mEq/L)	4.8	PIC (μg/mL)	7.4	Lipase (U/L)	63
Chloride (mEq/L)	110	Tumor marker		Hyaluronic acid (ng/mL)	10,400
Calcium (mEq/L)	7.4	Soluble interleukin-2 receptor (IU/mL)	717	Interleukin 6 (pg/mL)	1,430
Glucose (mg/dL)	82	Cancer antigen 125 (IU/mL)	129.8	Vascular endothelial growth factor (pg/mL)	112
C-reactive protein (mg/dL)	9.2	Cytokelatin 19 fragment (ng/mL)	13.6		
Procalcitonin (ng/mL)	7.3	Carbohydrate antigen 19-9 (ng/mL)	49.3		
Erythrocyte sedimentation rate (mm)	78	Carcinoembryonic antigen (ng/mL)	1.9		

pression.

We herein report a case of severe TAFRO syndrome that mimicked hepatorenal syndrome successfully treated with glucocorticoid, tocilizumab (TCZ: anti-IL-6 monoclonal antibody), and cyclosporin A (CsA). We also present a literature review on the renal reversibility and the time to recover from inflammation, renal dysfunction, and thrombocytopenia.

Case Report

A 60-year-old Japanese man was referred to our hospital for a fever, ascites, and general fatigue. He had a medical history of alcoholic fatty liver 20 years earlier. He had not been prescribed any medications. He regularly visited a doctor in the Department of Hepatology but continued to consume alcohol daily. Four months before admission, he had persistent cough and purulent rhinorrhea. He developed abdominal swelling, edema, and a decrease in appetite. He was therefore referred to our department for acute kidney injury.

The level of creatinine increased from 0.8 mg/dL to 2.8 mg/dL. On admission, his blood pressure was 124/71 mmHg, pulse rate was 100/min, temperature was 37.5°C, and body mass index was 26.5. A physical examination revealed abdominal fullness and leg edema without palpable lymph nodes, joint pain, or neurological disorders. Laboratory test results are shown in Table 1. The levels of creatinine, D-dimer, C-reactive protein (CRP), procalcitonin, total bilirubin, platelets, albumin, and cholinesterase were 2.8 mg/dL, 31 μg/mL, 9.2 mg/dL, 7.3 ng/mL, 1.3 mg/dL, 54×10^3/μL, 2.0 g/dL, and 89 IU/L on admission, respectively. The levels of interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) were also high. Anti SS-A antibody and SS-B antibody were positive, although he had no dry eyes and mouth, joint pain, or rash. Tests for infectious diseases were all negative, and none of the culture tests of

