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Case Report

Successful treatment for thrombotic thrombocytopenic purpura complicated with myeloperoxidase anti-neutrophil cytoplasmic autoantibody-associated vasculitis

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Abstract

Thrombotic thrombocytopenic purpura (TTP) complicated with myeloperoxidase anti-neutrophil cytoplasmic autoantibody (MPO-ANCA)-associated vasculitis is rare and generally has a serious prognosis. We report a case wherein TTP was successfully treated with repeated plasma exchange (PE) and MPO-ANCA-associated vasculitis with corticosteroids. The renal function consequently improved such that haemodialysis could be discontinued and the patient was discharged without any significant complications.

Keywords: myeloperoxidase anti-neutrophil cytoplasmic autoantibody (MPO-ANCA)-associated vasculitis; plasma exchange (PE); thrombotic thrombocytopenic purpura (TTP)

Background

Thrombotic thrombocytopenic purpura (TTP) is a multisystem disorder that is characterized by thrombotic microangiopathy and generally has a serious prognosis. TTP can develop idiopathically and also be caused by drugs and autoimmune diseases. TTP-associated autoimmune diseases primarily include systemic lupus erythematosus, systemic sclerosis, myositis and, in rare cases, forms of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis, including microscopic polyangiitis.

We report a case of successful treatment of both TTP and myeloperoxidase (MPO)-ANCA-associated vasculitis. A few case reports on TTP complicated with MPO-ANCA-associated vasculitis have been published. On the basis of these cases, we discuss the mechanism underlying the development of TTP with MPO-ANCA-associated vasculitis and the available treatment for the same.

Case report

A 59-year-old woman was referred to our hospital for fever and leg oedema. Urinalysis performed previously did not reveal any abnormality or renal dysfunction, and the patient had no familial history of renal disease. Clinical examination revealed a regular pulse of 76 bpm, a blood pressure of 142/78 mmHg and a temperature of 38.5°C. Pretibial pitting oedema and purpura were observed in both legs. Neurological examination revealed sensory disturbance of the lower limbs. Laboratory examination revealed the following values: haemoglobin (Hb) level, 81 g/L; white blood cell count, 19 300 × 10^9/L; platelet count, 340 × 10^9/L; serum creatinine level, 249.29 μmol/L; serum urea nitrogen level, 14.99 mmol/L; C-reactive protein (CRP) level, 170 mg/L; and MPO-ANCA level, 95 EU. No other major autoantibodies were detected. Urinalysis revealed the presence of protein (2+) and blood (3+), and the sediment contained >100 red blood cells (RBCs) per high-power field. The urinary protein excretion was 0.8 g/day. Computed tomography (CT) of the chest revealed bilateral pleural effusion and ground-glass opacity. Ultrasonography and abdominal CT revealed normal-sized kidneys. On the basis of the clinical course and findings, active nephritis was suspected and renal biopsy was performed. Light microscopy revealed 10 glomeruli—one with global sclerosis and two with cellular crescent formation. The remaining glomeruli exhibited segmental proliferation of mesangial cells and a moderate increase of the mesangial matrix. The renal interstitium exhibited inflammatory cell infiltration and focal atrophic tubules. Severe vasculitis and necrotic lesions were observed in small vessels. Immunofluorescence staining (immunoglobulin [Ig]G, IgA, IgM, C3 and C1q) yielded negative results. The histology was compatible with that of ANCA-related glomerulopathy.

The patient's clinical course is shown in Figure 1. She had multiple mononeuritis, purpura and haemorrhage of the digestive tract. Renal biopsy revealed extracapillary proliferative glomerulonephritis compatible with rapidly progressive glomerulonephritis. Laboratory data revealed elevated MPO-ANCA levels. On the basis of the above findings, the condition was diagnosed as microscopic

