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CASE REPORT

Successful treatment of thrombotic thrombocytopenic purpura with repeated plasma exchange in a patient with microscopic polyangitis

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Abstract Thrombotic thrombocytopenic purpura (TTP) is in rare cases associated with antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis, and often has a fatal outcome. We report the case of a 77-year-old woman with microscopic polyangitis (MPA) presenting with TTP. Rapidly progressive renal dysfunction and paralysis and sensory disturbance of the left lower limb were noted. Serum creatinine was 3.95 mg/dl, and the titer of myeloperoxidase-ANCA was 238 EU. She was diagnosed with MPA, and high-dose methylprednisolone was initiated, followed by 60 mg/day of prednisolone. Hemolytic anemia with red blood cell fragmentation, purpura, and thrombocytopenia developed during the course of active MPA. The activity of disintegrin and metalloproteinase with thrombospondin type 1 motifs 13 (ADAMTS13) was moderately decreased (27%). She was diagnosed with TTP, and plasma infusion was initiated, followed by plasma exchange (PE) with 40 units of fresh frozen plasma. Thrombocytopenia continued for more than a month (5–10 $\times$ 10^4/μl). PE was repeatedly performed two or three times a week during the first 8 weeks from the beginning of PE in addition to prednisolone. Her clinical and laboratory findings gradually improved, and ADAMTS13 activity increased to 68%. The findings in this case suggested that ANCA-associated vasculitis may be involved in the development and the pathogenesis of TTP, and that repeated PE may need to be performed in addition to immunosuppressive therapy.

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Introduction

Thrombotic thrombocytopenic purpura (TTP) is a microangiopathy characterized by thrombocytopenia, hemolytic anemia, neuropsychiatric symptoms, renal dysfunction, and fever [1]. TTP is divided into congenital TTP, i.e., Upshaw-Schulman syndrome, idiopathic TTP, and secondary TTP presenting in patients with connective tissue diseases (CTDs) and malignant disorders [2]. The CTDs associated with TTP are mainly systemic lupus erythematosus, systemic sclerosis, and myositis, and in rare cases antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis [3–9]. Patients with ANCA-associated vasculitis with TTP are treated with plasma infusion (PI) and/or plasma exchange (PE) for TTP simultaneously with immunosuppressive drugs for CTD, though typically with unfavorable response. We report here successful treatment of TTP with repeated PE in addition to corticosteroids in a patient with microscopic polyangitis (MPA).

Case report

A 77-year-old female was admitted to a local hospital because of fever and general fatigue on 24 May 2006. The white blood cell count (WBC) and serum level of C-reactive protein (CRP) were increased. The serum level of creatinine (Cr) was elevated to 2.80 mg/dl. Urinalysis revealed occult blood and proteinuria. Because her urine volume rapidly decreased after admission, she was treated with hemodialysis and referred to our hospital on 31 May.

Slight pitting edema was observed in the lower limbs. Coarse crackles were audible in both lower lung fields. Purpura was observed in her left lower limb. Neurological examination revealed paralysis and sensory disturbance of the left lower limb. On laboratory examination, WBC was 15,690/μl, hemoglobin 12.0 g/dl, and platelet count (PLT) 14.1 × 10^4/μl (Table 1). The serum levels of bilirubin, AST, LDH, and CRP were elevated, while the serum level of haptoglobin was beneath the limit of detection. Serum Cr was increased to 3.95 mg/dl. Staining for myeloperoxidase (MPO)-ANCA was positive (238 EU), while that for other autoantibodies was negative. Roentgenography and computed tomography of the chest revealed bilateral pleural effusion. Renal biopsy could not be performed because the patient's general condition was bad. Based on the above findings, she was diagnosed with MPA and hemolytic anemia, and high-dose methylprednisolone (1 g × 3 days) was initiated, followed by 60 mg/day of prednisolone (Fig. 1). Although serum CRP and the titer of MPO-ANCA rapidly decreased, hemoglobin and PLT gradually decreased. Red blood cell fragmentation was observed in peripheral blood on the 3rd hospital day. She was diagnosed with TTP, and PI was initiated, followed by PE with 40 units of fresh frozen plasma. The activity of disintegrin and metalloproteinase with thrombospondin type 1 motifs 13 (ADAMTS13) was moderately decreased (27%). There were no medications or infections associated with ANCA-associated vasculitis or TTP. Although red blood cell fragmentation disappeared 10 days after the initiation of PE, thrombocytopenia continued for more than a month (5–10 × 10^4/μl). PE was repeatedly performed two or three times a week during the first 8 weeks from the beginning of PE. PLT gradually increased, and the serum level of haptoglobin recovered to normal levels. ADAMTS13 activity increased to 68%. Her clinical and laboratory findings were improved, hemodialysis was discontinued on the 67th hospital day, and prednisolone tapered to 27.5 mg/day.

