Clinical Medicine Insights: Case Reports

CASE REPORT

Thrombotic Thrombocytopenic Purpura: Three Peripartum Cases and Diagnostic Challenges

Wan Suriana Wan Ab Rahman[1], Wan Zaidah Abdullah[2], Rapiaah Mustaffa[2], Suhair Abbas Ahmed[2], Mohd Nazri Hassan[2] and Azlan Husin[3]

[1]School of Dental Sciences, [2]Department of Hematology, [3]Department of Medicine, School of Medical Sciences, Universiti Sains Malaysia, Kelantan, Malaysia. Corresponding author email: wzaidah@kb.usm.my

Abstract: Thrombotic thrombocytopenic purpura (TTP) is a medical emergency characterized by occlusive microangiopathy due to intravascular platelet aggregation. This event results in damage to the red blood cells (RBCs) known as microangiopathic hemolytic anemia (MAHA). Schistocytes are circulating fragments of damaged RBCs that have different morphological features including keratocytes, helmet cells, and spherocytes. It is critical to report even a small number of these abnormal RBCs in the peripheral blood and to be alert for the possible diagnosis of TTP, especially in unexplained anemia and thrombocytopenia. The application of pentad criteria in the diagnosis has been reviewed, and the challenges still remained on the hematologic evidence of this disorder. In the 3 cases discussed here, the red cell morphological diagnosis gave an impact on TTP diagnosis, but overdiagnosis might be encountered in obstetrical patients due to nonspecific diagnostic criteria.

Keywords: thrombotic thrombocytopenic purpura, schistocytes, spherocytes, LDH

Clinical Medicine Insights: Case Reports 2013:6 141–146

doi: 10.4137/CCRep.S12122

This article is available from http://www.la-press.com.

Introduction

Thrombotic thrombocytopenic purpura (TTP) is characterized by occlusive microangiopathy due to intravascular platelet thrombi.[1] The pathophysiology of TTP is due to deficiency of von Willebrand factor cleaving protein known as ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13). This deficiency could be a congenital problem or acquired. Deregulation of the immune system may result in autoantibody formation toward this protein as, for example, in autoimmune diseases. Pregnancy, drugs, and infection might work through immune modulation effects, which precipitate TTP development.

Diagnosis should be based on clinical history, physical examination, and laboratory results. This could be achieved by routine blood investigation such as full blood count (FBC), full blood picture (FBP), reticulocyte count, liver function, and renal function tests. As microangiopathic hemolytic anemia (MAHA) is a striking feature of TTP, blood film is part of the initial investigation for this condition to look for the red cell fragments or schistocytes and presence of polychromatic cells. Current advances have allowed automated analysis to provide these parameters in order to aid the diagnosis of MAHA.

Schistocytes are circulating cytoplasmic fragments of damaged RBCs. These cells are usually absent or very rare in blood films of healthy individuals. The finding of schistocytes in the blood film together with anemia and thrombocytopenia should lead to a prompt action to exclude the presence of underlying thrombotic microangiopathy (TMA). This condition includes 2 well-known syndromes: thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). Other secondary causes of TMA include preeclampsia, antiphospholipid syndrome (APS), HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), Human immunodeficiency virus (HIV) infection, etc. Pregnancy related disorders, for example, severe preeclampsia and HELLP syndrome, may be difficult to differentiate from TTP.

There are many morphological descriptions for schistocyte, which include keratocyte, helmet cell, spherocyte, microcrescent, and others. Their characteristics were described and recommended for blood film reporting.[2] Interestingly, microspherocytes are not commonly reported in TTP; however, their presence with other schistocytic changes in clinically significant cases should indicate evidence of underlying TMA. The finding of spherocytes suggests a hemolytic etiology as a result of membrane damage to the red cells. In TTP, spherocytes are formed from recovered cytoplasmic fragments that have been partly lost as a result of mechanical fragmentation during blood flow through partially obstructed vessels produced by platelet thrombi.

