

OVERLAPPING FEATURES OF THROMBOTIC THROMBOCYTOPENIC PURPURA AND SYSTEMIC LUPUS ERYTHEMATOSUS, A DIAGNOSTIC AND A MANAGEMENT CHALLENGE

M. Krstevski¹, O. Janev², L. Krstic²

¹University Clinic of Internal Medicine, – Skopje, R. North Macedonia

²University Clinic of Rheumatology, – Skopje, R. North Macedonia

Abstract. *Thrombotic thrombocytopenic purpura (TTP) is a rare, potentially fatal blood disorder that can be challenging for clinicians to identify in the setting of autoimmune diseases such as systemic lupus erythematosus (SLE). SLE can present with thrombotic microangiopathy (TMA) and differentiation between the two diseases can be quite difficult. In this case report we present a 62-year-old female with a history of SLE who was hospitalized with thrombocytopenia, dysarthria, dizziness, paresthesia and altered mental status. The laboratory results revealed direct Coombs negative hemolytic anemia, severe thrombocytopenia, significant elevation of lactate dehydrogenase, leukocytosis and presence of few schistocytes in the peripheral film. In addition, we also present evidence for circulating anti-ADAMTS13 antibody/ADAMTS13 antigen. Based on clinical, hematological, and biochemical findings, we concluded that it was a case of TTP-like microangiopathy associated with SLE and indicated treatment with methylprednisolone pulses and plasmapheresis. Later on, she developed psychosis and made plasmapheresis difficult to perform. We continued corticosteroids (dose 1 mg/kg), RhoGAM, Chloroquine and Azathioprine, obtaining a satisfactory response after one week of treatment.*

Key words: *Thrombotic thrombocytopenic purpura, systemic lupus erythematosus, microangiopathic hemolytic anemia, ADAMTS13, immunosuppressants*

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy (TMA) that can be classified as idiopathic or in association with other pathological processes such as neoplasms, infections, and autoimmune diseases [1, 2]. The exact cause of TTP is not known. The disease is associated with a deficiency of an enzyme involved in blood clotting called the von Willebrand factor cleaving protease or a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (also called ADAMTS13). There is an acquired (non-inherited) form of TTP referred to as immune-mediated TTP (iTTP) and a familial form referred to as congenital TTP (cTTP). iTTP may appear later in life, in late childhood or adulthood, and affected individuals may have a single episode or recurring episodes. This form of TTP is considered to be an autoimmune disease and is caused when patients develop an antibody against the ADAMTS13 protease leading to low levels of the protease. If the disorder is present at birth (familial form), signs and symptoms may typically appear earlier, in infancy or early childhood. This is referred to as cTTP. Women with cTTP may also present with an acute TTP episode for the first

time at the time of their first pregnancy. Immune-mediated TTP can occur as a consequence of acquired immunodeficiency syndrome (AIDS), the AIDS-related complex, or the human immunodeficiency virus (HIV) infection or other autoimmune diseases. Patients with iTTP may also be diagnosed in the future with other autoimmune diseases as well [3]. SLE as an autoimmune disease may be present before the acute episode of TTP, but in a recent study from James N. George [4], three (7%) of the 42 surviving patients with idiopathic TTP and severe ADAMTS13 deficiency have subsequently developed SLE. The preliminary data from these series suggests that the frequency of rheumatic disease-associated autoantibodies is significantly greater in patients with severe ADAMTS13 deficiency than in the normal population. Therefore, the above mentioned author suggests assessing criteria for SLE during initial episodes and follow-up evaluations of TTP.

Thrombotic thrombocytopenic purpura (TTP) in patients with SLE is extremely rare. The overall incidence of TTP in SLE patients is unclear and has been reported to be as low as 0.5%. A review includes about 40 cases of TTP related to SLE. Very rarely TTP presents simultaneously with SLE in ICU. The clinical presentation of both entities (TTP

and SLE) is somewhat similar because they share clinical characteristics that can overlap. It is difficult to make the diagnostic differentiation in the first instance, which delays the decision with regards to the correct treatment.

We present a clinical case of a woman with a clinical presentation of SLE and TTP that was difficult to diagnose.

CASE REPORT

We report a case of a 62-year-old female with a history of SLE who was hospitalized with thrombocytopenia, dizziness, paresthesia and altered mental status. She has suffered from cerebral vascular accident in 2018.