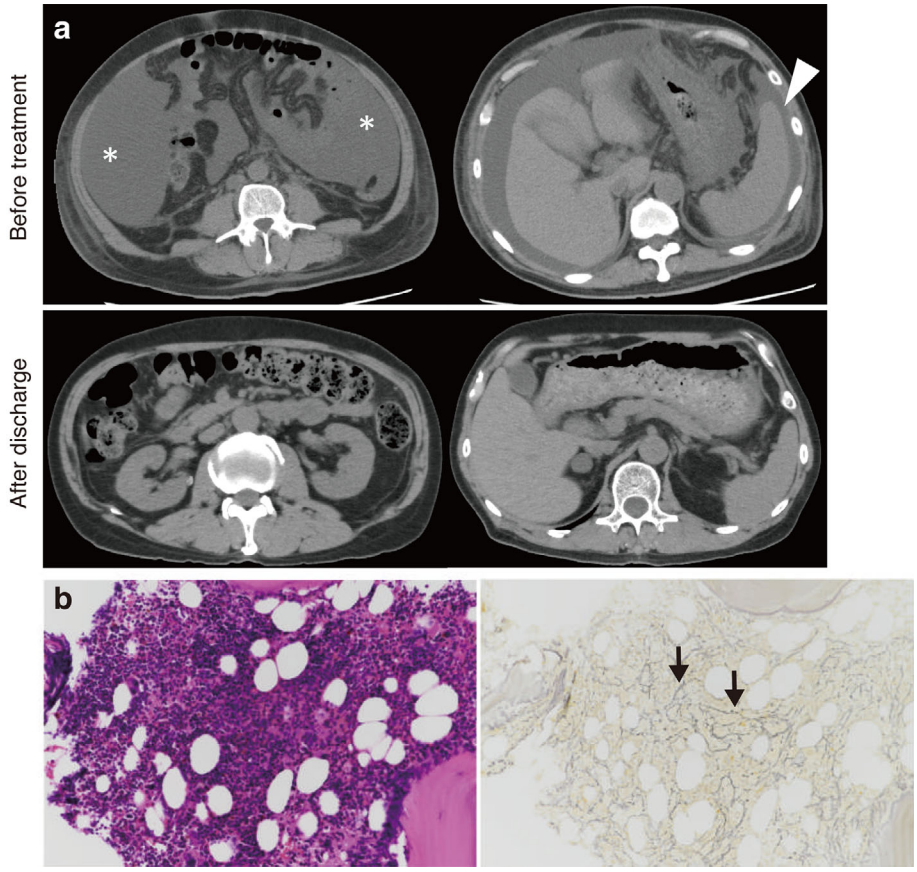


Figure 1. **(a) Plain CT shows the massive ascites (asterisk) and splenomegaly (arrowhead) before treatment. The splenomegaly and ascites improved after discharge. (b) The findings of the marrow biopsy show mildly hypercellular marrow (50% cellularity) with mild reticulin fibrosis (black arrow) (left panel: Hematoxylin and Eosin staining; right panel: silver stain, ×200).**

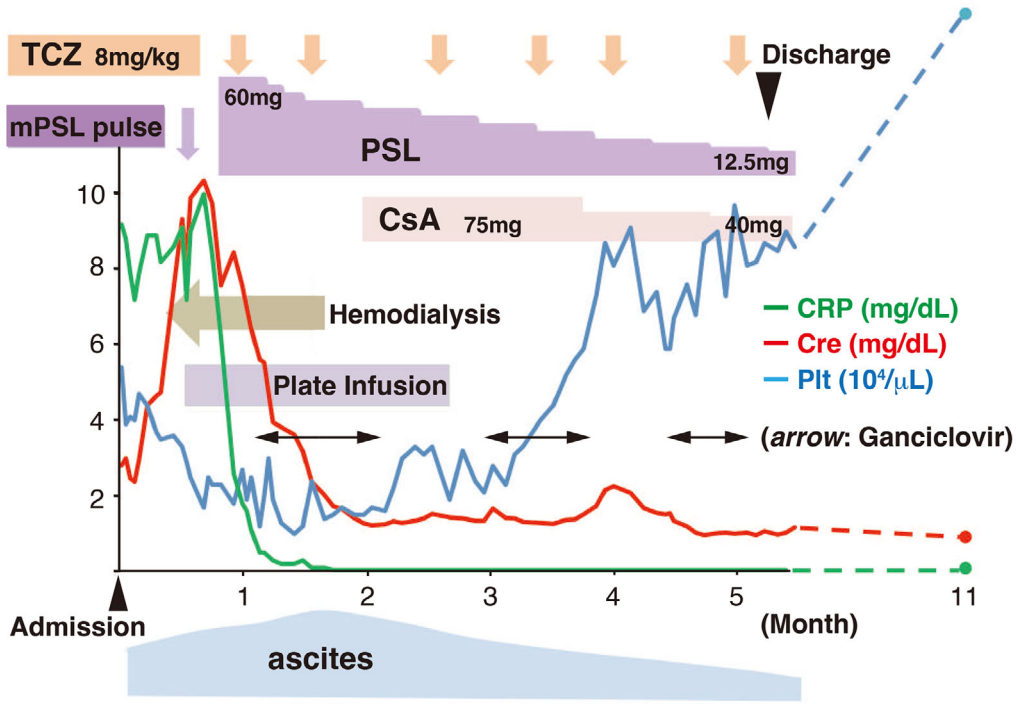
blood, sputum, urine, feces, or ascites showed any evidence of infection. A test of the ascites showed high hyaluronic acid (10,400 ng/mL), IL-6 (1,430 pg/mL), and VEGF (112 pg/mL) values (Table 1). The leukocyte count in the ascites was 200/μL (lymphocytes 21%, monocytes 79%).

Abdominal computed tomography showed massive ascites, slight hepatic atrophy, and splenomegaly without periaortic lymphadenopathy of a size insufficient for a biopsy (Fig. 1a). A bone marrow biopsy revealed mildly hypercellular marrow (50% of cellularity) with mild reticulin fibrosis (Fig. 1b). A renal biopsy could not be performed because of severe thrombocytopenia. Positron emission tomography with 2-deoxy-2-fluoro-D-glucose, upper gastrointestinal endoscopy, colonoscopy, and a random skin biopsy showed no signs of neoplasm.

