CASE REPORT

Thrombotic thrombocytopenic purpura as an initial presentation of systemic lupus erythematosus with acquired ADAMTS 13 antibody

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SUMMARY

We report a female patient presenting with headache, fatigue, ecchymoses and recent, excessive vaginal bleeding. Prompt review of the peripheral blood smear showed evidence of microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia. Thrombotic thrombocytopenic purpura (TTP) was suspected. Plasma exchange and corticosteroids were started urgently. The patient responded favourably to the treatment. Subsequently, positive serological markers returned and were compatible with systemic lupus erythematosus (SLE). A disintegrin and metalloproteinase with thrombospondin type 1 motifs, member 13 (ADAMTS 13) activity was remarkably low with a positive inhibitory ADAMTS 13 antibody. Mycophenolate and hydroxychloroquine were started along with a prolonged course and taper of corticosteroids. These medications have been maintained with an excellent response in 14 months of follow-up.

BACKGROUND

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy, which can be classified as idiopathic or in association with other disorders.^{1–3} An accurate diagnosis of an underlying disease is essential to guide prompt intervention. Despite rare coincidence, connective tissue diseases, particularly systemic lupus erythematosus (SLE), have been associated with TTP.^{4–6} Distinguishing between SLE and TTP is challenging due to shared clinical features including haemolytic anaemia and thrombocytopenia. Without timely recognition and intervention, TTP poses high mortality. The mainstay of treatment in TTP is plasma exchange.^{1–7} Even with treatment, SLE-associated TTP was reported to have a higher mortality, 34–62.5%, compared to idiopathic TTP, which was about 20% mortality.^{1–4–6–8–9} Some small studies showed a benefit of adding other immunosuppressive agents in SLE-associated TTP.⁹ A diagnosis of SLE is important regarding overall care of the patient, maintenance therapy, surveillance of disease activity and fatal complications. More severe disease activity in SLE includes a higher incidence of TTP.⁵

CASE PRESENTATION

A 35-year-old Filipina woman presented with headache and dizziness for approximately 10 days prior to admission. The patient had a significant medical history for occasionally irregular menstruation for a year. The dizziness started while she was sitting at her

office and was aggravated by postural changes. The headache, which began simultaneously, was throbbing, intermittent, moderately severe and frontal in location. The pain radiated to the neck with intermittently bilateral hands tingling. One week prior to admission, she experienced heavy menstrual bleeding for a few days, followed by persistent but less severe bleeding thereafter. Multiple bruises were also noticed on both legs. On the day of admission, she also reported of mild, non-radiating, sharp, mid-chest pain which was aggravated by deep inspiration. Naproxen, cyclobenzaprine, and ibuprofen/famotidine were prescribed for her headache initially. She took them 2–3 times per day for a week. Otherwise, she had been taking low-dose combined oral contraceptive pills for her irregular menses for about a year. She and her mother both denied autoimmune diseases in the family. Her surgical, family and social history was unremarkable. Her review of systems was significant for some skin lesions on her lower extremities, which were not painful and occurred intermittently on both legs over the past year.

On physical examination, the patient was stable and not in acute distress. Vital signs including orthostatics were normal. Pallor and pale conjunctivae were found. A systolic ejection murmur grade 3/6 at bilateral upper parasternal borders was heard on the date of admission. No hepatosplenomegaly was palpated. The skin was mildly jaundiced. Multiple ecchymoses were present on bilateral shins. Three 2–4 cm plaques of brownish, minimally coarse scales and without follicular plugs were observed on the anterior left leg and dorsum of left foot. No malar rash or other type of rash was present on sun-exposed areas. No tenderness or deformities were present in the joints. Neurological examination was normal. There was no evidence of active oral, vaginal or rectal bleeding.

INVESTIGATIONS

Initial complete blood count (CBC) showed profound anaemia, haemoglobin of 5.0 g/dL, and low platelet of 6000/ μ L. Multiple polychromasia and schistocytes were found on peripheral blood smear (figure 1). Work up for haemolysis was positive. Summary of laboratory data and imaging are shown in table 1.

DIFFERENTIAL DIAGNOSIS

Her dizziness was thought initially to be the result of severe anaemia caused by menorrhagia in the

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Figure 1 Patient peripheral blood smear.

setting of thrombocytopenia. However, she was found to have significant haemolysis, MAHA on peripheral blood smear and minor headache without fever or renal failure. TTP was suspected. Idiopathic TTP was diagnosed after excluding similar TTP-like diseases such as disseminated intravascular coagulopathy (DIC; due to normal coagulation profile), disseminated malignancy (due to normal chest X-ray and liver function test) and malignant hypertension (due to normal blood pressure). A concern about oral contraceptives inducing thrombosis was raised. No history or physical findings suggested systemic sclerosis or antiphospholipid antibody syndrome. Non-specific skin lesions on the left leg, pleuritic chest pain with small

pericardial effusion and thrombocytopenia with haemolytic anaemia raised concern for SLE.

