Thrombotic Thrombocytopenic Purpura with Severe Hypertension in a Patient with Systemic Sclerosis Sine Scleroderma and Polymyositis

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Abstract

We present the first documented case of thrombotic thrombocytopenic purpura (TTP) with severe hypertension complicated by polymyositis and systemic sclerosis sine scleroderma. TTP developed in the progressive phase of visceral fibrosis in the absence of skin thickening. ADAMTS13 activity was not useful for the diagnosis of TTP. Although TTP and scleroderma renal crisis (SRC) share similar findings of thrombotic microangiopathy, severe thrombocytopenia with multiple organ injuries and hemorrhagic manifestations suggested TTP rather than SRC. The patient’s condition improved dramatically with plasmapheresis.

Key words: Polymyositis, Systemic sclerosis sine scleroderma, Thrombotic microangiopathy, Thrombotic thrombocytopenic purpura


Introduction

Thrombotic thrombocytopenic purpura (TTP) is characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia and functional impairment of multiple organs, especially the brain and kidneys. Thrombocytopenia and MAHA are shared by many disorders, including hemolytic uremic syndrome (HUS), malignant hypertension, disseminated intravascular coagulation, drug-induced disorders, antiphospholipid syndrome and scleroderma renal crisis (SRC). TTP and HUS are often described as TTP-HUS syndrome because of the similar clinical features and the difficulty in distinguishing between the two conditions. The pathological findings are endothelial cell injury, and microvascular aggregation of platelets leading to ischemia, called thrombotic microangiopathy (TMA).

TTP is a rare complication of systemic sclerosis (SSc) and polymyositis, and has not been reported in association with SSc sine scleroderma (ssSSc). We present a case of TTP with severe hypertension, ssSSc and polymyositis, and discuss the clinical features of the present case and the differential diagnosis between TTP and SRC.

Case Report

A 70-year-old Japanese woman was admitted to our hospital in August 2008 with headache and epigastric pain. She had a 6-year history of polymyositis with anti-aminocytic tRNA synthetase antibody and anti-signal recognition particle antibody, which was under control with tapering of prednisolone from the initial dose of 60 mg. She also had a history of insulin-controlled diabetes with HbA1c of 6-7% and hypertension treated with candesartan for at least 6 years. In addition, she had been diagnosed as having scleroderma spectrum disorder, considered as ssSSc (1), with Raynaud’s phenomenon, contraction of lingual frenulum, bleeding of nailfold, telangiectasia, reflux esophagitis and interstitial pneumonia, in the absence of anti-centromere antibody, anti-topoisomerase I antibody and anti-U1-RNP antibody. No obvious skin thickening was observed on physical examination except for temporarily suspected sclerodactyly of one finger. Three months before admission, she presented with chest pain and pericardial effusion on echocardiography sugges-
Figure 1. Clinical course: laboratory data and treatment. LDH: lactate dehydrogenase, ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blocker, FFP: fresh frozen plasma

The patient had a high creatinine level with a decrease in hemoglobin and a reticulocyte count of 7.2%, increased levels of bilirubin (2.7 mg/dL) and lactate dehydrogenase (1,099 IU/L; reference range 125-237 IU/L) with normal ranges of aspartate aminotransferase (47 IU/L) and alanine aminotransferase (26 IU/L), undetectable haptoglobin, and fragmented erythrocytes indicated microangiopathic hemolytic anemia. Coombs' test was negative. Serum creatinine was elevated from 0.64 mg/dL one month before to 1.62 mg/dL. Normal ranges of prothrombin time (10.5 s), activated partial thromboplastin time (30.7 s), and fibrinogen (368 mg/dL) with small elevation of D-dimer (3.4 μg/mL; reference range 0-0.9 μg/mL), thrombin antithrombin complex (4.4 μg/mL; reference range 0-2.9 μg/mL), and no antiphospholipid antibodies ruled out coagulation disorders such as disseminated intravascular coagulation and antiphospholipid syndrome. Serum complement levels were C₃ 59 mg/dL, C₄ 8 mg/dL, and CH₅₀ 33.9 IU/mL. Plasma renin activity was high after diuretics use (47.5 ng/mL/h; reference range 0.2-2.7 ng/mL/h). Urinary findings included proteinuria of 1 g/day without hematuria, granular and red blood cell casts.

Upon a provisional diagnosis of TTP, plasmapheresis was initiated on hospital day 1 along with prednisolone 40 mg/day and intravenous nicardipin for hypertension in the state of disturbed consciousness, which did not permit oral administration of antihypertensive drugs. After plasmapheresis for two consecutive days, her consciousness level and thrombocytopenia were dramatically improved. Captopril, valsartan and nifedipine were added for uncontrolled hypertension. Abdominal pain was resolved within a week. Renal function was gradually improved (Fig. 1). Thrombocytopenia and hemolytic anemia repeatedly relapsed during plasmapheresis tapering but they responded well to daily plasmapheresis. Infusion of fresh frozen plasma was not effective. Renal function remained stable. She underwent plasmapheresis for two and a half months to sustain a remission. Follow-up CT showed improvement of intestinal wall thickening after withdrawal of plasmapheresis. Activity of ADAMTS13 (a disintegrin and metalloprotease domain, with thrombospondin type 1 motif 13) on admission was within the normal range (86%), and anti-ADAMTS13 inactivating antibodies were negative. She was readmitted for pseudo-obstruction and malnutrition associated with scleroderma and died of miliary tuberculosis 8 months later. Autopsy revealed fibrotic changes in the gastrointestinal tract, myocardium and skeletal muscles, and diabetic nephropathy with nodular lesions of the glomerular extracellular matrix, glomerulosclerosis, interstitial fibrosis and mild reduplication of the internal elastic lamina in small arteries of the kidney. There was no evidence of persistent TMA.
Discussion

