CASE REPORT

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Fatal case of TAFRO syndrome associated with over-immunosuppression: a case report and review of the literature

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ABSTRACT

TAFRO syndrome is a novel disease concept characterized by Thrombocytopenia, Anasarca, myelo-Fibrosis, Renal dysfunction, Organomegaly, multiple lymphadenopathy and a histopathological pattern of atypical Castleman's disease. A 58-year-old man was diagnosed as TAFRO syndrome by clinical and histopathological findings. After receiving intensive immunosuppressive therapy, his thrombocytopenia and anasarca had not improved. He developed complications such as methicillin-resistant *Staphylococcus aureus sepsis*, gastrointestinal bleeding, peritonitis caused by *Stenotrophomonas maltophilia*, gastrointestinal perforation, and disseminated candidiasis resulting in death. Autopsy revealed disseminated candidiasis and hemophagocytic lymphohistiocytosis, with no evidence of TAFRO syndrome. During treatment, we regarded his lasting thrombocytopenia and anasarca as insufficient control of TAFRO syndrome. However, the autopsy revealed that thrombocytopenia was caused by secondary hemophagocytic lymphohistiocytosis caused by over-immunosuppression. We reviewed the published literature to identify indicators of adequate treatment, which suggested improvement of platelet count and anasarca several weeks after initial therapy. This indicated that we could not depend on the platelet count and anasarca in acute medical care after initial treatment. We should treat TAFRO syndrome based on patients' clinical status and obviate the risk of treatment-related complications caused by over-immunosuppression.

Keywords: TAFRO syndrome, immunosuppression, course of treatment, disseminated candidiasis, hemophagocytic lymphohistiocytosis

Abbreviation:
CRP: C-reactive protein

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INTRODUCTION

TAFRO syndrome is a novel systemic inflammatory disorder characterized by Thrombocytopenia, Anasarca, myeloFibrosis, Renal dysfunction, Organomegaly, and multiple lymphadenopathy of mild degree, with histopathology of atypical Castleman's disease.[1,2] TAFRO syndrome was first reported in 2010,[3] and newly proposed diagnostic criteria were published in 2016.[4] The initial cases were reported from Japan,1 and there has been a recent increase in the number of reports worldwide.[5,6] Some TAFRO syndrome patients have been successfully treated with early aggressive treatments, such as glucocorticoids and/or immunosuppressants including cyclosporine A, tocilizumab, and rituximab[4,7]; in contrast, some patients have died from the disease or complications.[8-13] Here, we report the case of a Japanese man with TAFRO syndrome treated with glucocorticoid, tocilizumab, and intravenous immunoglobulin who subsequently died of disseminated candidiasis and secondary hemophagocytic lymphohistiocytosis because of over-immunosuppression. We were unable to determine whether the thrombocytopenia and anasarca were caused by insufficient treatment of TAFRO syndrome or over-immunosuppression. To identify clinical indicators of TAFRO syndrome, we reviewed past cases.

CASE REPORT

A 58-year-old Japanese man with lower abdominal pain and loss of appetite that had lasted for 2 weeks was admitted to our hospital. He underwent an upper gastrointestinal endoscopy without significant findings. His medical history showed aortic dissection (DeBakey IIIb) 8 years prior to admission, which was treated conservatively. Upon admission, his body temperature was 37.3°C. Physical examination revealed left abdominal tenderness with no swollen superficial lymph nodes and no leg edema. He had mild thrombocytopenia, hypoalbuminemia, and elevated C-reactive protein (CRP), alkaline phosphatase, γ-glutamyl transferase, creatinine, fibrinogen, and D-dimer levels. Serum soluble interleukin-2 receptor level and rheumatoid factor were also elevated. Antinuclear antibody index was 640 (speckled type) and anti-Sjögren's-syndrome-related antigen A antibody index was 240. Anti-Sjögren's-syndrome-related antigen B antibody and anti-platelet antibody were negative. Serum levels of β-D-glucan were normal (<6.0 pg/mL) and blood cultures were negative. Urine testing showed mild proteinuria without hematuria (Table 1). Enhanced whole-body computed tomography demonstrated small pleural effusion; however, there were no other abnormal findings without aortic dissection.

