第 43 回総会ポスター賞受賞記念論文
総　　説（推薦論文）
推薦者：第 43 回総会長　佐野　統

Successful treatment by rituximab in a patient with TAFRO syndrome with cardiomyopathy

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（Accepted December 18, 2015）

summary

TAFRO syndrome is a newly defined disease entity which is characterized by thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, and organomegaly. A histological pattern of multiple lymphadenopathy of atypical Castleman's disease (CD) is also an important characteristic. A 48-year-old man was referred to our hospital with fever, asthenia, bilateral pleural effusion, ascites, generalized edema, dyspnea, hypoalbuminemia, severe thrombocytopenia, anemia, renal failure and proteinuria, whereas bacterial culture and serological and PCR tests for various viruses were all negative. A CT scan showed multiple lymphadenopathy and tissue sampling of inguinal lymph nodes showed a compatible histology with plasma cell type CD. A diagnosis of TAFRO syndrome was made. Ten days after hospitalization, sudden cardiac insufficiency and anuria developed. Despite glucocorticoid pulse therapy, tocilizumab and plasmapheresis, clinical and laboratory features did not improve. On the 34th hospital day, we started rituximab. His general condition started to improve in several days, and by one month later anasarca had improved drastically. Thrombocytopenia and renal function gradually improved and finally normalized. Cardiac motion also improved. This is the first report of a TAFRO syndrome patient with cardiomyopathy, who was successfully treated with rituximab.

Key words—— TAFRO syndrome; Castleman's disease; rituximab; cardiomyopathy; tocilizumab

Introduction

Castleman-Kojima disease (TAFRO Syndrome) is a novel systemic inflammatory disorder characterized by thrombocytopenia, anasarca, myelofibrosis, renal dysfunction and organomegaly, and multiple lymphadenopathy of mild degree with histopathology of Castleman's disease (CD). This unique clinicopathologic variant of multicentric CD (MCD) has been recently reported in Japan[1)]. It is challenging to diagnose and understand this disease for clinicians and pathologists. Although elevated levels of interleukin-6 (IL-6) and vascular endothelial cell growth factor (VEGF) are seen in the serum and effusions of patients with TAFRO syndrome, the pathogenesis of the disease remains unclear[1)]. Previous reports[2–6, 7–15)] have shown that patients usually respond to immunosuppressive therapy, but in some patients the disease results in a fatal outcome[5, 6)]. No case of TAFRO syndrome with cardiomyopathy has been reported to date.

Here we report a case of a 48-year old Japanese man with TAFRO syndrome successfully treated with rituximab. This is the first report of the disease with cardiomyopathy.

Case Report

A 48-year-old Japanese man with no relevant medical or family history was admitted to our hospital for generalized edema, dyspnea and fever. The patient had been experiencing abdominal pain and distention and leg edema, so he visited a local hospital where he underwent a series of medical tests. Laboratory results revealed elevation of C-reactive protein (CRP), alkaline phosphatase (ALP) and brain natriuretic peptide (BNP). Contrast-enhanced CT showed multiple lymphadenopathy and splenomegaly with a few ascites. His general condition gradually took a turn for the worse.

Three weeks later, he was referred to our hospital and

was hospitalized. On admission, he was febrile (38°C) and had severe generalized edema and dyspnea. No skin lesions were visible. His cervical superficial lymph nodes were palpable. Further laboratory tests revealed mild renal dysfunction with microscopic hematuria and proteinuria, as well as several pathological casts, but repeated blood, peritoneum liquid and urine cultural samples were sterile (see **Table 1** and **Fig. 1**). Anti-HIV, anti-CMV, hepatitis C virus antibody and hepatitis B surface antigen tests were all negative. Moreover, PCR tests did not detect the presence of HSV-1, HSV-2, VZV, ParvoB19, HHV-6, HHV-7, HHV-8, CMV, BK, JC, EBV or HBV in the patient's blood. With regard to immune serology, anti-dsDNA, anti-cardiolipin, anti-β2GPI, and anti-neutrophil cytoplasmic antibodies were all negative, except low titer of ANA was detected (1/40, homogeneous and speckled), while anti-SS-A/Ro, anti-thyroid peroxidase (TPO), platelet-associated immunoglobulin (PA-IgG), and direct Coombs test were positive. The serum complement levels were normal. No monoclonal bands were observed in immunofixation tests. A bone marrow biopsy revealed no evidence of reticulin fibrosis, which is characteristic of TAFRO syndrome, and the specimen was examined by flow cytometric analysis, which did not detect any atypical phenotype populations. Inguinal lymph node (LN) biopsy revealed medullary hyperplasia with marked plasma cell infiltration (**Fig. 2**). IgG4 staining showed IgG4/IgG ratio < 0.01, and IgGκ and λ staining by in situ hybridization method showed no light chain restriction. CT showed multiple lymphadenopathy, splenomegaly with a large amount of ascites, and bilateral pleural effusion (**Fig. 3**). Multiple lymphadenopathy was shown on 18-fluorodeoxyglucose (^{18}FDG)-Positron Emission Tomography (PET) (**Fig. 4**).

