CASE REPORT

Atypical Morphological Changes in Thrombotic Microangiopathic Anaemia (TMA) With Southeast Asian Ovalocytosis (SAO) Coinheritance

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ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is a known life-threatening condition of thrombotic microangiopathic (TMA) syndrome. Schistocytes are the crucial morphological clue for the diagnosis, which is uncommon in the blood films of healthy people. The atypical presentation, signs, and symptoms that resemble other clinical conditions may mislead the diagnosis. We report a case of a pregnant lady with Southeast Asian ovalocytosis (SAO) who developed TTP without an obvious schistocyte on the peripheral blood film. We hypothesise an individual with underlying SAO will exhibit less evidence of schistocytes due to red cell membrane rigidity. A high index of suspicion is crucial for early diagnosis of TTP, and daily monitoring of peripheral blood films may improve the outcomes. This case report highlights the atypical TTP and emphasises the importance of considering TTP as a potential diagnosis even in the absence of schistocytes.
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INTRODUCTION

Southeast Asian ovalocytosis (SAO) is an inherited disorder caused by a genetic defect of the band 3 protein. In Malaysia, the prevalence of SAO is around 4% within the Malay ethnic group (1). The mutation leads to protein misfolding and alters the red cell's mechanical stability. This influences morphological findings of peripheral blood film when combined with other underlying illnesses. Homozygous SAO is considered lethal, whereas heterozygous SAO carriers are generally asymptomatic and characterised by the presence of stomatocytes, macro-ovalocytes and ovalocytes (1). Coinheritance of SAO with other illnesses poses challenges in patients' precise diagnosis. It is possible that underlying SAO with acute haemolysis conditions may not produce the typical morphologic presentation of red cell features, like schistocytes in the peripheral blood film.

Meanwhile, the presence of schistocytes is a haematological emergency requiring prompt thrombotic microangiopathic (TMA) investigation. The presence of more than 1% schistocytes in the peripheral blood film is an important criterion for diagnosing TMA (2). It is not found on normal blood films and may occur as an artefact due to manual red cell fragmentation during venesection or manual spreading of the blood film smear. It also may be seen in other conditions unrelated to microangiopathy, including haematological malignancy, prosthetic heart valves, megaloblastic anaemia, iron deficiency, and thalassemia. In this context, they are not the predominant red cell abnormality, comprising only a minor component of a more global anisopoikilocytosis. When a blood film shows concurrent major morphological abnormalities consistent with these alternative diagnoses, quantitation of schistocytes is not recommended. Hence the significance of schistocytes on the blood film is much reduced.

Pregnancy-related haemostatic and immunologic changes that result in a hypercoagulable condition are the main reasons for the correlation between TMA and pregnancy. An early TTP detection is crucial to ensure a favourable outcome for both the mother and the fetus. The diagnosis of TTP should be considered in the presence of thrombocytopenia and microangiopathic haemolytic anaemia features. Apart from daily peripheral blood film

monitoring, the classical pentad features in TTP should be considered and monitored closely.

CASE REPORT

A 26-year-old woman, gravida 2, para 1, at 20 weeks of gestation with no known medical illness presented with subacute onset of bilateral lower limb weakness for 9 days. The lower limb weakness gradually progressed to the upper limb and neck on day 7 of the illness. She also had difficulty uttering words and twitching her mouth. The patient had a fever and cough for one week before developing limb weakness. Illicit drug abuse was refuted. Upon examination, she was afebrile and exhibited greater weakness in her lower limbs than her upper limbs. She had reduced muscle tone with hyporeflexia. She also had a tinge of jaundice. She had been normotensive all the while. Her full blood count revealed leukocytosis, thrombocytopenia with platelet counts of 35 × 109/L, and mild normochromic normocytic anaemia (haemoglobin was 10.0 g/dL). The creatinine kinase 118 umol/L (44.2-106.1 umol/L) and lactate dehydrogenase levels were increased (Table I). Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were normal.

Table I: Summary of selected laboratory parameters

Laboratory parameters (reference range)	On admission	D1	D2	D3	D4
WBC (4.0-11.0 x10^9)/L	15	16.5	17.2	19	20
Hb (12.0-15.0) g/dL	10	9.8	9	8.2	7.9
Platelet (150-410 x 10^9) /L	35	37	38	40	39
Reticulocyte (<1%)	1.5	1.8	2.5	3.1	4.6
LDH (125-220 U/L)	633	700	838	1055	1126
Bilirubin (3.4 - 20.5 umol/L)	33	39	40	40	45
AST (5-34 U/L)	165	170	169	180	174
ALT (0 -33 U/L)	99	100	101	121	108

The initial peripheral blood film showed increased spherocytes, nucleated red cells, and polychromasia. There were only occasional schistocytes. The background of ovalostomatocytes was evident with true thrombocytopenia. The peripheral blood film was suggestive of haemolysis however, TMA cannot be excluded. At this point, TTP was kept low on the differential diagnosis as the appearance of the schistocytes was not convincing. Based on the clinical presentation, she was diagnosed clinically as having Guillain-Barre syndrome (GBS) and intravenous immunoglobulin (IVIG) was administered over two days.

Serial peripheral blood film showed the schistocyte count was still infrequent. Still, the blood film prominently showed spherocytes and ovalostomatocytosis (Figure 1). The Coombs test was negative. The PT of 11.7s (9.64-12.51 s), aPTT 29.3 (25.28- 40.10 s), and fibrinogen 300 mg/dL (200-400 mg/dL) levels were normal, making disseminated intravascular coagulation (DIC) unlikely. Serial blood tests showed worsening anaemia and thrombocytopenia with increased reticulocytes (Table I). The liver function test was abnormal, and the lactate dehydrogenase (LDH) was elevated (Table I).