Regarding the diagnostic criteria of TAFRO syndrome (5), the patient met all three major categories (anasarca, thrombocytopenia, and systemic inflammation) and three of the four minor categories (reticulin myelofibrosis, organomegaly, and progressive renal insufficiency). Thrombocytopenia and positive platelet associated IgG are findings associated with idiopathic thrombocytopenic purpura (ITP), but complications of enlarged lymph nodes, splenomegaly, and renal failure were not consistent with ITP. The finding of reticulin myelofibrosis on a bone marrow examination is typical of TAFRO syndrome and is generally uncommon in ITP. Other potential etiologies, including malignant tumor, sepsis, collagen diseases, and IgG4-related disease, with the exception of hepatorenal syndrome, were incompatible with the examinations and clinical findings.

Because the diagnosis of spontaneous bacterial peritonitis (SBP) is based on positive ascitic fluid bacterial cultures and the detection of an elevated polymorphonuclear neutrophil count in the ascites (>250/μL), the patient was deemed to not be complicated with SBP. No triggers for hepatorenal syndrome, such as SBP, were found. Hypercytokinemia and the absence of portosystemic collateral pathways were suggestive of TAFRO syndrome rather than hepatorenal syndrome. We concluded that the hypergammaglobulinemia and high hyaluronic acid levels in ascites on admission had been caused by exacerbation of chronic liver disease. Based on these findings, we made a diagnosis of TAFRO syndrome complicated with liver injury.

The clinical course of the patient is shown in Fig. 2. The maximum levels of creatinine, D-dimer, CRP, procalcitonin, and total bilirubin were increased remarkably up to 10.3 mg/dL, 151 μg/mL, 10.0 mg/dL, 18.7 ng/mL, and 6.7 mg/dL after admission, respectively. The minimum levels of platelets, albumin, and cholinesterase were 10×10^3/μL, 2.0 g/dL, and 52 IU/L, respectively. These findings indicated a



					normal range
Plasma IL-6	22 ↑	13 ↑	435 ↑↑	405 ↑↑	< 8 pg/mL
Ascites IL-6	1430	2140	N/A	6800	----
Plasma VEGF	99 ↑	50 ↑	< 15.6 ↓	< 15.6 ↓	< 38 pg/mL
Ascites VEGF	112	296	N/A	65	----

Figure 2. **Clinical course after admission. TCZ: tocilizumab, mPSL: methylprednisolone, CsA: cyclosporin, IL-6: interleukin-6, VEGF: vascular endothelial growth factor**

clinically serious case. Hemodialysis and platelet transfusion were initiated on days 10 and 13 of admission, respectively. Intravenous methylprednisolone pulse therapy (1,000 mg/day ×3 days) and oral prednisolone (60 mg/day) after the pulse therapy were started on day 16 of admission. After the initiation of glucocorticoid therapy, the level of CRP decreased rapidly. We added TCZ (8 mg/kg) on day 30 of admission. Subsequently, the renal function improved gradually, and hemodialysis was withdrawn 33 days after the initiation of immunosuppressive therapy (on day 48 of admission). The level of urinary N-acetyl-β-(D)-glucosaminidase (NAG) declined sensitively, reflecting an improvement in the renal function (Fig. 3). However, severe thrombocytopenia persisted after the second administration of TCZ. We therefore added a further 75 mg of CsA per day on day 60 of admission. When the level of plasma D-dimer fell below 20 μg/mL, the platelet count conversely started to increase (Fig. 3). Transfusion was discontinued on day 79 of admission, and the platelet count remarkably increased in the following month. Massive ascites was still present, despite the improvement in spleen organomegaly on day 63 after admission. Cytomegalovirus (CMV) infection was detected from the very early period (16 days after the initiation of glucocorticoid therapy) and required the administration of ganciclovir. An increase in serum creatinine was observed again on day 120 of admission. A high CsA concentration and late peak (C2, 389 ng/mL; C4, 1,350 ng/mL) were detected, which might have been caused by complications of liver damage. The emergence of decoy cells in the urine was also found.

