Pregnancy-Associated Thrombotic Thrombocytopenic Purpura with Anti-Centromere Antibody-Positive Raynaud’s Syndrome

Ryu Watanabe, Tsuyoshi Shirai, Yumi Tajima, Hirotu Ohguchi, Yasushi Onishi, Hiroshi Fujii, Naruhiko Takasawa, Tomonori Ishii and Hideo Harigae

Abstract

Thrombotic thrombocytopenic purpura (TTP), scleroderma renal crisis (SRC), and hemolysis, elevated liver enzyme levels, and a low platelet count (HELLP) syndrome display common symptoms that include microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. Therefore, it is important to distinguish between them because their treatments vary; however, the differential diagnosis is sometimes difficult. We report a 32-year-old woman who was referred to our department for further examination of microangiopathic hemolytic anemia, thrombocytopenia, and a slightly elevated serum creatinine level with anti-centromere antibody-positive Raynaud’s syndrome in the early puerperal period. TTP, SRC, and HELLP syndrome were considered in the differential diagnosis, but the measurement of a disintegrin-like metalloprotease with thrombospondin type 1 motifs 13 (ADAMTS13) activity and its inhibitor level led to the diagnosis of TTP. She was successfully treated by plasma exchange and high-dose prednisolone and angiotensin-converting enzyme inhibitor. If microangiopathic hemolytic anemia and thrombocytopenia are observed in perinatal women or patients with signs of systemic sclerosis, the measurement of ADAMTS13 activity and its inhibitor level are essential for diagnosis and therapeutic choice.

Key words: anti-centromere antibody (ACA), pregnancy, and thrombotic thrombocytopenic purpura (TTP)

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Introduction

Thrombotic thrombocytopenic purpura (TTP) is a potentially fatal disorder characterized by microangiopathic hemolytic anemia (MAHA) and thrombocytopenia, and it is often associated with neurological dysfunction, renal failure, and fever (1). Idiopathic and congenital TTP have also been reported. Most patients have underlying factors and conditions such as drugs, autoimmune diseases, infections, post-stem cell transplantation, or pregnancy (2). Deficiency of a disintegrin-like metalloprotease with thrombospondin type 1 motifs 13 (ADAMTS13), a von Willebrand factor-cleaving protease, has been recently reported to be the cause of TTP (1). For assessing TTP, it is critical to exclude other differential diagnoses. The evaluation of pregnant women is particularly difficult because the characteristic signs of TTP may also occur in patients with severe preeclampsia, eclampsia, and hemolysis, elevated liver enzyme levels, and a low platelet count (HELLP) syndrome (2).

Systemic sclerosis (SSc or scleroderma) is a heterogeneous autoimmune rheumatic disease characterized by inflammation and fibrosis of the skin and visceral organs, and vascular abnormalities (3). Anti-centromere antibodies (ACA) have been reported in 20% to 30% of SSc patients (4). Scleroderma renal crisis (SRC) is one of the most severe complications associated with hypertension and rapidly progressive renal failure and occurs in 5% to 10% of SSc patients (5). In patients with SRC, MAHA, thrombocytopenia, and renal failure are frequently observed, which are often confused with TTP (6). To our knowledge, 15 cases of TTP associated with SSc have been reported (6-18), but no
case with an ACA-positive TTP has been reported.

Here, we present a 32-year-old woman with MAHA, thrombocytopenia, and a slightly elevated serum creatinine level in the early puerperal period. She had been followed up for ACA-positive Raynaud’s syndrome. The measurement of ADAMTS13 activity and its inhibitor level led to the diagnosis of TTP, and she was successfully treated by plasma exchange, high-dose prednisolone (PSL), and enalapril, an angiotensin-converting enzyme inhibitor (ACEI).