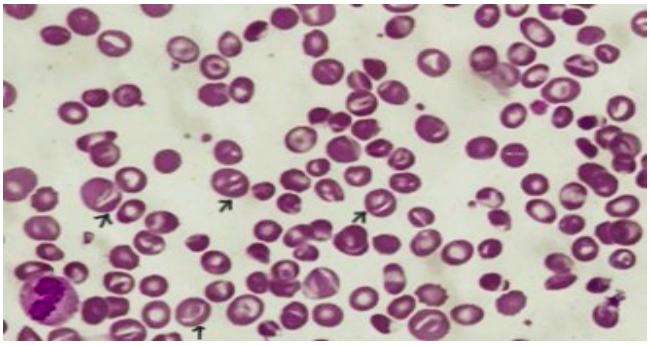

Figure 1: SAO with TTP showed macro-ovalostomatocytosis (black arrow) with no obvious schistocytes. (Magnification x 40).

Despite IVIG, thrombocytopenia did not improve and her condition worsened. She started developing fever, blurring of vision, headache, nausea and vomiting. Subsequently, she had a complete abortion. Since her clinical conditions did not improve, atypical TTP was considered as an alternative diagnosis and plasma exchange was started. The first course of plasma exchange produced no clinical response, and the second course out of five planned plasma exchanges was performed. However, her condition worsened with severe respiratory distress and she succumbed to death. After her death, AdamTS-13 activity was revealed as 12%. Double-stranded DNA (dsDNA) and antinuclear antibody (ANA) were positive, with titers of 1:80 and 1:320, respectively.

DISCUSSION

TTP is a life-threatening disease, usually diagnosed with a high index of suspicion. Early diagnosis is crucial as without treatment, TTP is associated with a high mortality rate. The classical pentad of microangiopathic haemolytic anaemia (MAHA), thrombocytopenia, neurological dysfunction, kidney dysfunction and fever are seen only in 40% of the patients. The schistocyte counts above 1% indicate a TMA diagnosis (2). However, the number of schistocytes is usually much greater than 1% in TMA.

If there is clinical suspicion of TMA despite the absence of schistocytes, a peripheral blood smear to look for schistocytes should be repeated daily. Schistocytes may sometimes not appear until several days later (3). The lack of schistocytes may delay diagnosing TTP and commencing plasma exchange, potentially increasing mortality risk (3).

In our case, a patient with SAO has less prominent

schistocytes but increased spherocytes during an acute crisis of haemolysis even after serial peripheral blood film monitoring. The presence of SAO alongside TTP illustrates the different morphological changes in TMA that caused a delay in the diagnosis. We hypothesised that the reduced or absence of schistocytes was most likely due to rigidity and hyper-stable red cells of SAO. The less evidence of schistocytes may be due to ovalocyte membranes being less elastic than normal red cell membranes (1). Most people with SAO usually exhibit a marked increase in membrane rigidity and experience a minimal clinical manifestation of haemolysis (1). The membrane properties may cause the red cells to be trapped in the splenic pulp. It may lead to extravascular haemolysis, producing more spherocytes than fragmented red cells (1). Morphologic findings must be interpreted cautiously when dealing with SAO concurrent with TTP. The percentage of schistocytes may be lower due to the unique properties of SAO cells.

Grall *et al.* reported that many patients did not show significant schistocytes during presentation but were positive in the following days (4). The findings were supported by Paul *et al.*, who found that schistocytes were absent in 30% of patients and recommended peripheral blood smear evaluation should be done regularly (3). In exceptional instances, schistocytes may not be observed during TMA episodes (2). Upon encountering the atypical presentation of TTP, Kevin *et al.* suggested the possibility that the thrombus formation may not be extensive enough to cause the fragmentation of red blood cells (5). Grall *et al.* added another challenging condition when 10% of patients had a positive, low-titer direct anti-globulin test (DAT), which suggests autoimmune haemolytic anaemia (4).

The measurement of ADAMTS13 serves as a definitive diagnostic test for TTP, and a level of less than 20% suggests the diagnosis. The deficiency is often caused by autoantibodies, causing large von Willebrand factor multimers to accumulate, trapping platelets, and resulting in microvascular platelet thrombi (3). The test requires considerable time, and not all centres provide the service. Results are often delayed, making a presumptive diagnosis imperative. A strong clinical suspicion of TTP warrants immediate initiation of therapeutic plasma exchange without waiting for ADAMTS13 test results, even without schistocytes (3). A trial of plasmapheresis is a therapeutic option even when TTP diagnosis is inconclusive. Whenever there is an improvement, TTP is the most likely diagnosis compared to other clinical diagnoses.

Physiological changes during pregnancy lead to a hypercoagulable state and are prone to developing thrombotic microangiopathies. The other two major syndromes are HELLP syndrome (haemolysis, elevated liver function tests, low platelets) and haemolytic uremic syndrome (HUS). The typical symptoms of HELLP syndrome are epigastric or right upper abdominal quadrant pain, nausea, and vomiting. It occurs in 0.1–0.2% of pregnancies and is commonly in women with hypertension and proteinuria. In HUS, the triad of microangiopathic haemolytic anaemia, thrombocytopenia and acute kidney injury are more prominent. An elevated serum creatinine level is an important criterion for diagnosis. The clinical features might overlap with HELLP syndrome, but HUS is typically distinguished by severe, persistent renal failure.

CONCLUSION

This case serves as a reminder of atypical TTP, especially when a patient has other background red cell abnormalities such as SAO. The diagnosis should be considered despite the absence of schistocytes. A strong clinical judgement should precede laboratory parameters.

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