After admission, the patient's platelet count decreased gradually, ascites and pleural effusion increased, and renal insufficiency showed progression (blood urea nitrogen 46.7 mg/dL and creatinine 2.16 mg/dL). We conducted a bone marrow biopsy, which revealed severely hypocellular marrow. A whole body 18-F-fluorodeoxyglucose-positron emission tomography/computed tomography scan showed 18-F-fluorodeoxyglucose uptake by the left cervical and submandibular lymph nodes (Fig. 1).

We performed a cervical lymph node biopsy after prophylactic platelet transfusion, and began pulse therapy with methylprednisolone (1000 mg daily for 3 days) from day 16 because his general condition had worsened. The size of the lymph node was normal (8×5 mm). Although the number of germinal centers was preserved, all germinal centers were remarkably atrophic and contained high endothelial venules (Fig. 2A). High endothelial venules observed in interfollicular zones were surrounded by plasma cell infiltration (Fig. 2B).

These findings were consistent with TAFRO syndrome (2). The serum level of interleukin-6 was 72.7 pg/mL (<4.0 pg/mL). Human herpes virus-8 was not found in the serum. Overall,

Table 1 Laboratory data of the present case

Complete blood count		Biochemistry		Virologic test	
White blood cells	9.000/μL	Total protein	6.3 g/dL	HIV Ab	0.1 s/co
Segmented	86%	Albumin	2.2 g/dL	HBs Ag	0.00 IU/mL
Lymphocytes	3%	BUN	33.0 mg/dL	HCV Ab	0.1 s/co
Monocytes	8%	Creatinine	1.89 mg/dL	IGRA	(-)
Atypical Lymphocytes	3%	Uric acid	6.4 mg/dL	HHV-8-DNA	(-)
Red blood cells	3.95 ×	Total bilirubin	1.4 mg/dL	Immunologic test	
	10^6/μL	AST	21 IU/L	IgG	1,508 mg/dL
Hemoglobin	12.1 g/dL	ALT	5 IU/L	IgA	185 mg/dL
Hematocrit	35.7%	LDH	260 IU/L	IgM	64 mg/dL
MCV	90.4 fL	ALP	851 IU/L	C3	98.9 mg/dL
MCH	30.6 pg	γ-GTP	206 IU/L	C4	20.8 mg/dL
MCHC	33.9 g/dL	Na	131 mEq/L	ANA	× 640
Platelet	86,000 /μL	K	3.3 mEq/L		Speckled
IPF	21.8%	Cl	92 mEq/L	RF	37.1 IU/mL
Coagulation test		Ca	7.6 mg/dL	Anti-SS-A	> 240 index
Prothrombin time	14.6 sec	CK	123 IU/L	antibody	
APTT	35.9 sec	CRP	34.54 mg/dL	Anti-SS-B	1.7 index
Fibrinogen	877 mg/dL	Glucose	81 mg/dL	antibody	
D-dimer	3.17 μg/dL	Ferritin	559 ng/mL	Anti-dsDNA	0.7 IU/mL
		Haptoglobin	293 mg/dL	antibody	
Urine test		Cytokines		PR-3 ANCA	< 1.0 U/mL
U-glucose	(-)	sIL-2R	4,660 U/mL	MPO-ANCA	< 1.0 U/mL
U-protein	(1+)	IL-6	72.7 pg/mL	Anti-platelet	(-)
U-occult blood	(-)		(NR<4)	antibody	
				β-D-glucan	< 6.0 pg/ml

MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, IPF: immature platelet fraction, APTT: activated partial thromboplastin, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transferase, CK: creatine kinase, CRP: C-reactive protein, HIV Ab: human immunodeficiency virus antibody, HBs Ag: hepatitis B antigen, HCV Ab: hepatitis C virus antibody, IGRA: interferon gamma release assay, HHV-8: human herpesvirus-8, IgG, A, M: immunoglobulin G, A, M, C3, 4: complement 3, 4, ANA: anti-nuclear antibody, RF: rheumatoid factor, SS-A: Sjögren's-syndrome-related antigen A, SS-B: Sjögren's-syndrome-related antigen B, PR3-ANCA: proteinase-3 anti-neutrophil cytoplasmic antibody, MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic, sIL-2R: soluble interleukin-2 receptor, IL-6: interleukin-6, NR: Normal Range.

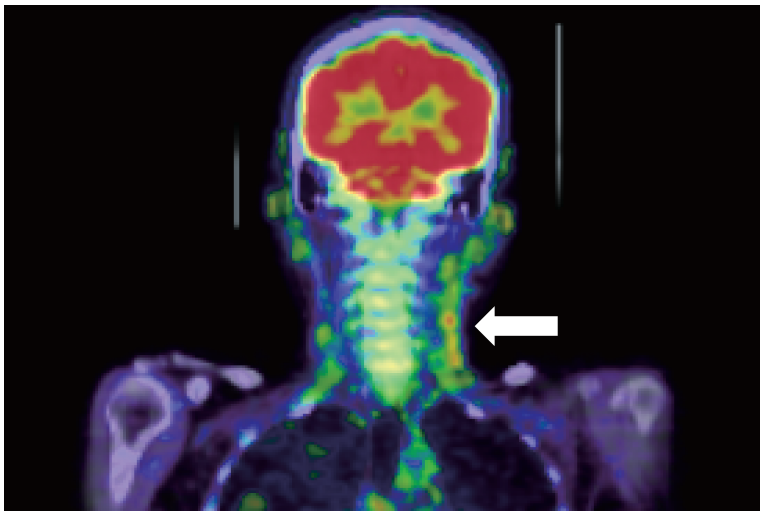

Fig. 1 Positron emission tomography
Whole body 18-F-fluorodeoxyglucose-positron emission tomography findings at 11 days after admission. 18-F-fluorodeoxyglucose uptake was observed in the left cervical and submandibular lymph nodes (arrow).

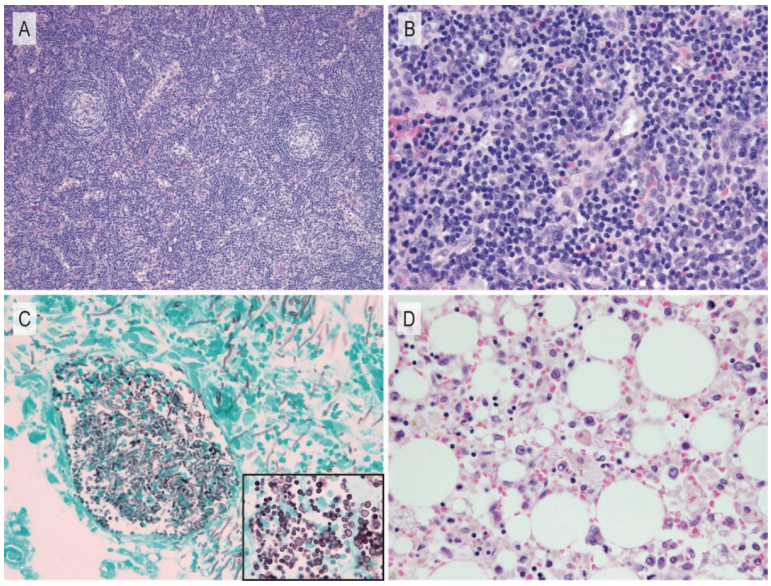

Fig. 2 Pathological findings of the present case
Cervical lymph node biopsy sample on admission (A: ×100; B: ×400). Germinal centers are atrophic (A). Plasma cell infiltration is observed in the interfollicular zone around the high endothelial venules (B). Lung tissue from autopsy sample (C: ×400). Candida proliferated in the blood vessels and grew as pseudohyphae and yeast (inset). Bone marrow tissue from autopsy sample (D: ×400). The marked infiltration of macrophages and hemophagocytosis suggests hemophagocytic lymphohistiocytosis.