After reducing the dose of CsA, the kidney function recovered quickly, and decoy cells disappeared. Although CMV infection and BK virus infection occurred, these complications were diagnosed in the early stages and successfully treated. Finally, combination treatment with glucocorticoid, TCZ, and CsA led to complete remission of TAFRO syndrome. The patient was discharged on day 160. Six months after discharge, the ascites had disappeared (Fig. 1a) with a creatinine level of 1.0 mg/dL, platelet count of 15×10^4/μL, and negative CRP values.

Discussion

We encountered a 60-year-old man diagnosed with grade 5 TAFRO syndrome and successfully treated by glucocorticoid, tocilizumab, and ciclosporin despite virus infection. The patient presented with severe renal dysfunction and prolonged thrombocytopenia. Notably, the time required for recovery from various symptoms, such as systemic inflammation, renal dysfunction, thrombocytopenia, anasarca, and organomegaly, was different.

Information on the time required for recovery helps clini-

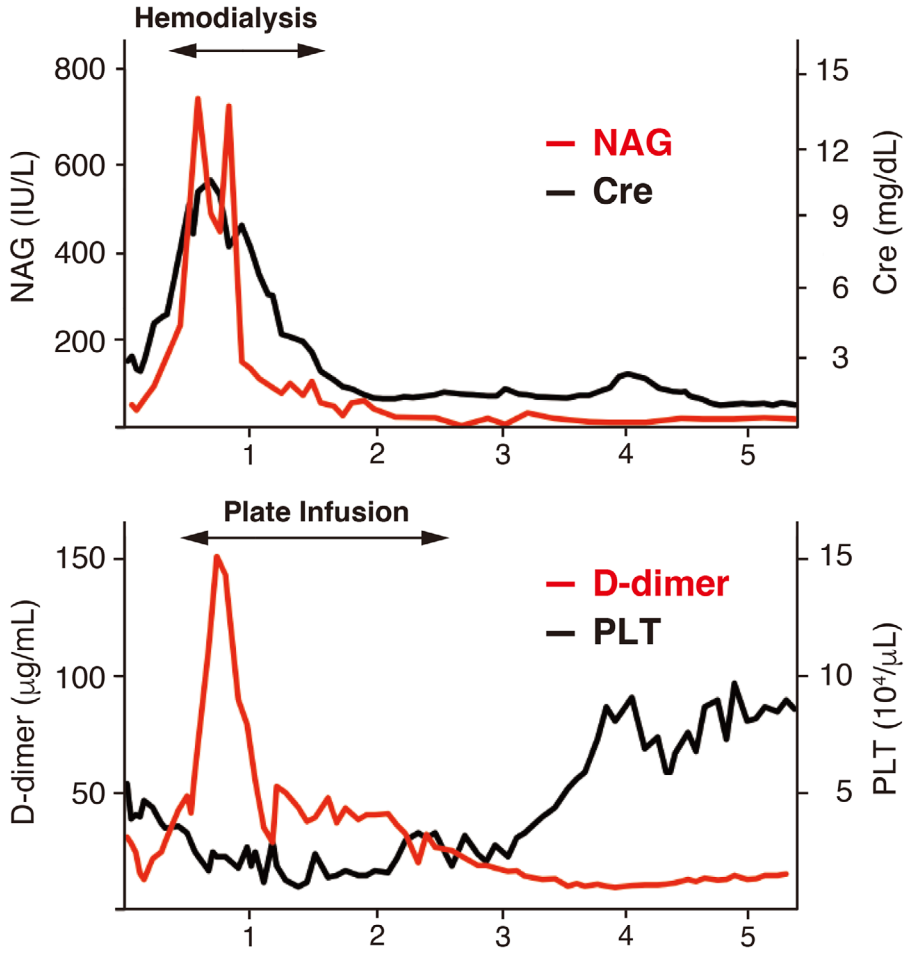


Figure 3. **The association between the levels of NAG and creatinine, and the inverse correlation between those of D-dimmer and platelet. NAG: N-acetyl-β-(D)-glucosaminidase, Cre: creatinine, PLT: platelet**