TREATMENT AND OUTCOME

Plasma exchange was started immediately. Packed red blood cells were transfused. Methylprednisone 1 g was given intravenously for 3 days initially. The patient responded well to treatment. Headache, dizziness and chest pain resolved. Her platelet count normalised on day 6. Daily plasma exchange was continued for eight consecutive days. Further serological results suggested SLE. Hydroxychloroquine 200 mg orally twice a day and prednisone 40 mg orally daily were started during hospitalisation. Oral contraceptive use was discontinued. Mycophenolate was started subsequently. She was discharged on day 9 without complication. Over the ensuing year, she had followed up with a rheumatologist, haematologist and gynaecologist. Prednisone was tapered off. She had been taking hydroxychloroquine and mycophenolate without SLE flare or recurrence of TTP thus far.

DISCUSSION

TTP is diagnosed clinically by the presence of MAHA, thrombocytopenia, with or without neurological and renal involvement and without another identifiable cause.¹⁻³ The original descriptive pentad of TTP (fever, neurological and renal abnormalities, MAHA and thrombocytopenia) is found in only 5% of cases.^{1 10} Some conditions that also present with systemic microvascular thrombosis are: drug-associated (eg, quinine), SLE, antiphospholipid antibody syndrome, scleroderma, malignant hypertension, Haemolysis Elevated Liver enzymes Low Platelet count, post-haematopoietic stem cell transplantation, DIC and disseminated malignancy.¹⁻³ Some consider these entities to be acquired forms of TTP associated with their

Table 1 Patient diagnostic data

CBC	<p>↓ Haemoglobin 5.0 g/dL, Normal MCV 92.3 fL, ↑ RDW 24.8%</p> <p>↓ Platelet 6000/μL</p> <p>Normal WCC 3700/μL (PMN 62%, Lymph 35%, Band 3%)</p>
Haemolysis evaluation	<p>↑ Total bilirubin 2.0 mg/dL and indirect bilirubin 1.6 mg/dL</p> <p>↑ LDH 1123 U/L (normal 135–250 IU/L)</p> <p>↓ Haptoglobin <20 mg/dL (normal 30–200 mg/dL)</p> <p>↑ Reticulocyte count 14.1%</p> <p>Negative Direct Coomb's test</p>
Serology	<p>↑ ANA 5120, Speckled pattern (normal=or <40)</p> <p>↑ Anti-Smith 2.1 AI (normal=or <0.9 AI)</p> <p>Borderline Anti-dsDNA 5.0 IU/mL (indeterminate 5–9 IU/mL)</p> <p>↑ Anti-RNP >8.0 AI (normal=or <0.9 AI)</p> <p>↓ C3 77 mg/dL (normal 90–180 mg/dL)</p> <p>↓ C4 9 mg/dL (normal 10–40 mg/dL)</p> <p>Negative Anticardiolipin, β-2 glycoprotein I antibody, Rheumatoid factor, Anti-CCP, ANCA screening, CH50 and CRP</p>
Renal function and urinalysis	<p>Normal BUN 8 mg/dL</p> <p>Normal Creatinine 0.7 mg/dL</p> <p>Urinalysis showed large blood, WCC 6–20 cells/hpf</p> <p>Non-dysmorphic RBC 6–20 cells/hpf and Negative Protein</p>
Pregnancy test	Negative Serum and urine β-HCG
ADAMTS 13	<p>↓ ADAMTS 13 <1% activity (normal 68–163%)</p> <p>↑ ADAMTS 13 inhibitor 4.0 BEU (normal <0.4 BEU)</p>
Coagulation	<p>Normal PT, INR, PTT and fibrinogen level</p> <p>↑ D-dimer 1.3 (normal <0.5 μg/mL)</p>
Infection work up	Negative Blood culture, urine culture, anti-HIV, anti-HBV and anti-HCV
Miscellaneous studies of additional pertinence	<p>Normal Liver function test</p> <p>Echocardiogram showed small sized pericardial effusion and mild to moderate mitral regurgitation</p>

ADAMTS 13, a disintegrin and metalloproteinase with thrombospondin type 1 motifs, member 13; ANCA, antineutrophil cytoplasmic autoantibody; Anti-HBV, antihepatitis B virus; Anti-HCV, antihepatitis C virus; Anti-CCP, anticyclic citrullinated peptide; Anti-RNP, antiribonucleoprotein; β-HCG, β-human chorionic gonadotropin; BEU, Bethesda equivalent units; BUN, blood urea nitrogen; CRP, C reactive protein; INR, international normalised ratio; LDH, lactate dehydrogenase; MCV, mean corpuscular volume; PT, prothrombin time; PTT, partial thromboplastin time; RDW, red blood cell distribution width; RBC, red blood cells; WCC, white cell count.