On physical examination, a confused state, and ecchymosis on the legs and arms were found. The cardiovascular and pulmonary systems had no alterations, and she was hemodynamically stable. Computer tomography (CT) of the brain showed no evidence for the new ischemic lesions. No other abnormalities were detected. The patient's first laboratory findings revealed severe hemolytic anemia and thrombocytopenia. The hemoglobin level (Hb) was at 97 g/L (reference range 120-160 g/L), hematocrit 23% (reference range 36-45%), mean corpuscular volume 86.0 fL (reference range 80-95 fL), reticulocyte count 4.47% (reference range 0.5-2.5%), the platelet count was $6 \times 10^3/\text{L}$ (reference range $(150-450) \times 10^3/\text{L}$), white blood cells count $12.1 \times 10^9/\text{L}$ (reference range $(4-11) \times 10^9/\text{L}$), lactate dehydrogenase level (LDH) was elevated to 1150 IU/L (reference range 200-400 IU/L), D-dimers 6396 ng/ml (reference range up to 500 ng/ml), short aPTT value of 19s (reference range 21-35 s), total bilirubin level was 4.3 mg/dL (normal range 0.1-1.2 mg/dL), and indirect bilirubin was 3.4 mg/dL (reference range 0.2-0.8 mg/dL). Peripheral blood smear test revealed few fragmented red blood cells (RBCs). This made us suspect that it was a case of thrombotic microangiopathy (TMA) with hemolytic anemia. We indicated ADAMTS13 and Coombs tests, in which we found that direct and indirect Coombs tests were negative. While waiting for the result for ADAMTS13, patient initially received two packed red blood cells transfusions to correct the anemic condition.

After transfusion and supportive treatment, our patient became better, her Hb level was 113 g/L (reference range 120-160 g/L) and platelet count $24 \times 10^3/\text{L}$ (reference range $(150-450) \times 10^3/\text{L}$) and white blood cells became $17.4 \times 10^9/\text{L}$ (reference range $(4-11) \times 10^9/\text{L}$).

Treatment with intravenous methylprednisolone (500 mg for 3 days) was started followed by oral administration of prednisone (1 mg/kg/day) and plasma exchange was planned; however, two days after the beginning of treatment, she developed psychosis with severe fear of intravenous treatment and agony whenever she saw a male physician or any male hospital worker. This situation made plasma exchange difficult to perform. With precautions and with an extremely careful assessment due to the patients paranoid state, with lots of speaking and calmness during visits, we continued corticosteroids (dose 1 mg/kg), RhoGAM, chloroquine and azathioprine, obtaining a satisfactory response (her platelet count, LDH and Hb were corrected) after one week of treatment.

Later, the obtained ADAMTS13 testing showed ADAMTS13 antigen levels were low to undetectable 0.01 IU/ml (reference range 0.36-1.17 IU/mL). Evidence for circulating anti-ADAMTS13 antibody was also presented 71 IU/ml (reference range 1.4-12.5 IU/mL), and diagnosis for TTP-like microangiopathy was established.

With a regression in her neurological and psychological condition and improvement in the laboratory results, the patient was discharged 10 days after hospitalization with a medical prescription of prednisolone at a dose of 0.5 mg/kg/day PO, hydroxychloroquine at a dose of 200 mg/day and azathioprine of 50 mg/2 x day. The patient is regularly followed up by her rheumatologist and so far she does not have any worsening of the initial disease.

DISCUSSION

TTP is one of the TMA, considered hematological emergency. Although TTP and SLE are different diseases, they may present as overlapping for each other although the association between them has not been well defined [1]. There are many hypotheses being found to explain this association that include abnormal endothelial activation, elevated levels of D-dimers, ADAMTS13-resistant von Willebrand Factor and defects in the complement system regulation [7].

Patients with SLE who develop TTP are significantly clinically worse than those with idiopathic TTP. One study recorded 34% mortality in reported cases of TTP in SLE alone [5] and another reported a much higher mortality of 62.5% [2]. It is very likely that due to the reporting bias in favor of positive outcomes, the mortality of TTP in SLE is even higher than these figures portray. The management of

TTP in SLE has been modelled around the protocols used in idiopathic TTP.