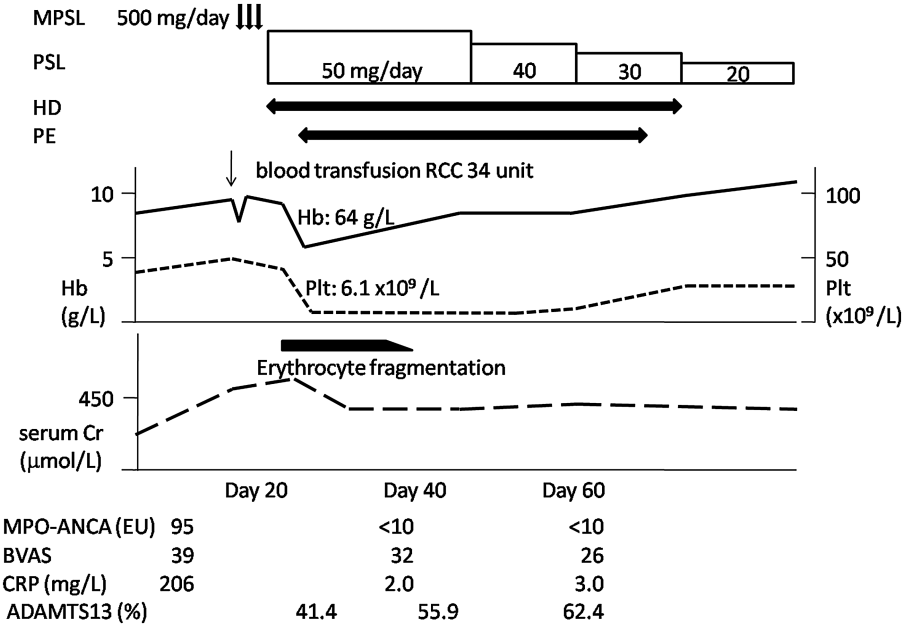

Fig. 1. Clinical and therapeutic course (MPSL, methylprednisolone pulse therapy; PSL, prednisolone; HD, haemodialysis; PE, plasma exchange; RCC, red cell concentrate; Hb, haemoglobin; Plt, platelet; Cr, creatinine; MPO-ANCA, myeloperoxidase anti-neutrophil cytoplasmic autoantibody; BVAS, Birmingham vasculitis activity score; CRP, C-reactive protein; ADAMTS13, activity of disintegrin and metalloproteinases with thrombospondin type 1 motif 13).

polyangiitis with a Birmingham vasculitis activity score (BVAS) of 39. On Day 20 of hospitalization, severe haemorrhage of the digestive tract was noted. Therefore, steroid pulse therapy with methylprednisolone at a dose of 0.5 g/day for 3 days was initiated according to the guidelines of the Japanese Society of Nephrology, and prednisolone (PSL) at a dose of 50 mg/day was subsequently administered intravenously. On hospitalization Day 22, haemodialysis was initiated because of progressive renal dysfunction. Immediately after steroid therapy was initiated, the patient's condition, including fever and general fatigue, improved and the serum CRP and MPO-ANCA values gradually decreased to <0.2 mg/dL and <10 EU, respectively. However, on hospitalization Day 28, haemolytic anaemia (Hb level, 64 g/L) with RBC fragmentation and thrombocytopenia (61×10^9/L) developed. At this time, the lactate dehydrogenase level was 680 U/L and the haptoglobin level reduced to <1 μmol/L. We suspected TTP and initiated plasma exchange (PE) with 3600 mL of fresh-frozen plasma as the replacement fluid. After a PE session, we confirmed a 41% reduction in the activity of disintegrin and metalloproteinases with thrombospondin type 1 motif 13 (ADAMTS13). Anti-ADAMTS13 IgG autoantibodies were not detected. A few days later, psychosis (delirium) and pyrexia developed. The diagnosis of TTP was confirmed, and 17 consecutive PE sessions were conducted. Thereafter, the clinical and laboratory findings gradually improved. Steroid therapy proved effective against microscopic polyangiitis, and the disease activity reduced such that haemodialysis was not warranted, even after the PSL dose was tapered. Finally, the patient was discharged without any significant complications and eventually resumed work.

Discussion

TTP with ANCA-associated vasculitis was initially described in 1995 [1]. In 2008, Nagai *et al*. [2] reported one case and discussed eight other cases reported previously in the English or Japanese literature. They found that all the concerned patients were middle-aged women. All patients developed TTP during the active phase of vasculitis. No relationship was noted between the outcomes and the degree of angiitis or the ANCA titre. Furthermore, patients with a platelet count of $<50 \times 10^9$/L had a poor prognosis, whereas the proposed severity scoring index predicting the survival of TTP patients does not include the platelet count [3]. In the present case, the patient was a 59-year-old woman who developed TTP during the active phase of MPO-ANCA-associated vasculitis.