respective and specific diseases.^{2 3} Approximately half of idiopathic TTP shows severe deficiency of a disintegrin and metalloproteinase with thrombospondin type 1 motifs, member 13 (ADAMTS 13) activity (<10%).¹ A reduction of enzyme ADAMTS 13 which plays a role in the cleavage of large multimers of von Willebrand factor in order to regulate appropriate platelet aggregation is thought to be the main defect. An inhibitor is sometimes detected.¹¹ Hemolytic uremic syndrome (HUS) is a similar syndrome, but is predominated by renal failure and occurs mostly in children.¹

Connective tissue diseases, especially SLE, are associated with TTP. Almost 170 patients with SLE-related TTP were reported in literature.^{1 4 6} TTP-like syndrome and lupus-related TTP-like MAHA were also proposed due to possible difference in pathogenesis and clinical outcome.⁹ One review showed that approximately 2.2% of 1203 patients with SLE were admitted for TTP in Korea. High SLE disease activity and lupus nephritis were also found to be related to TTP manifestations.⁵ In the other reviews of 40 and 105 SLE-associated TTP patients, both conditions occurred simultaneously in about 12–45%. Prior SLE was reported in about 50–73%. Only 3.8–15% were diagnosed with SLE subsequently.^{4 6} The role of ADAMTS13 autoantibody in SLE may contribute to TTP but it is still unclear. In patients with SLE with positive anti-dsDNA, ADAMTS 13 levels were found to be lower, however, the inhibitory antibody was not significantly increased. The low ADAMTS 13 level also correlated with high cumulative tissue damage in SLE.¹² Only 10% of TTP in SLE showed ADAMTS 13 activity <10% in another report.¹

Our patient had no history of SLE. She presented with a clinical picture of TTP. Overlapping clinical picture of TTP and active SLE was found at presentation. Peripheral blood smear and serology for SLE helped diagnose concomitant TTP and SLE. According to the American College of Rheumatology (ACR) 1997 criteria for diagnosis of SLE, the patient was considered definite SLE due to high antinuclear antibody, high anti-Smith, thrombocytopenia and pericarditis.¹³ In addition, her chronically recurrent cutaneous lesions on her legs were questionable, but did not fit well with cutaneous lupus erythematosus.¹⁴ The suspected diagnosis of TTP required only MAHA and thrombocytopenia for initiating urgent plasma exchange. Peripheral blood smear is a simple, yet crucial test. Two or more schistocytes per 100 magnification of microscopic field and polychromasia are characteristic of MAHA. Indirect hyperbilirubinemia, high lactate dehydrogenase, negative direct Coomb's test and blood in urinalysis are supportive of non-immune mediated haemolysis.^{1–3} Regarding the patient's medication, oral contraceptive use may be associated with TTP, but the evidence is limited.¹⁵ Interestingly, hormonal effects play a role in pathogenesis of SLE and oral contraceptive use poses an increased risk.¹⁶

Daily plasma exchange, regardless of ADAMTS 13 activity, is critical, and recommended until platelet counts normalise for two successive days. Temporarily, plasma replacement is reasonable while awaiting plasma exchange. Suppressing ADAMTS 13 inhibitor production with corticosteroids may be appropriate in TTP.^{1 7} Rituximab (anti-CD 20) also showed good response with less relapse.¹⁷ Other immunosuppressive agents for example, vincristine, cyclophosphamide or cyclosporine showed benefit in small case series.³ In a systematic review, poor outcomes were not observed with platelet transfusions, which may indicate that this is an obsolete belief.¹⁸ Overall mortality rate was about 20% with plasma exchange. Small case series reported higher mortality in TTP related to SLE.⁸ Our patient presented with simultaneously TTP and SLE and responded well to plasma exchange and corticosteroids. Immunosuppressive agents were

started in hospital and maintained for SLE. Her outcome has been favourable.

Learning points

- ▶ Thrombotic thrombocytopenic purpura (TTP) must always be considered in patients presenting with haemolytic anaemia and thrombocytopenia.
- ▶ Prompt inspection of the peripheral blood smear and observation of schistocytes and polychromasia (microangiopathic haemolytic anaemia, MAHA) are essential for diagnosing TTP.
- ▶ Particularly in young women, TTP and systemic lupus erythematosus (SLE) can occur concomitantly and can share similar haematological manifestations including MAHA and thrombocytopenia.
- ▶ Since TTP and SLE share an association, patients diagnosed with TTP should undergo a very careful evaluation for SLE.
- ▶ A patient with concomitant TTP and SLE requires targeted treatment of both diseases including immunomodulators.

Competing interests None.

Patient consent Obtained.

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