Case Report

A 32-year-old woman was referred to our department of Hematology and Rheumatology for evaluation and therapy of MAHA, thrombocytopenia, and a slightly elevated serum creatinine level. She had a history of Raynaud’s phenomenon for two years and her grandmother suffered from rheumatoid arthritis. Serological tests showed positive antinuclear antibody (×1,280-fold, discrete speckled type) and ACA (205 index). Tests for other autoantibodies including anti-DNA, anti-RNP, anti-Sm, anti-SS-A, anti-SS-B, anti-Scl-70, and anti-Jo-1 antibody were all negative. Because of the lack of other specific findings such as skin sclerosis, she was diagnosed with Raynaud’s syndrome and followed up in her family clinic. One year later, she became pregnant. During the gestational period, no abnormal findings such as hypertension, proteinuria, and pretibial edema were observed. Mean blood pressure was about 110/60 mmHg and serum creatinine level was 0.6 mg/dL, and other laboratory tests including platelet count and lactate dehydrogenase (LDH) level were within normal limits. She delivered a baby with little bleeding and was discharged without incidence. Eight days after delivery, she presented with bilateral discolored vision and was referred to the department of ophthalmology in our hospital. Ophthalmological examinations revealed bilateral chorioretinitis and serological tests showed severe thrombocytopenia (7,000/μL). The next day, she was admitted to our department for further examination.

On admission, her blood pressure was 137/68 mmHg and body temperature was 36.7°C. She was conscious and oriented with no observable neurological deficits. Physical examinations of the heart, lungs, and abdomen were normal, but petechiae were present in bilateral lower extremities. Laboratory tests showed MAHA, thrombocytopenia, and a slightly elevated serum creatinine level (Table 1). Red cell fragmentation was observed in peripheral blood smear and bone marrow aspiration revealed no findings of malignancy. TTP, SRC, HELLP syndrome were considered for the differential diagnoses. She was administered 10 units of fresh frozen plasma and 10 mg of enalapril, an ACEI. The following day, she presented with epigastralgia, and her body temperature increased to 37.6°C, and serum hemoglobin level decreased to 5.7 g/dL. We clinically diagnosed TTP and began a plasma exchange (PE) of 30 units/day and administered daily 60 mg of oral PSL. These combination therapies dramatically normalized serum hemoglobin level, platelet count, and LDH level (Fig. 1) and plasma D-Dimer level gradually decreased. Her epigastralgia also improved immediately. ADAMTS13 activity before PE remarkably decreased (2.9%) and she was positive for the ADAMTS13 inhibitor (0.9 Bethesda unit/mL). These findings led to the conclusive diagnosis of TTP. In order to differentially diagnose SRC, a skin biopsy of the right forearm was taken, but it showed normal appearance without fibrosis. Computed tomography also revealed no shadow of interstitial pneumonia or fibrosis of the lung.

PE was administered four times and then discontinued, since the platelet count exceeded 15,000/μL for two consecutive days; this is in accordance with a previous study (2). ADAMTS13 activity increased to 28% and its inhibitors were not detected for two weeks since PE initiation. We then tapered with the dose of PSL while maintaining the same dose of enalapril. Bilateral chorioretinitis, which was present before admission, was not detected in subsequent

<table>
<thead>
<tr>
<th>Table 1. Laboratory Findings of Our Patient</th>
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<tr>
<td>Complete blood cell counts</td>
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<tr>
<td>WBC 7,900 /μL</td>
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<tr>
<td>Band 10 %</td>
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<tr>
<td>Seg 66 %</td>
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<tr>
<td>Lym 16 %</td>
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<tr>
<td>Mon 5 %</td>
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<td>Eos 1 %</td>
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<tr>
<td>Bas 0 %</td>
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<tr>
<td>RBC 252×10⁴ /μL</td>
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<tr>
<td>Hb 7.4 g/dL</td>
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<tr>
<td>MCV 86.6 fl</td>
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<tr>
<td>Hct 21.8 %</td>
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<tr>
<td>Ret 6.7 %</td>
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<tr>
<td>Plt 0.8×10¹² /μL</td>
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<tr>
<td>Coagulation</td>
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<tr>
<td>PT 94.0 %</td>
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<tr>
<td>APTT 27.1 sec</td>
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<td>Fbg 345 mg/dL</td>
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<tr>
<td>D-Dimer 14.2 μg/mL</td>
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Hematology and Rheumatology for evaluation and therapy of MAHA, thrombocytopenia, and a slightly elevated serum creatinine level in the early puerperal period. She had been followed up for ACA-positive Raynaud’s syndrome. The measurement of ADAMTS13 activity and its inhibitor level led to the diagnosis of TTP, and she was successfully treated by plasma exchange, high-dose prednisolone (PSL), and enalapril, an angiotensin-converting enzyme inhibitor (ACEI).
ophthalmological examinations. After discharge, PSL dose was gradually tapered, and currently there are no signs of relapse for nine months.