Table 1 Laboratory data after admission

Variable	Reference range	On admission, at our hospital	19th day, at our hospital	85th day, at our hospital
Complete blood count				
White-cell count (× 10^6/L)	3200−9600	3450	3880	7340
Hematocrit (%)	36.5−49.8	23	22.8	31.5
Hemoglobin (g/dl)	12.2−16.8	7.1	7.1	10.5
Platelet count (× 10^9/L)	13.9−36.0	1.6	1.6	15.8
Reticulocyte (%)	6.7−18.1	64.1	51.4	42.1
Coagulation test				
Prothrombin time (sec)		12.5	13.9	
APTT (sec)	24−35	33.1	32.8	
Fibrinogen (mg/dl)	200−400	236		
D-dimer (μg/mL)	≤ 1.0	20	25.2	2.3
Urine test				
U-protein	−	3+	3+	2+
U-occult blood	−	3+	3+	−
Granular casts		1~9/1		
N-acetyl-castglucosaminidase (U/L)	0.5−9.1	45.8	65.4	27.8
Biochemistry				
Total protein (g/dL)	6.3−8.1	6.1	6	5.6
Albumin (g/dL)	3.9−5.1	2	2.1	2.9
Urea nitrogen(BUN) (mg/dL)	8−22	33	48	15
Creatinine (mg/dL)	0.65−1.06	1.5	1.63	0.56
Uric acid (mg/dL)	3.8−7.0	6.1	7.2	4.5
Total bilirubin (mg/dL)	0.3−1.3	0.8	0.8	0.8
Aspartate aminotransferase (IU/L)	12−30	56	36	38
Alanine aminotransferase (IU/L)	10−42	22	22	74
ALP (IU/L)	115−359	1105	1281	511
γGTP (IU/L)	9−54	162	264	570
Lactate dehydrogenase (IU/L)	124−226	486	380	374
CRP (mg/dL)	≤ 0.2	2.5	4.3	0
BNP (pg/ml)	≤ 18.4	170.5	433.5	66.4
PA-IgG (ng/10^7 cells)	5.0−25.0	294	198	19.6