ssSSc is characterized by visceral involvement typical of SSc including esophageal hypomotility, small bowel hypomotility, pulmonary interstitial fibrosis, pulmonary arterial hypertension and scleroderma renal crisis, and peripheral vascular involvement such as Raynaud’s phenomenon, digital pitting scars, digital-tip ulcers and abnormal nailfold capillaries, without skin sclerosis. It is thought to be in the spectrum of SSc (1). Cases of SRC sine scleroderma were reported previously and have been shown to have poor renal prognosis even with the use of angiotensin-converting enzyme inhibitors (2). TMA with acute renal dysfunction and hypertension may be primarily regarded as hypertensive SRC in the course of scleroderma, as well as in ssSSc (3). It is often difficult to distinguish TTP from SRC because of similar clinical and pathological features of TMA. However, the differentiation of TTP from SRC is indispensable, since these are life-threatening diseases that require different management strategies.

In the present case, purpura, severe thrombocytopenia, fluctuating levels of consciousness, multiple organ injury, and dramatic improvement in thrombocytopenia and consciousness after the initial course of plasmapheresis strongly suggest TTP rather than SRC. TTP may have caused injuries to multiple organs including the kidneys, brain and intestine in the present case, although TMA was pathologically unproven. In previous reports, abdominal pain was noted as a presenting complaint in 11-14% of patients with TTP (4) and intestinal involvement was reported in TTP (5). Severe thrombocytopenia was the initial finding that made us suspect TTP in this case since thrombocytopenia is generally not severe in SRC. A higher incidence of profound thrombocytopenia and a significantly reduced survival were reported previously in patients with “normotensive SRC” (6). However, TTP may not have been accurately distinguished from SRC due to a significantly high rate of marked anemia with microangiopathy and hemorrhagic manifestations.

The trigger for TTP was unknown in the present case. However, the development of TTP may be relevant to the pathogenesis of TTP-HUS syndrome. Matsuyama found severe deficiency of TTP in the present case. Patients with idiopathic TTP do not typically have severe hypertension, though SSc-associated TTP is often accompanied by mild to severe hypertension (7). In the present case, antihypertensive drug withdrawal before admission may have resulted in exacerbation of essential hypertension. It is difficult, however, to associate the high plasma renin activity during hospitalization with SRC on the grounds of the clinical response to plasmapheresis and histological findings from autopsy. High plasma renin activity may suggest renal hypoperfusion. Apart from the use of diuretics, thrombi in renal arteries and arterioles may activate the renin-angiotensin system. There was no evidence of renovascular hypertension.

Deficient activity of von Willebrand factor (VWF) cleaving protease, also known as ADAMTS13, has been shown to provide useful diagnostic information and serve as a marker of treatment responsiveness in congenital and acquired idopathic TTP. The therapeutic outcomes of patients with normal ADAMTS13 activity tended to be worse than patients with severe deficiency (10). A previous report described a case of scleroderma-associated TTP with severe deficiency of ADAMTS13 activity (7). However, ADAMTS13 activity did not facilitate the decision in making the diagnosis of TTP in the present case.

Underlying mechanisms of TTP-HUS syndrome are heterogeneous. Matsuyama found severe deficiency of ADAMTS13 activity only in 17% of patients with connective tissue disease (CTD) -TMA, which was associated with inhibitory autoantibodies against ADAMTS13 (10). Other autoantibodies may be involved in the pathogenesis of TTP. Autoantibodies against CD36, a transmembrane protein on endothelial cells of microvasculature and platelets, may interfere with binding of CD36 to ADAMTS13 and impair the enzymatic function of ADAMTS13 cleaving unusually-large VWF multimers (11, 12). On the other hand, elucidating abnormalities of the complement system with gene mutations of complement regulators and activators including factor H, factor I and membrane co-factor protein, and autoantibodies against factor H contributed to the understanding of different etiologies of atypical HUS other than Shiga-like toxin (13). Another possible pathogenetic mechanism of TTP, inferred from a high plasma VWF level and a slight decrease in ADAMTS13 activity in CTD, is disequilibrium between the enzyme, ADAMTS13, and the substrate, unusually-large VWF multimers (10, 14).

No specific diagnostic marker has been established in
Table 1. Findings Suggestive of TTP Rather Than SRC in Scleroderma

| Severe thrombocytopenia (especially < 50,000/µL) with MAHA |
| Hemorrhagic manifestations including purpura |
| Fever |
| Normal blood pressure |
| Treatment failure of ACE inhibitors |
| Severe deficiency of ADAMTS-13 activity with anti-ADAMTS13 antibody |

TTP: Thrombotic thrombocytopenic purpura, MAHA: microangiopathic hemolytic anemia, SRC: scleroderma renal crisis, ACE: angiotensin converting enzyme

TTP. Its diagnosis is still based on routine blood tests and clinical findings. Table 1 shows the findings that led us to suspect TTP rather than SRC. Severe thrombocytopenia with MAHA and purpura were found in this case. Plasmapheresis should be considered when at least one of these findings, especially severe thrombocytopenia with MAHA, is present, because TTP is a potentially life-threatening disease.

In conclusion, this is the first documented case of TTP with hypertension in a patient with ssSSc and polymyositis who exhibited normal ADAMTS13 activity. Her condition was successfully managed with urgent plasmapheresis, despite difficulty differentiating TTP from SRC because of severe hypertension.

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

References