Discussion

Thrombotic thrombocytopenic purpura secondary to ANCA-associated vasculitis is a rare and fatal disease. Table 2 shows nine reported cases of TTP with ANCA-associated vasculitis including our own: four of nine cases were MPA [3–5]; one was ANCA-associated vasculitis [6]; one was ANCA-positive Goodpasture syndrome [6]; one was Wegener's granulomatosis [7]; two were ANCA-positive polyarteritis nodosa [8, 9]. All patients were middle-aged females. Rapid progressive glomerulonephritis was observed in eight of nine patients. They were treated with corticosteroids and cyclophosphamide for vasculitis, and with PE and/or PI for TTP. There was no relationship between outcome and the disease activity of angitis or ANCA titer. TTP developed during the active course of vasculitis in all nine patients. Four of five patients with less than 5 × 10^4/μl PLT died. TTP thus appears to be a prognostic factor in patients with ANCA-associated vasculitis.

TTP is characterized by thrombotic microangiopathy and platelet activation [1]. Microangiopathy causes hemolytic

Table 1 Laboratory findings on admission

Urinalysis		Chemical analysis		Serological test	
Red blood cells	>100/HPF	Total protein	6.9 g/dl	Rheumatoid factor	(–)
White blood cells	<1/HPF	Albumin	3.0 g/dl	Antinuclear Ab	(–)
Glucose	–	Total bilirubin	3.7 mg/dl	Anti ds-DNA Ab	(–)
Protein	2+	AST	45 U/l	Anti RNP Ab	(–)
Occult blood	3+	ALT	11 U/l	Anti SS-A Ab	(–)
Granular casts	–	LDH	539 U/l	MPO-ANCA	238 EU
Complete blood cell counts		ALP	424 U/l	PR3-ANCA	(–)
White blood cells	15,690/μl	Creatine kinase	18 U/l	Anti GBM Ab	(–)
Neutrocytes	87.5%	Amylase	85 U/l	Anti β2-GPI Ab	(–)
Monocytes	5.0%	Blood urea nitrogen	39 mg/dl	Lupus anticoagulant	(–)
Eosinocytes	8.4%	Creatinine	3.95 mg/dl	Coagulation test	
Lymphcytes	5.0%	Glucose	110 mg/dl	PT-INR	1.12
Red blood cells	400 × 10^4 /μl	Total-cholesterol	238 mg/dl	APTT	35.1 s
Hemoglobin	12.0 g/dl	Triglyceride	200 mg/dl	FDP	24.7 μg/ml
Platelets	14.1 × 10^4 /μl	C-reactive protein	4.24 mg/dl		
Reticulocytes	10.8 × 10^4 /μl	Haptoglobin	<6.4 mg/dl		

Ab antibody, *GBM* glomerular basement membrane, *GPI* glycoprotein I

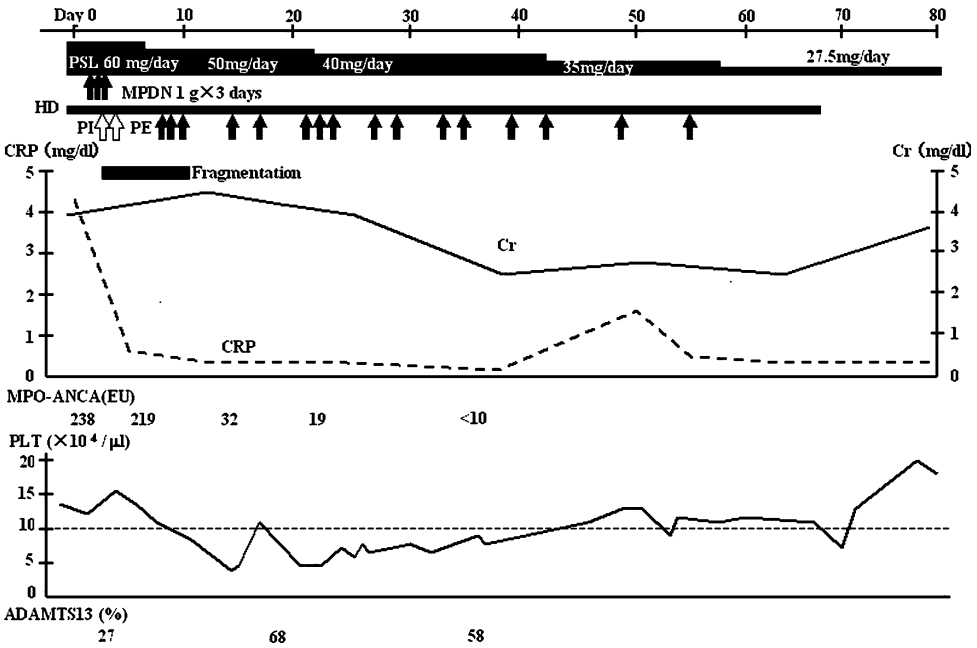

Fig. 1 Clinical course: *PSL* prednisolone, *MPDN* methylprednisolone, *HD* hemodialysis, *PI* plasma infusion, *PE* plasma exchange, *fragmentation* fragmentation of peripheral red blood cells, *CRP* C-reactive protein, *Cr* creatinine, *PLT* platelets, *ADAMTS 13* a disintegrin and metalloproteinase with thrombospondin type 1 motifs 13