**Discussion**

In the present case, MAHA, thrombocytopenia, and a slightly elevated serum creatinine level were observed in addition to ACA-positive Raynaud’s syndrome during the perinatal period. Therefore, we proposed three possibilities for the differential diagnosis: HELLP syndrome, SRC, and TTP. It is extremely important to distinguish between them because therapies for SRC, HELLP syndrome, and TTP are very different, especially when administering PE and PSL. In a previous study, it has been reported that treatment with high-dose PSL in SSC is a risk factor of SRC (19), and PE might not be effective in SRC. To date, the only established treatment in SRC is ACEI (3). However, TTP should be treated with PE and high-dose PSL (2).

First, the presence of HELLP syndrome in the puerperal period was considered. HELLP syndrome is often associated with preeclampsia and highly elevated levels of liver enzymes (usually AST and/or ALT >70 IU/L). However, the present patient had no episodes of preeclampsia such as hypertension, proteinuria, and pretibial edema. Furthermore, her epigastralgia and liver dysfunction were mild. Second, SRC, in which MAHA and thrombocytopenia are observed frequently, was also considered because she was positive for ACA. Although she did not present with skin sclerosis, scleroderma sine scleroderma, a rare type of SSC, is infrequently observed (20). This type of SSC is unique in that patients can exhibit any characteristic feature of internal organ involvement without detectable skin features. Therefore, considering this observation, it was difficult to deny a connection between her clinical condition and SSC. However, her blood pressure was within normal limits and renal dysfunction was very mild. We therefore supposed that the probability of SRC was low. Finally, we considered TTP, although her body temperature was normal and she had no neurological abnormalities. Each differential diagnosis was atypical, and therefore it was very difficult to distinguish between them. But on the day after admission, we clinically diagnosed TTP because of fever and a further decrease in her serum hemoglobin level. Eventually the measurement of ADAMTS13 activity and its inhibitor level, which was identified a few days later, confirmed the diagnosis of TTP. Latuada et al reported that none of the pregnant women in their study who were diagnosed with HELLP syndrome had undetectable ADAMTS13 activity, suggesting that this protease was useful for distinguishing TTP from HELLP syndrome (21). There is no available evidence regarding ADAMTS13 activity in SRC and it is difficult to differentiate SRC from TTP; however Manadan et al discussed that fever and hemorrhagic manifestations, which were also observed in the present case, are only observed in TTP (6). In addition to decreased ADAMTS13 activity, the dramatic clinical improvement after PE suggested TTP diagnosis in the present case. We finally diagnosed her with pregnancy-associated ACA-positive TTP. To our knowledge, 15 cases of SSC-associated TTP have been reported (6-18). Among them, anti-Scl-70 antibody, which is also characteristic of SSC, was present in five cases, but no cases of ACA-positive TTP case have been reported.

The incidence of pregnancy-associated TTP is about only one in 25,000 pregnancies (22), but accounts for approximately 10% of all TTP cases (23). Specific proteins in pla-
The relationship between TTP and chorioretinitis is unclear. Although a case of Behcet’s disease with TTP has been reported, in the present case, she had no apparent findings such as oral and genital ulcers and erythema nodosum. We suspected chorioretinitis was due to TTP itself, because her visual symptoms dramatically improved after initiation of PE.

In conclusion, we presented a case of pregnancy-associated ACA-positive TTP, successfully treated with PE, high-dose PSL and enalapril. An accurate diagnosis of TTP is challenging when symptoms occur in perinatal women or patients with signs of SSc. Therefore, the most important laboratory data to guide the correct choice of treatment is ADAMTS13 activity and its inhibitor level.

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References