cians tailor the intensity of the treatment by assessing precisely the effectiveness of the drug against the dangers of excessive immunosuppression. Therefore, we reviewed remission cases reported previously, and analyzed the recovery durations of the various symptoms of TAFRO syndrome. We also examined the recovery of the renal function. We searched PubMed using the term TAFRO syndrome and the following additional filters: text availability, full text; publication date, from 2017/01/01 to 2020/06/30; and language, English (Fig. 4a). The exclusion criteria included 1) not consistent with the criteria proposed in 2019 by Masaki et al. (5); 2) a lack of full remission; 3) a lack of all recovery period data for systemic inflammation, renal dysfunction and thrombocytopenia; and 4) a lack of the duration of renal replacement therapy. After applying these criteria to our search results, we were left with 14 cases (13 reports) (6-18). For these cases, we first collected patient information, including the age, sex, race, TAFRO grade, complications, treatments, and trends in creatinine levels. We also investigated whether or not a kidney biopsy and dialysis had been performed. Next, we calculated the approximate number of days required for recovery from systemic inflammation, renal dysfunction, and thrombocytopenia, as well as dialysis duration, taking the data from texts, tables, and the graphs of clinical courses in these reports. We then divided the 15 cases (14 cases plus our present case) into 2 groups: cases with and without critical complications of cardiac, hemorrhagic or septic shock. Finally, in each group, we analyzed the dialysis duration and days required for recovery from systemic inflammation, renal dysfunction, and thrombocytopenia, as well as the level of creatinine at discharge. Data are shown as the median and interquartile range (IQR; 25-75%). We defined the recovery duration from systemic inflammation, thrombocytopenia, and renal dysfunction after the initiation of immunosuppression therapy as follows (Fig. 4b): 1) levels of CRP <1 mg/dL; 2) the platelet count >10×10^4/μL; 3) two-stage reduction from peak acute kidney injury (AKI) stage according to the KDIGO criteria, or recovery of serum creatinine to below 1.0 mg/dL for men and 0.8 mg/dL for women. To evaluate the AKI stage by KDIGO, the serum creatinine values before the onset of AKI caused by TAFRO syndrome were assumed to be 1.0 mg/dL for men and 0.8 mg/dL for women when the value was unavailable.

The clinical characteristics and recovery duration of all cases are shown in Table 2. All of the cases have been re-