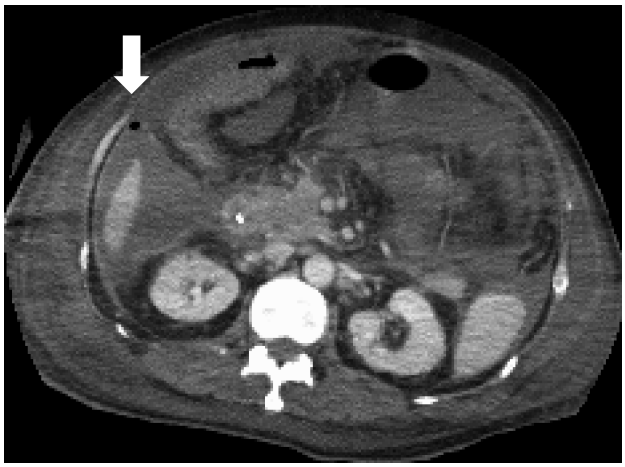

Fig. 3 Computed tomography images
Computed tomography findings at 46 days after admission. The abdominal computed tomography scan shows free air in the ascites (arrow), which indicates gastrointestinal perforation.

based on the diagnostic criteria of TAFRO syndrome (4), the patients fulfilled the three major categories (anasarca, thrombocytopenia, and systemic inflammation) and two minor categories (Castleman's disease-like features on lymph node biopsy and progressive renal insufficiency). We diagnosed the patient as TAFRO syndrome. After pulse therapy, the thrombocytopenia and massive ascites had not improved. The patient required multiple blood and platelet transfusions, but the beneficial effect was temporary. Tocilizumab (8 mg/kg body weight) was initiated on day 21 in addition to 1 mg/kg/day of prednisolone; however, the patient's anasarca and renal function worsened. The patient was then transferred to the intensive care unit, put on a ventilator, and given continuous hemofiltration because of his deteriorating hemodynamic status. Five consecutive blood cultures taken during this period were sterile, indicating that he did not develop infection, although his TAFRO syndrome activity was still high. We restarted pulse therapy from day 25, added intravenous immunoglobulin from day 27, and initiated tocilizumab (8 mg/kg body weight) on day 29. However, the patient's condition, including thrombocytopenia and massive ascites, deteriorated gradually. After the second administration of tocilizumab, he developed gastrointestinal bleeding and methicillin-resistant *Staphylococcus aureus* sepsis, which was treated with meropenem and teicoplanin. He developed bacterial peritonitis, and his ascitic fluid cultures showed *Stenotrophomonas maltophilia* on day 37; therefore, we changed antibiotics (daptomycin and tazobactam/piperacillin with ciprofloxacin added at a later timepoint). He developed gastrointestinal perforation on day 46 (Fig. 3).

His general condition made the perforation inoperable. On day 51, candidemia (blood cultures showed *Candida glabrata* and *Candida lusitaniae*) was observed and his β-D-glucan level was elevated to 193.3 pg/mL; therefore, we administered micafungin and trimethoprim-sulfamethoxazole (to treat *Stenotrophomonas maltophilia* on the basis of antimicrobial susceptibility testing), but he eventually died on day 57 (Fig. 4).