Table 2 Patient profiles of ANCA-associated vasculitis with TTP

Age/ sex	Angitis	RPGN	DAH	Platelets (/μl)	Angitis-related antibody (EU)	ADAMTS13 activity (%)	Complications	Therapy	Prognosis/causes of death	References
66/F	MPA	+	–	98,000	P-ANCA 320	ND	Myocarditis	PSL, MPDN, CPA, PE	Alive	[3]
76/F	MPA	+	–	43,000	MPO-ANCA > 640	ND	Cerebral bleeding	PSL, MPDN, PI	Dead/ cerebral bleeding	[4]
73/F	MPA	+	+	12,000	MPO-ANCA 113	ND	Gastrointestinal bleeding	PSL,MPDN, CPA, PE	Dead/ sepsis, cerebrovascular accident	[5]
50/F	ANCA-AV	+	ND	103,000	MPO-ANCA 991, PR3-ANCA 14	ND	ND	PSL, PI	Alive	[6]
68/F	GPS	+	ND	16,000	MPO-ANCA 25, Anti-GBM 220	48	ND	PSL, MPDN, IVCY, PE	Dead/complication of hemodialysis	[6]
66/F	WG	+	+	141,000	C-ANCA 640	ND	–	PSL, MPDN, CPA, PE	Alive	[7]
70/F	PN	+	–	ND	MPO-ANCA 21	7	–	PSL, MPDN, CPA, PE	Dead/ cerebral bleeding	[8]
56/F	PN	ND	–	15,000	MPO-ANCA 201	ND	Duodenal ulcer	MPDN,IVCY, PI, PE	Dead/ gastrointestinal bleeding	[9]
77/F	MPA	+	–	48,000	MPO-ANCA 238	27	–	PSL, MPDN, PI, PE	Alive	This report

TTP thrombotic thrombocytopenic purpura, *RPGN* rapid progressive glomerulonephritis, *DAH* diffuse alveolar hemorrhage, *MPA* microscopic polyangitis, *ANCA-AV* ANCA-associated vasculitis, *GPS* Goodpasture syndrome, *WG* Wegener's granulomatosis, *PN* polyarteritis nodosa, *GBM* glomerular basement membrane, *PSL* prednisolone, *MPDN* methylprednisolone pulse therapy, *CPA* cyclophosphamide, *IVCY* intravenous pulse cyclophosphamide, *PI* plasma infusion, *PE* plasma exchange, *ND* not described

anemia with red cell fragmentation [10]. Unusually large multimers of von-Willebrand factor (vWF) are detected in the serum of TTP patients, which probably lead to platelet activation, thrombosis, and thrombocytopenia. Recent studies identified ADAMTS13 as an enzyme that cleaves multimers of vWF to smaller forms and is involved in the pathogenesis of TTP [11–13]. On the one hand, in idiopathic TTP, IgG-class antibody to ADAMTS13, acting as an

inhibitor of it, is observed in serum and reduces the cleaving activity of ADAMTS13. PE and PI can remove this inhibitor and replenish ADAMTS13, yielding favorable improvement. On the other hand, individual CTD patients with TTP varied in ADAMTS13 activity, which ranged from marked decrease to normal level. The inhibitor was detected in the serum in half of these patients [14]. PE and/or PI was also performed in patients with TTP secondary to CTD, with variable response [15, 16]. Factors other than the decreased activity of ADAMTS13 may thus contribute to the pathogenesis of TTP secondary to CTD [17].

The activity of ADAMTS13 in ANCA-associated vasculitis with TTP appears to vary, as in other CTDs, although it was previously measured in only three reported cases (Table 2). PE and/or PI was performed for the treatment of TTP, with poor response. In our case, thrombocytopenia persisted for more than a month despite PE. Although little is known concerning the relationship between ANCA-associated vasculitis and TTP, vascular endothelial damage is observed in capillaries and small arteries in these diseases [1]. Thus, ANCA-associated vasculitis may be involved in the development and pathogenesis of TTP. Repeated PE may need to be performed in addition to immunosuppressive therapy until repair of the vascular endothelium. Although the prevalence of ANCA in patients with TTP has never been examined, TTP progressed concomitantly with MPA in this case. TTP may be involved in the production of ANCA. Further studies are needed to test these hypotheses.

We have reported a rare case of MPA associated with TTP. Although thrombocytopenia persisted for more than a month, repeated PE was effective for TTP when added to corticosteroids.

Conflict of interest statement The authors have declared no conflicts of interest.

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