An estimation of the number of schistocytes could be made easy with the newer generation of hematology analyzer. Automated counting of RBC fragments is also recommended by the International Council for Standardization in Hematology (ICSH) working group as a useful complement to the microscope according to its high predictive value of negative results; however, further research on this aspect is required.[2]

High in serum lactate dehydrogenase (LDH) is an indicator of hemolysis in TMA conditions. Serum LDH was reported as extremely high, and the source of LDH could come from hemolyzed red cells as well as necrotic and ischemic tissues.[3] The severity of thrombocytopenia and LDH levels may reflect the extent of the microvascular aggregation of platelets. Pentad criteria are 5 reported classical presentations of TTP consisting of thrombocytopenia, MAHA, fluctuating neurological signs, renal impairment, and fever. The diagnosis has been reviewed in view of many nonclassical cases that have been reported. The revised diagnostic criteria stated that TTP must be considered in unexplained cases of thrombocytopenia and MAHA.[4]

Diagnosis of TTP could be difficult as there are no specific clinical and laboratory criteria.[5] Other clinical conditions may present as TTP but are secondary to a different etiology, such as APS, certain drugs, and malignancy. The spectrum of pregnancy-related disorders such as severe preeclampsia, disseminated intravascular coagulation (DIC), and HELLP syndrome mimic TTP, in which TMA is also involved in the pathophysiology of these disorders and, hence, added to the diagnostic challenges. The mainstay treatment for TTP is plasma exchange (PE), and delay in making diagnosis may lead to a preventable mortality.

Case Presentations

Incidence of TTP was reported as rare, but untreated cases were associated with a high mortality rate.[6]

We report 3 unrelated cases involving young women who presented during the peripartum period in our institution. The diagnosis of TTP was considered during the course of their illness based on clinical and serial laboratory findings. All these patients had persistent anemia and thrombocytopenia, but none of them had clear classical pentad presentations.

Case 1

A 30-year-old woman, gravida 5, para 4, at 20 weeks of gestation had a fainting episode at home and was admitted for further management. She was found to have had thrombocytopenia 2 weeks prior to this admission in another hospital. She was advised for further investigation but defaulted until she presented to our hospital with this problem.

At presentation, her platelet count was 45×10^9/L with mild normochromic normocytic anemia (hemoglobin was 10.3 g/dL). Initial FBP showed occasional schistocytes with true thrombocytopenia. A diagnosis of immune thrombocytopenic purpura was made and treated with 2-day course of intravenous immunoglobulin (IVIG). However, thrombocytopenia was not improved and even worsened. On the following day, she developed unexplained headache, nausea, vomiting, and blurring of vision despite documented normal blood pressure. At that time, the diagnosis of TTP was considered. She continued to deteriorate further with severe respiratory distress and did not improve despite intensive respiratory and circulatory supports including inotropic agents. The schistocyte count (based on classical triangular hyperchromatic RBCs) was slightly increased after a serial investigation, but microspherocytes were obvious in the blood film. Direct antiglobulin test (DAT) was negative. Clinically she had no fever and no bleeding tendency.

Serial blood investigations noted worsening of anemia (8.4 g/dL) and thrombocytopenia (11×10^3/uL) with reticulocytosis (7.5%). Lactate dehydrogenase (LDH) was 929 U/L (high) and liver function test (LFT) was abnormal. AST, ALT, and total bilirubin were 95 U/L, 99 U/L, and 32 umol/L, respectively. Results of a renal function test and coagulation screening tests (PT, APTT, and fibrinogen) were normal. D-dimer was elevated (3.68 ug/mL). Autoimmune profile (results reported after deceased) were positive for antinuclear antibody (ANA) and double stranded DNA (dsDNA) showing titer of 1:320 and 1:80, respectively.

She succumbed to the disease on day 5 of admission, most likely due to thrombotic complications. Plasma exchange (PE) was postponed as the patient deteriorated rapidly and was hemodynamically unstable for the procedure but plasma transfusion was substituted.

In view of these findings, this patient was diagnosed as TTP, which might have been secondary to systemic lupus erythematosus (SLE), based on the results above.