An autopsy revealed large amounts of pleural effusion and ascites (1.5 L, 1.5 L, 5 L for left pleural effusion, right pleural effusion, and ascites, respectively). Disseminated candidiasis was histologically observed in multiple organs including bilateral lungs, pleura, the gastrointestinal tract, peritoneum, liver, both kidneys, heart, diaphragm, and thyroid gland. Candida had invaded

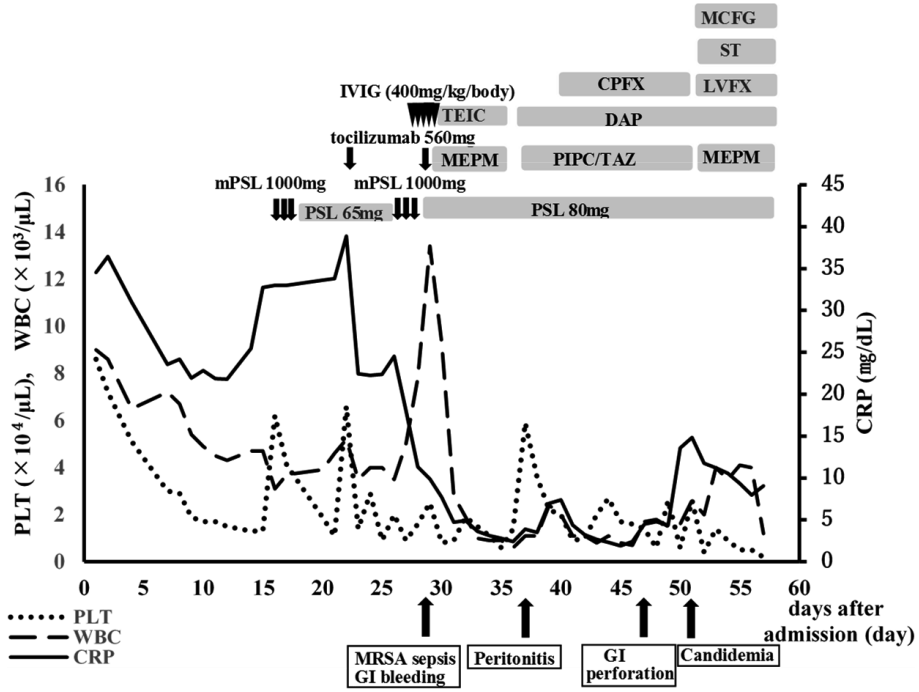

Fig. 4 Clinical course after admission
The clinical course of the patient receiving intensive immunosuppressive drugs. After the introduction of methylprednisolone and tocilizumab, C-reactive protein began to decrease but did not reach <1.0 mg/dL. Thrombocytopenia deteriorated gradually despite multiple platelet transfusions. The patient developed methicillin-resistant *Staphylococcus aureus* sepsis, gastrointestinal bleeding, and peritonitis caused by *Stenotrophomonas maltophilia* treated by antibiotics. He eventually developed gastrointestinal perforation, leading to death.
Abbreviations: CRP: C-reactive protein, CPFX: Ciprofloxacin, DAP: Daptomycin, GI: gastrointestinal, IVIG: intravenous immunoglobulin, LVFX: Levofloxacin, MCFG: Micafungin, MEPM: Meropenem, mPSL: methylprednisolone, MRSA: methicillin-resistant *Staphylococcus aureus*, PIPC/TAZ: Piperacillin/Tazobactam, PLT: platelet, PSL: prednisolone, ST: Sulfamethoxazole Trimethoprim, TCZ: tocilizumab, TEIC: Teicoplanin, WBC: white blood cell.

the blood vessel walls and proliferated in the blood vessels (Fig. 2C) growing as yeast and pseudohyphae (Fig 2C, inset); however, we could not identify specific *Candida* species. In the bone marrow, the infiltration of macrophages was prominent and hemophagocytosis was observed. These features suggested hemophagocytic lymphohistiocytosis (Fig. 2D). The small and large intestines were ischemic and partially necrotic, but macroscopic perforation was not detected. Lymph node samples taken during autopsy indicated they were of normal size and findings suggestive of TAFRO syndrome were not observed.