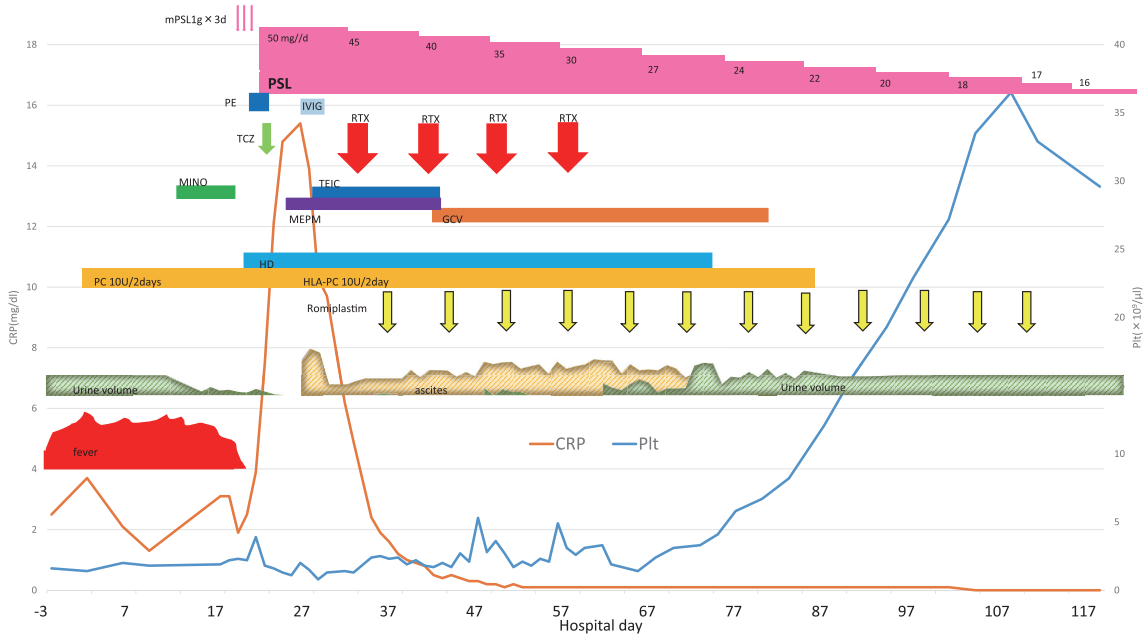

Fig. 1 Clinical course of our case

mPSL; methylprednisolone, PE; plasma exchange, PSL; prednisolone, IVIG; intravenous immunoglobulin, TCZ; tocilizumab, RTX; rituximab, MINO; minocycline, TEIC; teicoplanin, MEPM; meropenem, GCV; ganciclovir, HD; hemodialysis, PC; platelet transfusion, HLA-PC; HLA-matched platelet transfusion. Ascites are shown by the amount of ascites drained.

Cardiac ultrasonography showed no vegetation on the valves, although diffuse hypokinesis (LVEF 52%) and moderate pericardial infusion were detected (**Fig. 5**). The serum level of IL-6 was 16.8 pg/ml (reference range 0−4 pg/ml), whereas IL-6 level in pleural effusion was much higher (945 pg/ml) than that in serum. After admission, continuous fever (> 38°C) persisted, and platelet, albumin and red blood cell transfusions were required. Additionally, the patient's renal function rapidly deteriorated. Nineteen days after admission, he suddenly developed cardiogenic shock with difficulty in breathing, low blood pressure and dysuria. He was transferred to the intensive care unit and underwent non-invasive positive pressure ventilation and was administered catecholamine. Cardiac ultrasonography showed diffuse hypokinesis of the left ventricle (LV) and moderate pericardial effusion. Treatment with pulse methylprednisolone (1 g/day for three days) was effective only for fever but not for the rest of the symptoms, such as anasarca, severe thrombocytopenia and renal dysfunction with dysuria. On day 21, hemodialysis and plasma exchange were initiated because the patient's urine volume had decreased to below 50 mL/day and it was difficult to hemodyalize without infusion of a bulk of plasma. On day 23, tocilizumab (400 mg ivd) was injected. After day 26, occasional drainage of

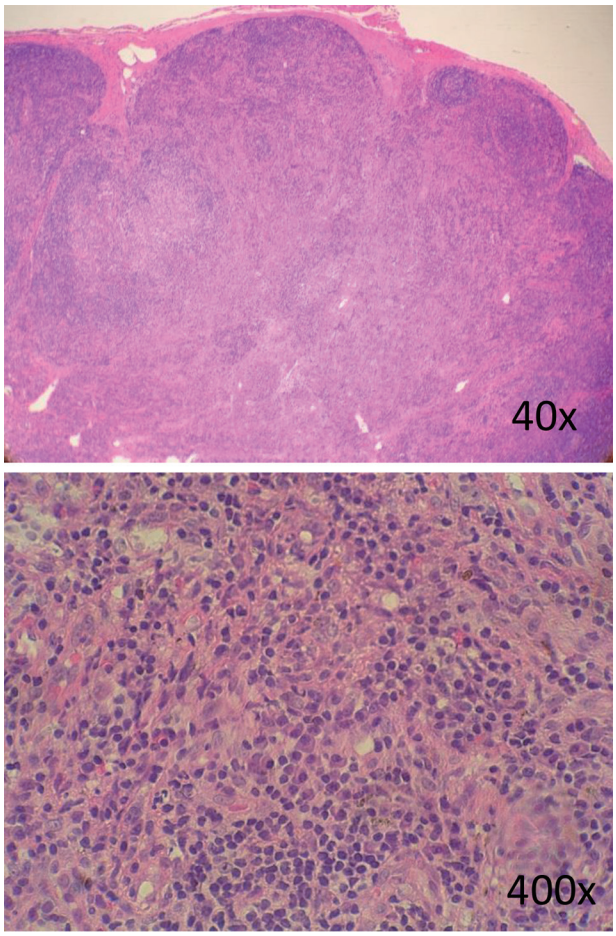

Fig. 2 Inguinal lymph node biopsy histology section by hematoxylin and eosin staining