The key diagnostic clues are from the laboratory evaluation. The presence of both anemia and thrombocytopenia (in the absence of leukopenia) suggests the diagnosis. The following evidence of microangiopathic hemolytic anemia provides support (but is not specific) for the diagnosis: fragmented red cells (schistocytes) and polychromatophilic red cells (reticulocytes) on the peripheral-blood smear, increased serum levels of lactate dehydrogenase and indirect-reacting bilirubin, and a negative direct Coombs' test. Examination of the blood smear is critical [10].

Although investigations of Microangiopathic hemolytic anemia (MAHA) as blood smear for fragmented RBCs and low platelet counts are very important, it is not specific for TTP because they may be present in other disorders with TMA. So, it is important to measure ADAMTS13 level which is the unique marker, sensitive and specific for TTP, but reliable results of ADAMTS13 level usually cannot be available in emergency, this explains why urgent management is usually decided depending on the clinical symptoms of TTP and not depend on the ADAMTS13 results [11].

Plasma exchange, the main treatment for TTP must be started urgently once the TTP diagnosis is established and if not available in emergency, steroids can be started. The use of steroids in the treatment of acquired TTP supports its autoimmune nature [11].

In addition, because of the evidence of active SLE in many of these patients, immunosuppressive medications traditionally used for SLE, such as Chloroquine and Azathioprine, have been used for TTP also. Some have suggested that the early use of immunosuppressants in patients with other evidence of SLE activity may result in more favorable outcomes in patients with concomitant TTP [12]. However, this approach is not met with universal acceptance and the assessment of patients with TTP in SLE remains a real challenge.

Several studies have found that treatment with glucocorticoids and plasma exchange can achieve remission of 65.7% in patients with SLE and TTP [12, 13]. and it has been observed that some treatment options such as rituximab are used for refractory cases, achieving a good prognosis [12]. (Table 1).

In this case, the initial treatment was followed with high dose methylprednisolone (MP) and immunosuppressive medications because it was focused mainly on active SLE. However, the high doses of corticosteroids were not favorable because after two consecutive days the clinical picture, mainly the neurological one, got worse and we needed to lower the dose to 1mg/kg per day. Therefore, plasma exchange was an option but due to the psychological condition of the patient, plasma exchange was not performed at the time and other treatment options were adopted.

Table 1. Spectrum of demographic, clinical, laboratory and treatment options in SLE – TTP patients reported in the literature

Author	Age at diagnosis	gender	Signs and symptoms	ADAMTS13	Initial diagnosis	Treatment
Shen-ju Liang et al.	28-year-old	male	palm petechiae, strong tawny urine, and yellow stained skin and sclera	Significant deficiency	Subsequently diagnosed with SLE-TTP	Belimumab (10 mg/kg) was administered after six plasma exchanges
Jian Chen et al.	63-year-old	female	weakness for 10 d and unconsciousness for 6 d.	Significant deficiency	refractory TTP	Plasma exchange (PEX) Rituximab
Neha V Chiruvolu et al.	44-year-old	female	Acute on chronic anemia, thrombocytopenia, altered mental status.	Mildly deficiency	SLE	plasmapheresis
Mohammad Abu-Hishmeh et al.	34-year-old	female	Dizziness, flu-like symptoms, thrombocytopenia, hemolytic anemia.	No data	Subsequently diagnosed with TTP	plasmapheresis and high-dose steroids, rituximab
Ali Taha A. Hassan et al.	17-year-old	female	High grade fever, persistent headache, hemolytic anemia, thrombocytopenia	No data	SLE	plasmapheresis, steroids and cyclophosphamide.

CONCLUSION

This case illustrates the heterogeneity of TTP and the difficulty of making a diagnosis of TTP. ADAMTS13 activity assay can be useful in the differential diagnosis of diseases with clinical features of thrombotic microangiopathy in patients with SLE, although it is not a definite marker of the disease without the whole typical clinical presentation. Once the condition is established, treatments need to be decided carefully case-by-case. After a remission is obtained, patients ought to be followed up by their physicians with a particular observation on their platelet count in order to promptly recognize, immediately diagnose and treat a possible recurrence of TTP.

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✉ *Correspondence address:*
M. Krstevski
University Clinic of Internal Medicine
Skopje, R. North Macedonia