DISCUSSION

During the course of treatment, the patient's condition (including thrombocytopenia and massive ascites) deteriorated, and we were unable to decrease the immunosuppressive treatment. Based on the autopsy finding, the cause of the patient's death was proven to be disseminated candidiasis. In the postmortem lymph node samples, the histological features suggestive of

TAFRO syndrome had disappeared, suggesting that the treatment of TAFRO syndrome itself was successful. The thrombocytopenia was caused by secondary hemophagocytic lymphohistiocytosis syndrome, which might be induced by candidiasis and sepsis because of over-immunosuppression. Although we should have avoided over-immunosuppression, it is unknown what kind of clinical index is useful to judge the efficacy of treatment for TAFRO syndrome. We searched PubMed and the ICHUSHI web (a Japanese document database hosted by the Japan Medical Abstract Society) between May 2010 and September 2017 using "TAFRO syndrome" as a keyword. The exclusion criteria included: 1) not consistent with the 2015 diagnostic criteria for TAFRO syndrome as determined by the All Japan TAFRO Syndrome Research Group in the Research Program for Intractable Disease of the Ministry of Health, Labor and Welfare (MHLW) Japan[4]; 2) histological diagnosis was not provided (to exclude malignancies including lymphoma)— we defined histological diagnosis as atrophic germinal centers with penetrating hyalinized vessels and plasma cell proliferation after consultation with our pathologist (MN)[14]; 3) could not determine the start date of therapy and values provided were difficult to assess; and 4) not written in English or Japanese. We retrieved a total of 46 articles, 22 of which included 23 cases that met the inclusion criteria (Table 2). We investigated which clinical indicators showed clinical improvement after treatment. We checked platelet count, CRP, and anasarca (pleural effusion and ascites). We assessed the day on which CRP and platelet count began to improve. In addition, we recorded the days on which platelet count exceeded 100,000/μL, CRP was below 1.0 mg/dL, and anasarca resolved, because these points were important predictors for the improvement of TAFRO syndrome. Anasarca resolved and platelet counts recovered were noted in all survivors; however, there were no improvements in platelet count or anasarca in fatal cases, including our case.[9] Of note, the improvement in platelet count and anasarca did not occur until several weeks after the initial therapy in most patients who showed improvement. The improvement in platelet count and resolution of anasarca are not acute phase indicators of TAFRO syndrome; therefore, they should not influence the strategy for managing TAFRO syndrome after initial therapy. CRP levels improved immediately after initial therapy. The possibility of complications should be considered if CRP initially declines but does not continue to be in the normal range, even during the administration of tocilizumab, as shown here and as previously reported.[26-28,30] Our case showed that CRP decreased without reaching < 1.0 mg/dL, and that thrombocytopenia and anasarca did not improve until death. At autopsy, we could not identify any characteristics of TAFRO syndrome. Thrombocytopenia was caused by hemophagocytic syndrome. The clinical course of our case suggests that the incomplete decline of CRP was caused by complications rather than incomplete treatment for TAFRO syndrome. We could not determine the patient's clinical index, which is useful when adjusting treatment with immunosuppressive drugs. The important finding from this study is that clinicians should pay attention to the balance between insufficient treatment and over-immunosuppression to avoid treatment-related complications, including opportunistic infection and adverse effects related to individual immunosuppressive therapy, such as gastrointestinal perforation associated with tocilizumab.[33]

In conclusion, we report the case of a Japanese man with TAFRO syndrome treated with intensive immunosuppression therapy who subsequently died of disseminated candidiasis and secondary hemophagocytic lymphohistiocytosis syndrome. A retrospective review of TAFRO syndrome suggests that platelet count and anasarca take several weeks to improve after initial therapy.