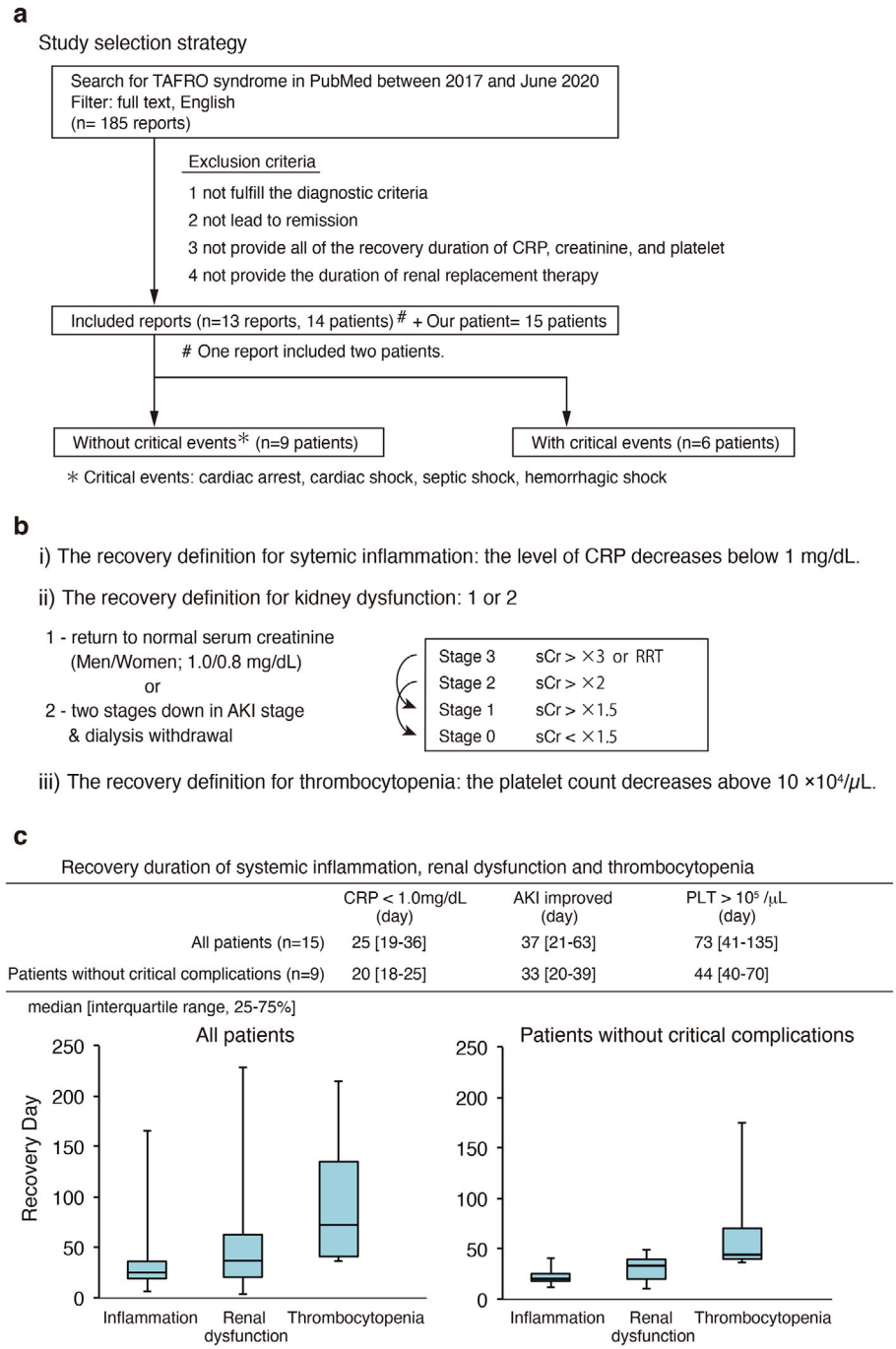


Figure 4. **(a) Study selection strategy. (b) The recovery definitions for inflammation, kidney dysfunction, and thrombocytopenia. (c) The recovery duration of inflammation, renal dysfunction, and thrombocytopenia in our reviewed patients. AKI: acute kidney injury, PLT: platelet**

ported from Asia, and 13 of these were from Japan, as shown in Table 2. There were 9 men and 6 women, from 17 to 85 years old (median: 59 years old). There were two patients with TAFRO grade 2, three with grade 3, five patients with grade 4, and five patients with grade 5. Six patients presented with critical complications of cardiogenic, hemorrhagic or septic shock, and cardiac arrest. Four patients with grade 5 TAFRO, not including our own patient, experienced a critical complication. Various opportunistic infections occurred during treatment. In particular, CMV infection occurred most frequently (Table 2). As for the treatment of TAFRO syndrome, all patients were initially treated with glucocorticoids, but the combination of medications used varied (Table 2). Ten patients received renal replacement therapy (RRT) (Table 3). All patients with grade 5 disease, including our case, received RRT. Renal biopsies were performed in four patients, two of whom received the biopsy in the acute phase. No patients with grade 5 received a renal biopsy (Table 3).

The median recovery periods for inflammation, renal dysfunction, and thrombocytopenia were 25 [19-36], 37 [21-63], and 73 [41-135] days, respectively (Fig. 4c). Excluding

Table 2. Clinical Characteristics and Recovery Duration of Our Reviewed Patients. The Recovery Day of Thrombocytopenia in Case 11 Is Described as "NA" (*) because the Platelet Count Remained above $10\times10^4/\mu L$ throughout the Entire Hospitalization Period. These Data are Not Included in the Analysis.

	Case	Race	Age/ Sex	TAFRO grade	Critical complications before remission	Infections	Treatment	CRP <1.0mg/dL (day)	AKI improved (day)	PLT $>10^5$ /L (day)	Reference
without critical complications	1	Japanese	51 F	2	None	NA	mPSL pulse, PSL	20	10	40	6
	2	Japanese	38 M	3	None	NA	mPSL pulse, PSL, CsA, TCZ	15	33	38	7
	3	Japanese	85 F	3	None	NA	PSL	12	15	40	8
	4	Japanese	76 F	4	None	NA	PSL	32	49	70	9
	5	Japanese	46 M	4	None	NA	mPSL pulse, PSL, TCZ	25	34	36	10
	6	Chinese	52 F	4	None	Pneumonia before remission (unknown etiology)	mPSL, PSL, BOR, CPA, DEX	25	20	44	11
	7	Japanese	69 M	4	None	*CMV*, cholecystitis after remission (unknown etiology), *Mycobacterium tuberculosis* after remission	mPSL pulse, PSL, CsA	40	45	175	12
	8	Japanese	48 F	4	None	NA	mPSL pulse, PSL, TCZ, CsA	20	21	51	13
	9	Japanese	60 M	5	None	CMV, BK virus	mPSL pulse, PSL, TCZ, CsA	18	39	169	Our case
with critical complications	10	Japanese	68 F	2	Septic shock	*Staphylococcus aureus*	PSL, TCZ, CsA, TAC	131	221	120	14
	11	Japanese	17 M	3	Cardiogenic shock	NA	mPSL pulse, PSL, TAC	6	3	NA	14
	12	Japanese	72 M	5	Cardiac arrest	*Corynebacterium*	mPSL pulse, PSL, TCA, CPA	28	120	140	15
	13	Japanese	59 M	5	Cardiac arrest	NA	mPSL pulse, PSL, TCZ, CsA	23	37	88	16
	14	Japanese	25 M	5	Cardiac arrest	NA	PSL, CPA, TCZ	49	76	75	17
	15	Japanese	59 M	5	Hemorrhagic shock	*Pneumocystis jirovecii, Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Clostridium difficile, Escherichia coli, CMV, Candida*	mPSL pulse, PSL, TCZ	166	228	215	18