TTP may be congenital, as in the case of Upshaw–Schulman syndrome, or acquired, as in the case of autoimmune diseases, infection, malignancy, pregnancy, drugs including cancer chemotherapy and idiopathic type. Anti-ADAMTS13 IgG autoantibodies, which reduce ADAMTS13 activity, have been detected in TTP patients. ADAMTS13 deficiency is responsible for most cases of acquired TTP. Therefore, PE was performed to supplement ADAMTS13 and to eliminate anti-ADAMTS13 IgG autoantibodies and very high-molecular-weight von Willebrand factor multimers. In TTP secondary to autoimmune diseases, ADAMTS13 activity can vary from normal to markedly reduced. However, in some cases, anti-ADAMTS13 IgG antibodies are not detected, as in the present case. Thus, factors other than decreased ADAMTS13 activity may contribute to the pathogenesis of TTP secondary to autoimmune diseases [4]. We per-

Table 1. Profiles of patients with TTP complicated with ANCA-associated vasculitis, requiring PE and haemodialysis

Author and year	Ref. no.	Age in years/sex	Angiitis	Therapy	ADAMTS13 activity (%)	Angiitis-related antibody (EU)	Platelet count ($\times 10^9$/L)	Outcome
Hirsch *et al*. 1995	1	66/F	MPA	PSL, MPSL, CPA, PE	ND	MPO-ANCA (340)	9.8	Alive
Lim *et al*. 1998		66/F	WG	PSL, MPSL, CPA, PE	ND	PR3-ANCA (640)	2.8	Alive
Yamasaki *et al*. 2001		56/F	PN	MPSL, IVCY, PI, PE	ND	MPO-ANCA (201)	1.5	Dead
Fujisaki *et al*. 2005		70/F	PN	PSL, MPSL, CPA, PE	7	MPO-ANCA (21)	ND	Dead
Nagai *et al*. 2008	2	77/F	MPA	PSL, MPSL, PI, PE	27	MPO-ANCA (238)	4.8	Alive
Present case		59/F	MPA	PSL, MPSL, PI, PE	41	MPO-ANCA (95)	6.1	Alive

MPA, microscopic polyangiitis; WG, Wegener granulomatosis; PN, polyarteritis nodosa; PSL, prednisolone; MPSL, methylprednisolone pulse therapy; CPA, cyclophosphamide; IVCY, intravenous pulse cyclophosphamide; PI, plasma infusion; PE, plasma exchange; ND, not described.

formed PE in the present case to eliminate some unknown factor(s) inhibiting ADAMTS13.

The relationship between TTP and ANCA-associated vasculitis remains unclear. Cases of TTP complicated with ANCA-associated vasculitis, requiring PE and haemodialysis, have been reported previously (Table 1). In all these cases, TTP developed rather early after glucocorticoid therapy was initiated. Given that TTP is characterized by thrombotic microangiopathy, endothelial damage due to ANCA-associated vasculitis and/or the process of endothelial healing after glucocorticoid therapy may promote the development of TTP. Therefore, careful observation is necessary when glucocorticoid therapy is initiated for various diseases, including ANCA-associated vasculitis. In two of the six described cases, haemodialysis was discontinued; in the present case, the patient was discharged. The degree of renal dysfunction in the early phase seems to reflect the renal outcome. Of the six reported cases, five involved Asian patients and the sixth was a Canadian patient. The prevalence of MPO-ANCA-associated vasculitis, which is higher than that of Wegener granulomatosis in Asia, may be attributed to the bias.

The risk of PE should be recognized. In a 9-year cohort study on 206 consecutive patients treated for TTP [5], 26% of the patients had major PE-associated complications, including systemic infection, venous thrombosis and hypotension warranting dopamine treatment, and 2% of the patients died of such complications (one died of haemorrhage owing to the insertion of a central venous catheter and one died of catheter-related sepsis). However, the mortality rate of TTP is currently only 12–14% in PE-treated patients [3,6] but approximately 90% without PE treatment [6–8]. The above findings indicate that the potential risk of TTP exceeds that of PE treatment. PE should be initiated even if the diagnosis of TTP is not confirmed [9,10]. In our case, PE was initiated immediately after TTP was suspected. After 17 PE sessions, the clinical and laboratory findings gradually improved. We emphasize that TTP should be considered in the differential diagnosis in cases of thrombocytopenia with vasculitis. Early appropriate treatment of TTP can improve the patient morbidity and mortality.

Conflict of interest statement. None declared.

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