Medullary hyperplasia with strong plasma cell infiltration was seen (upper panel: ×40, lower panel: ×400).

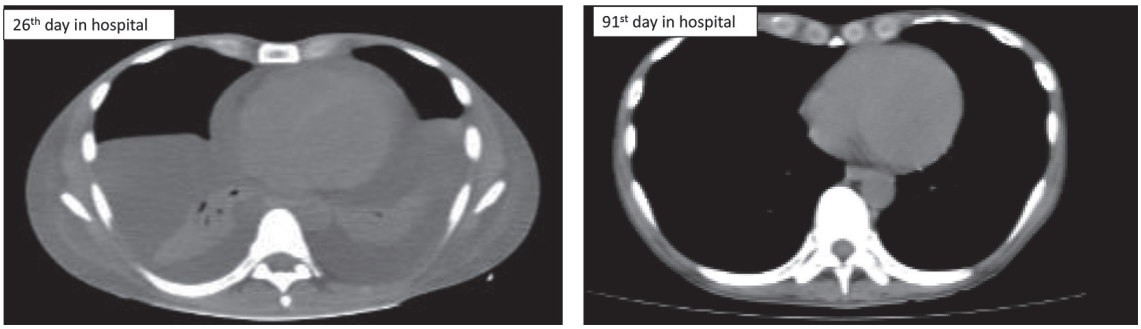

Fig. 3 Clinical course of pleural and pericardial effusion (CT scans at the heart level)
Large amount of bilateral pleural effusion and moderate amount of pericardial effusion were detected on the 26th hospital day, which disappeared on the 91st hospital day.

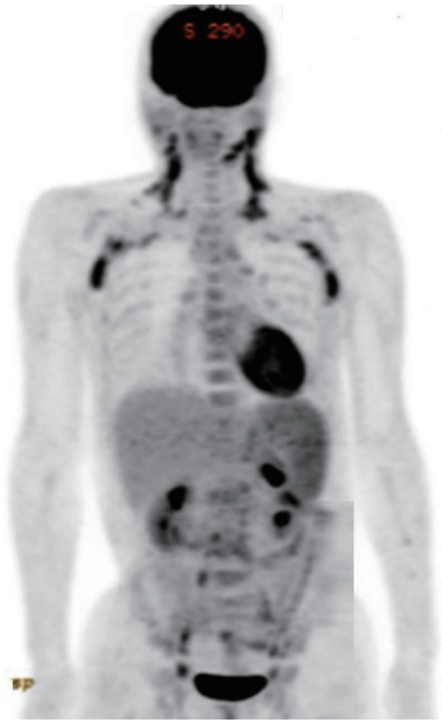

Fig. 4 18-fluorodeoxyglucose (^{18}FDG)-Positron Emission Tomography (PET) findings
Multiple lymphadenopathy and splenomegaly were detected.

the ascites and pleural effusion were performed to relieve the patient's abdominal distention and dyspnea. Although CRP gradually decreased, thrombocytopenia continued and platelet transfusion was needed every other day. On day 29, high-dose immunoglobulin therapy was started for thrombocytopenia because of positive PA-IgG, but was not effective. HLA-matched platelet transfusion was started because of elevated anti-HLA antibody, but platelet elevation was similar to that with non-HLA-matched platelet transfusion. On day 34, a total of four cycles of rituximab (600 mg/body: 375 mg/m^2, weekly) was started with written informed consent after approval of the ethical committee at our institute. After day 35, romiplostim, a TPO receptor agonist, was started for refractory thrombocytopenia. The patient's urine volume suddenly increased to over 100 mL/day on day 50, then to over 1000 mL/day on day 73, and hemodialysis was discontinued on day 76. After day 75, the platelet count finally started to elevate, so platelet transfusion was discontinued on day 87. After day 78, tachycardia continued and cardiac ultrasonography repeatedly showed persistence of diffuse hypokinesis (LVEF 43.9%). On day 85, contrast-enhanced cardiac MRI also showed diffuse hypokinesis (LVEF 36.8%), and serum troponin T was slightly elevated. Cardiomyopathy was suspected to be caused by TAFRO syndrome because no other etiologies were identified. On day 92, a CT scan revealed no ascites, pleural effusion or lymphadenopathy. On day 120, cardiac ultrasonography showed improvement of LV wall motion (LVEF 47.3%) and pericardial effusion (**Fig. 5**). He was discharged on foot on day 135.