AKI: acute kidney injury, PLT: platelet, CMV: cytomegalovirus, mPSL: methyl prednisolone, PSL: prednisolone, CsA: ciclosporin, TCZ: tocilizumab, BOR: bortezomib, CPA: cyclophosphamide, DEX: dexamethasone

the patients with critical complications, the median recovery periods for inflammation, renal dysfunction, and thrombocytopenia were 20 (18-25), 33 (20-39), and 44 (40-70) days, respectively (Fig. 4c). In cases where the recovery from thrombocytopenia required more than 120 days, CMV infection, bacterial infection, and drug-induced thrombocytopenia were detected.

Regarding the renal function (Table 3), the median levels of creatinine on admission and at discharge were 1.4 (1.2-2.1) and 0.9 (0.8-1.2) mg/dL, respectively. The maximum level of creatinine after initiation of treatment was 4.2 (1.9-5.5) mg/dL. The maximum creatinine in our case was 10.4 mg/dL, which was the highest among all patients. All 10 patients who required dialysis were successfully withdrawn from dialysis, and their median level of creatinine was 1.0 (0.8-1.4) mg/dL at discharge, which indicates the reversibility of renal function impairment in TAFRO syndrome. In addition, all patients who developed chronic kidney disease after remission were over 60 years old.

Our literature review and analysis directly demonstrated crucial differences in the recovery periods of various symptoms and prolonged thrombocytopenia in TAFRO syndrome, and these findings are interesting features of TAFRO syndrome. The cause of the temporal lag between symptoms might be explained by different organ-specific recovery capacity and etiologies, as follows: 1) systemic inflammation caused by autoimmunity or undetermined infection; 2) renal dysfunction caused by endothelial injury; 3) thrombocytopenia caused by autoimmunity, coagulative disorder, or megakaryocyte dysfunction; and 4) ascites and hepatic dysfunction caused by the elevation of vascular permeability or hepatobiliary infection with an undetermined patho-

Table 3. Trends in the Renal Function in Our Reviewed Patients.

	Case	Age/ sex	TAFRO grade	Renal biopsy	RRT duration (day)	AKI improved (day)	AKI recovery definition (#)	Creatinine before the onset of TAFRO syndrome	Creatinine on admission	Max creatinine after treatment	Minimum creatinine after treatment	Creatinine at dischage	AKI to CKD
without critical complications	1	51 F	2	Acute phase	None	10	1	NA	1	1.2	0.6	0.8	Unidentified
	2	38 M	3	No	31	33	2	NA	2.8	5.0	0.8	0.8	Unidentified
	3	85 F	3	No	None	15	1	NA	1.1	1.6	0.8	1.2	Probably yes *
	4	76 F	4	Chronic phase	40	49	2	NA	3.0	6.5	1.4	1.5	Probably yes *
	5	46 M	4	No	None	34	1	NA	0.9	1.5	0.9	0.9	Unidentified
	6	52 F	4	No	13	20	2	NA	1.9	7.2	0.4	0.5	Unidentified
	7	69 M	4	Chronic phase	17	45	2	NA	2.2	4.3	1.2	1.7	Probably yes *
	8	48 F	4	Acute phase	17	21	2	NA	1.3	4.2	0.6	0.6	Unidentified
	9 (Our case)	60 M	5	No	39	39	2	0.8	2.8	10.4	1.1	1.2	Yes
with critical complications	10	68 F	2	No	None	221	1	NA	1.6	1.5	0.7	0.7	Unidentified
	11	17 M	3	No	None	3	1	NA	1.6	2.7	0.6	0.8	Unidentified
	12	72 M	5	No	106	120	2	NA	1.3	6.0	0.9	1.5	Probably yes *
	13	59 M	5	No	19	37	2	NA	1.3	2.2	0.9	1	Unidentified
	14	25 M	5	No	76	76	2	NA	1.0	4.2	0.8	0.8	Unidentified
	15	59 M	5	No	151	228	2	NA	1.4	4.5	0.8	1	Unidentified