Table 2 Characteristics of reported cases with TAFRO syndrome*

	Ref	Age	Sex	1st T	2nd T	3rd/ 4th/ 5th T	PLT improved (day)†	PLT >10^5/μL (day)†	Anasarca disappeared (day)†	CRP improved (day)†§	CRP <1.0 mg/dL (day)†	Complication
Improved without complications	15	39	M	mPSL‡	-	-	-35	-22	50	NA	NA	None
	16	49	F	DEX	CyA	-	20	41	17	0	4	None
	17	61	M	mPSL	TCZ	CyA	33	52	65	0	5	None
	18	41	M	PSL	CyA	IVCY	34	53	134	NA	NA	None
	19	43	F	mPSL	RTX	TCZ	39	52	27	0	12	None
	20	50	M	mPSL	TCZ	-	45	75	85	0	11	None
	21	48	F	IVIG	PSL	RTX	60	127	NA	NA	NA	None
	22	56	M	mPSL	PE	TCZ RTX	73	95	91	1	13	None
	23	21	F	mPSL	TCZ	R-CVP RTX	83	120	180	Soon	25	None
	24	48	M	PSL	-	-	NA	NA	24	NA	NA	None
	6	22	M	TCZ	RTX ETP	-	NA	NA	56	NA	NA	None
	25	57	M	GC	TCZ	-	NA	NA	81	NA	NA	None
Improved with complications	26	15	M	mPSL	TCZ	IVIG	15	18	88	8	17	Blister Toxic epidermal necrolysis
	27	47	F	mPSL	TCZ	-	42	103	131	0	56	CMV pneumonia
	28	48	M	mPSL	TCZ	IVIG RTX Romi plostim	56	62	73	8	19	Cardiomyopathy
	29	29	F	mPSL	CHOP	CEPP	62	78	65	5	20	Cardiomyopathy due to adriamycin
	30	77	F	TCZ	PSL	RTX CyA	77	107	96	3	30	PCP
	31	46	F	mPSL	CyA	-	95	113	137	0	42	Pulmonary Aspergillosis
	32	49	F	mPSL	TCZ	-	NA	NA	123	NA	NA	AHRU CNS sepsis
Died	9	73	M	mPSL	-	-	NA	NA	No	7	No	Sepsis Bacterial myelitis
	9	57	F	mPSL	CHOEP	-	No	No	No	0	38	Systemic candida infection
	Ours	59	M	mPSL	TCZ	IVIG	No	No	No	6	No	Bacterial sepsis GI Perforation Fungemia

*We defined day 0 as initial therapy.
†The items were defined as follows: PLT improved: platelet count started to increase, PLT >100,000/μL: platelet count exceeds 100,000/μL, CRP improved: CRP started to decrease, CRP <1.0 mg/dL: CRP below1.0 mg/dL, Anasarca disappeared: pleural effusion and ascites had disappeared.
‡The patient was diagnosed with TAFRO syndrome after antibiotic therapy for cholangitis and infective endocarditis.
§0 day indicates CRP improved soon after initial therapy.
PLT: platelet, CRP:C-reactive protein, M: male, F: female, NA: not available, mPSL: methylprednisolone, DEX: dexamethasone, PSL: prednisolone, IVIG: intravenous immunoglobulin, TCZ: tocilizumab, GC: Glucocorticoid, Cy A: cyclosporine A, RTX: rituximab, PE: plasma exchange, ETP: etoposide, CHOP: cyclophosphamide, adriamycin, vincristine and prednisolone, CHOEP: cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisolone, IVCY: intermittent pulse intravenous cyclophosphamide therapy, R-CVP: rituximab, cyclophosphamide, vincristine and prednisolone, CEPP: cyclophosphamide, etoposide, procarbazine, and prednisolone, CMV: Cytomegalovirus, PCP: Pneumocystis pneumonia, AHRU: acute hemorrhagic rectal ulcer, CNS: coagulase negative staphylococci, GI: Gastrointestinal, T: treatment, Ref: reference.

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CONFLICT OF INTERESTS

The authors declared no conflict of interests for this article.

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