Discussion

The pathogenesis of this syndrome is not clearly understood, but is considered to be a cytokine storm involving IL-6 and VEGF, as was MCD[3, 4]. Dysregulated and overproduced IL-6 stimulates the production of acute phase reactants in the liver, resulting in constitutional symptoms, including fever, sweats, and fatigue, and laboratory abnormalities, such as anemia and hypoalbuminemia. IL-6 also induces B cell proliferation and VEGF expression, leading to angiogenesis. IL-6 has emerged as a therapeutic target in CD based on its critical role in the pathogenesis and driving of symptomatology. The currently available treatments of CD are glucocorticoids, single-agent and combination chemotherapy, antiviral strategies, and monoclonal antibodies targeting CD20

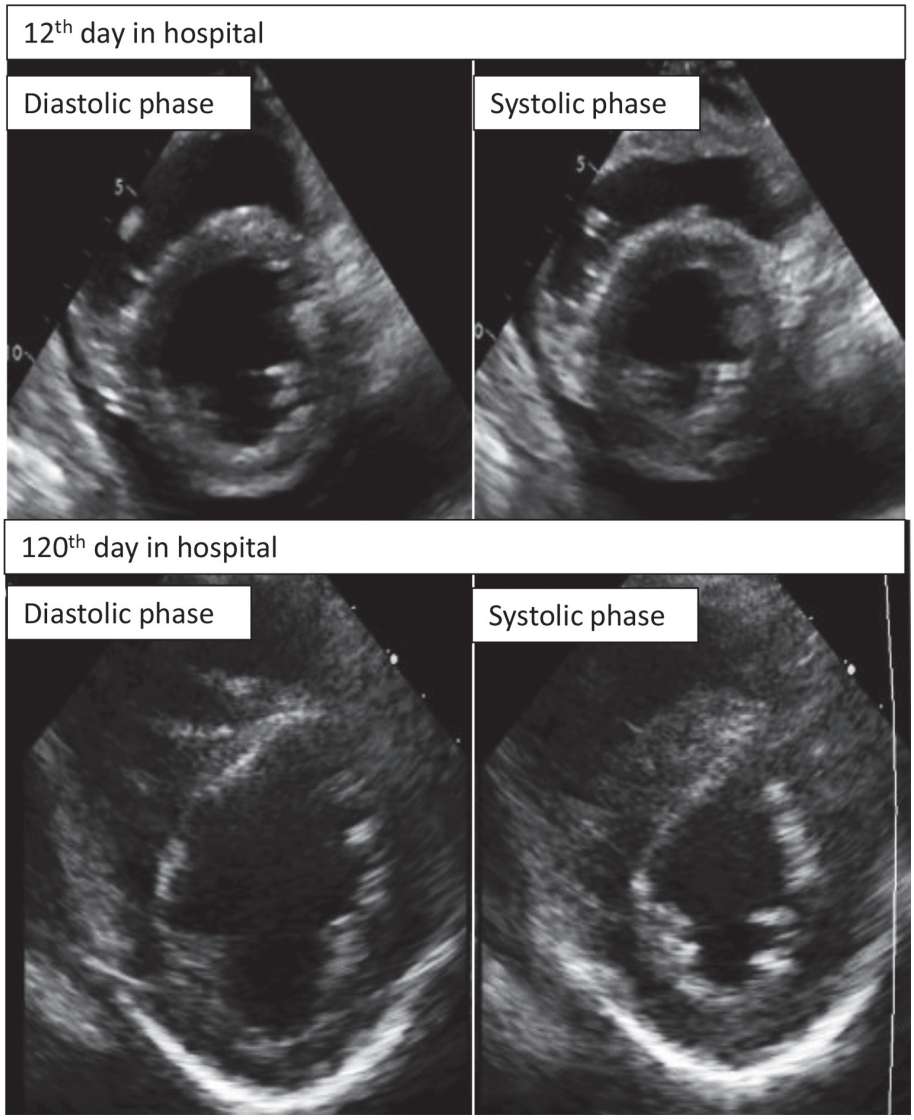

Fig. 5 Clinical course of cardiomyopathy (echocardiogram)
Mild diffuse hypokinesis (LVEF 52%) and mild pericardial effusion were detected on the 12th hospital day. On the 19th hospital day, sudden cardiogenic shock occurred. (No image stored. Severe diffuse hypokinesis described by chart description.) By the 120th hospital day, pericardial effusion had disappeared and wall motion had improved (LVEF 47.3%).

(rituximab) or IL-6 (tocilizumab)[16]. We chose rituximab because high-dose glucocorticoid had minimal effect and tocilizumab would not remain in the body due to the frequent drainage of pleural effusion and ascites to relieve the severe discomfort. In some cases, cyclosporine A (CyA) is effective (see **Table 2**), which suggests the involvement of T lymphocytes in the pathogenesis of TAFRO syndrome. Notably, our case showed various autoimmune findings, including positive tests for PA-IgG, direct Coombs, anti-SS-A (Ro) antibody, anti-TPO antibody, and anti-HLA antibody, relatively soon after platelet transfusion. Regarding the trigger of this syndrome, there was a report implicating HHV-6 infection[11], but it was negative in our case. Of note, our patient works for a meat slaughtering company and there was an incident a few weeks before the first symptoms in which he dropped a block of meat on his foot, which might have caused an infection of unknown microorganisms, leading to this syndrome.