	Dialysis duration	Cre on admission	Maximum Cre	Cre at discharge
All patients	35 [18-67]	1.4 [1.2-2.1]	4.2 [1.9-5.5]	0.9 [0.8-1.2]
Patients without critical complications median [interquartile range, 25-75%]	24 [17-37]	1.9 [1.1-2.8]	4.3 [1.6-6.5]	0.9 [0.8-1.2]

The cases described as "probably Yes" (*) have no record of creatinine before the onset of TAFRO syndrome. The AKI recovery definition (#) is shown in Fig. 4b.

RRT: renal replacement therapy, AKI: acute kidney injury, CKD: chronic kidney disease, Cre: creatinine

gen (19, 20).

Previous studies have also reported on prolonged thrombocytopenia in patients with TAFRO syndrome (21, 22). Yamaguchi et al. also showed that the median recovery periods from prolonged thrombocytopenia in TAFRO syndrome patients were 25 and 50 days for patients treated with mono-therapy and combination therapy, respectively (defined as the time to increase the platelet count above $5\times10^4/\mu L$) (22). In typical ITP, platelet counts recover to above $5\times10^4/\mu L$ in 1-2 weeks with glucocorticoid or IVIG treatment (23-25). Therefore, platelet recovery takes longer with TAFRO syndrome than with ITP. In the present case, it is notable that the recovery of platelets took an extremely long time - much longer than the median duration in our reviewed cases. We assumed that persistent thrombocytopenia was mainly due to the severity of TAFRO syndrome and partly to chronic liver injury, CMV virus infection, and administration of ganciclovir.

One of the remarkable features of the present case was the dramatic improvement from very severe kidney dysfunction. Previous studies have reported that the pathological diagnosis of patients with TAFRO syndrome involves thrombotic microangiopathy or membranoproliferative glomerulonephritis, including endothelial cell swelling, mesangiolysis, and double contours of glomerular basement membrane, which cause abnormal urinalysis findings (13, 20, 26). Tubulointerstitial injury accompanied with glomerular lesions was also reported in some cases (13, 26). Our patient had only mild proteinuria and a low fractional excretion of sodium (FENa) on admission. As the kidney function declined,

glomerular hematuria appeared. The level of urinary NAG, a marker of tubular injury, elevated sharply to 735 IU/L, but improved rapidly. We suspect that the reduction in glomerular perfusion and micro-hemodynamic alterations may induce extremely low FENa and oliguric AKI, ultimately leading to acute tubular cell injury. Taken together, these findings indicate that ischemic acute tubular injury also plays an important role in the pathogenesis of AKI in TAFRO syndrome, especially in the most severe cases that require dialysis, and this might have contributed to the dramatic and rapid recovery of the renal function upon treatment in our patient. Our investigation also suggested that the renal recovery rate of remission patients with TAFRO syndrome was good and that an advanced age might be a risk factor for the AKI-CKD transition (Table 3).

The limitations of our analysis are its small size and bias in race and severity of cases. Since we needed to collect cases with complete data, the number of cases was small, and the reviewed cases included many severe patients. In addition, the duration of recovery will vary depending on the definition of recovery, so it is necessary to be careful in interpreting the recovery periods.

Our analysis of the recovery duration might aid clinicians in deciding the intensity of immunosuppression. Furthermore, our analysis of peer-reviewed cases demonstrated crucial differences in the recovery durations of the various symptoms of TAFRO syndrome. We also found that the renal impairments seen in TAFRO syndrome can be reversed with appropriate treatment.

Conclusion

We experienced a case of severe TAFRO syndrome with exacerbation of chronic liver disease successfully treated by a multidisciplinary approach. Our investigation also suggested that the renal recovery rate of remission patients with TAFRO syndrome was good. Furthermore, our findings on the crucial differences in recovery periods of various symptoms might help clinicians plan treatments and tailor the intensity of immunosuppression.

Written consent for publication of this case report was obtained from the patient.

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

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