Our case is the first report of TAFRO syndrome with cardiomyopathy. In cases of MCD, 7 cases with cardiac complications have been reported to date[17, 18]. Diffuse hypokinesis of LV wall motion was evident on echocardiograms in all these cases. Cardiac amyloidosis was diagnosed in 1 case by Congo red staining of the myocardium biopsy specimen, but the etiology of the cardiac dysfunction was not determined in the other 6 cases. Cardiac function and systemic symptoms were restored

Table 2 Previous case reports on TAFRO syndrome

Journal (author, year)	Age/Sex	Bone marrow biopsy	Thrombocytopenia		Liver failure			Heart failure	Renal failure				Treatment	Outcome
			Plt (10^3/μL)	PA-IgG (ng/10^7 cells)	T.bil (mg/dl)	ALP (IU/L)	Liver biopsy		Cre (mg/dl)	U-P	U-B	ARF/HD		
Inoue, 2013[2]	49, F	mild fibrosis	17	488	0.6	179			0.96	1+			DEX, PSL, CyA	remission
Iwaki, 2013[3]	43, F		135	98	1.0	1357			0.86	±			mPSL, PSL, RTX, TCZ	remission
Kawabata, 2013[4]	47, F	reticulin fibrosis	39	normal		660			1.4			HD	PSL, mPSL, TCZ	remission
Masaki, 2013[5]	57, F	without fibrosis	13	86.7	2.3	710			1.34	mild	microscopic	ARF	mPSL, PSL, CHOEP	died (candida infection)
	73, M	mild fibrosis	24		1.1	630			1.45	mild	microscopic		mPSL, PSL	died (MOF)
Takai, 2013[6]	47, F	reticulin fibrosis	14	> 300	1.5	1258	normal		0.7	1+	2+		CHOP, PSL	remission
	56, M	reticulin fibrosis	19	320	0.7	390	normal		1.9	3+	3+	ARF	mPSL, IVIG, CyA	remission
	49, M	reticulin fibrosis	10	300	0.7	756			0.9	−	−		mPSL, IVIG	died (CMV infection)
	53, F	reticulin fibrosis	38		1.9	1696	normal		0.7	1+	−		PSL, splenectomy CsA, IVCY	remission
	56, F	reticulin fibrosis	44	21.9	0.4	242			1.53	1+	2+	HD	mPSL, CyA	remission
Awano, 2013[7]	78, F	mild fibrosis	160	normal		459		BNP 126.0 UCG: normal	0.93				mPSL, PSL, TCZ	died (exacerbation)
Ozawa, 2014[8]	48, F	reticulin fibrosis	23	42.2	0.38	172		BNP 60.7	0.72	1+			PSL, RTX	remission
Tedesco, 2015[9]	21, F	reticulin fibrosis	7						1.6	1.96 g/d		ARF	PSL, PSL, TCZ, R-CVP	remission
Kubokawa, 2014[10]	15, M	reticulin fibrosis	thrombo-cytopenia				normal			0.4 g/gCre	−		mPSL, TCZ, IVIG PSL	remission
Jain, 2015[11]	28, M	reticulin fibrosis	75						2.5	1+	2+	HD	PSL, RTX	remission
Ishii, 2014[12]	50, M	reticulin fibrosis	65		1.4	753			3.24			ARF	TCZ, PSL	remission
Konishi, 2015[13]	77, F	no fibrosis	44	96	0.9	387			0.93				TCZ, PSL, RTX→CyA (maintenance)	remission
Tatekawa, 2015[14]	56, M	no fibrosis	76			1007			1.43				PSL+TCZ, thalidomide	remission
Kawashima, 2015[15]	39, M	no fibrosis	36	positive	0.3	1793				−	−		mPSL, PSL	remission
	38, M		202	positive	0.5	358	normal		2.59	+	+	ARF	PSL	remission
Our case	48, M	no fibrosis	16	294	0.8	1105		MRI: EF37%	1.50	3+	3+	HD	PSL, TCZ, IVIG, RTX	remission

U-P; urine protein, U-B; urine blood, DEX; dexamethasone, PSL; prednisolone, CyA; cyclosporine, mPSL; methylprednisolone, RTX; rituximab, TCZ; tocilizumab, CHOEP; cyclophosphamide, doxorubicin, etoposide, vincristine and prednisolone, CHOP; cyclophosphamide, doxorubicin, vincristine and prednisolone, IVIG; intravenous immunoglobulin, IVCY; intravenous cyclophosphamide, R-CVP; cyclophosphamide, vincristine, prednisolone, rituximab, HD; hemodialysis, ARF; acute renal failure

in 2 cases with the administration of glucocorticoid and in 2 cases with tocilizumab. An association between IL-6 and cardiovascular diseases has been implicated in both clinical and experimental settings. Hirota et al. reported that the circulating level of IL-6 is elevated in patients with congestive heart failure, implying an association of IL-6 with cardiac dysfunction[19]. Ancey et al. showed that human cardiomyocyte hypertrophy can be induced by gp130 (a counterpart of IL-6 receptor) stimulation in vitro, and this action was associated with STAT3 pathway activation[20]. Double-transgenic mice overexpressing both IL-6 and IL-6 receptor showed constitutive tyrosine phosphorylation of gp130 and STAT3 in the heart, and concentric hypertrophy and decreased LV volume were observed in these mice[21]. Thus, tocilizumab can be an effective treatment for CD-associated cardiomyopathy. Rituximab may deplete B cells that produce by IL-6.

As shown in **Table 2**, 21 cases of TAFRO syndrome have been reported. Median age was 49 years old and 11 were female (52%). Fourteen cases had myeloid fibrosis, all cases had severe thrombocytopenia, and 11 cases were positive for PA-IgG. Thirteen cases showed elevation of ALP, but liver biopsies in some cases showed no specific abnormalities. ALP isozyme analysis was liver type dominant. All cases had severe anasarca; the peritoneal biopsy of one case had no specific abnormalities. Eleven cases showed elevation of creatinine, 12 cases were positive for urinary protein or occult blood, and the renal biopsies in two cases showed mild to moderate proliferation of mesangial cells and thickened basement membrane with double contour and spike formation[15]. Treatments with glucocorticoid, tocilizumab, rituximab, CyA, and intravenous immunoglobulin were reported to be effective, but 4 cases died of infection or exacerbation of the disease. Our case had very severe generalized edema and intravascular dehydration probably because of cytokine storm, which may have been associated with the cardiac complications.

Conclusion

We reported a case of TAFRO syndrome with cardiomyopathy that was successfully treated with rituximab.

Conflict of Interest

None.

References

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