Case 2

A woman in her late teens had retained placenta complicated with postpartum hemorrhage (PPH). On arrival to hospital, her platelet count was normal but progressively reduced after she developed DIC secondary to the retained placenta. She underwent emergency manual removal of placenta and was stable after blood transfusion support with DIC regiment. Remission of DIC was observed on the following day based on the laboratory results and clinical assessment. However, her platelet count was persistently low and continued dropping, which was documented serially without specific reason (platelet count $<30 \times 10^9$/L). At the same time, she also had renal impairment with proteinuria. FBP showed true thrombocytopenia with many schistocytes. Her blood pressure (BP) and other vital signs including temperature were normal.

Blood investigations at this stage showed normalization of coagulation profile (treated DIC). Hemoglobin reduced from 9.3 to 7.6 g/dL and platelet count dropped significantly from 47 to 12×10^3/uL (despite platelet support). Reticulocyte count increased from 3.6% to 5.8%. DAT was negative, and LDH was very high (2134 U/L). Persistent albuminuria of 2+ was noted, and the results of a renal function test showed urea, sodium, and potassium were 14.6, 138, and 3.6 mmol/L, respectively. Creatinine was 136 umol/L, and results of LFT were normal. Screening of autoimmune disease with ANA was negative.

TTP was considered here based on a few reasons, which included no evidence of sepsis, unexplained persistent thrombocytopenia, evidence of MAHA, worsening of platelet counts following platelet transfusion, renal impairment, and elevated LDH level.

She underwent regular therapeutic PE (daily for 1 week followed by twice a week), and serial FBP

showed a reduced number of schistocytes in the blood film with increasing platelet count. Her condition improved, and she was discharged well after 20 days of admission following sustained normalization of platelet count, hemoglobin, and LDH levels.

Case 3

A 30-year-old woman, para 1, had a cesarean section for severe preeclampsia. Platelet transfusion was given intraoperatively in view of the low platelet count. Continuing reduction and downward trend of the platelet count was noted postoperatively. Blood film revealed anemia, true thrombocytopenia with occasional schistocytes. Her blood pressure was high at the early postpartum period with an average of 180/100 mm/Hg, and, fortunately this was reduced with treatment later on. She had epigastric pain but no neurological manifestation.

Her blood investigations post Cesarean section showed hemoglobin dropped from 8.9 to 7.6 g/dL and platelet count reduced from 78 to 46 $\times$ 10^3/uL. The reticulocyte count was 2.8%, and DAT was negative. Coagulation tests showed normal PT, APTT, and fibrinogen with elevated D-dimer (4.26 ug/mL). Liver enzymes were increased, and LDH level was very high (2055 U/L). Renal function test was normal. She had persistent thrombocytopenia documented serially, which was worsened after platelet transfusion.

Differential diagnoses of HELLP syndrome and TTP were considered at that time. At that stage, TTP was unable to be ruled out in view of normalized BP (less likely related to hypertensive crisis) and persistent abnormal laboratory findings. To avoid treatment delay, therapeutic PE was initiated for her. She had therapeutic PE twice a week, and serial FBP showed rapidly increasing platelet count and normalization of other laboratory results. Her LFT results before and after plasma exchange showed AST of 166 and 66 U/L, ALT of 91 and 64 U/L, and total bilirubin of 24 and 10 umol/L, respectively. She was discharged well, and FBC during her last follow-up a few months later was normal.

Discussion

Thrombotic thrombocytopenic purpura (TTP) was first described by Moschowitz in 1924.[6] The understanding of the pathogenesis and pathophysiology of this condition has improved dramatically over the last 15 years. Deficiency of ADAMTS13 is the core feature leading to clinical manifestation of this disorder, which should be differentiated from a collective disorder known as TMA.[4] TMA is a spectrum of diseases that have overlapping features, typically MAHA and thrombocytopenia with the presence of schistocytes in blood film. Therapeutic PE is an effective treatment for adult TTP-HUS, while this modality is not a standard therapy for other TMAs.

The presence of schistocytes on a blood smear is the morphologic hallmark of the disease, but no guidelines exist as to the number of schistocytes required to differentiate TTP from other TMAs. Lack of standardization may lead to inconsistency or misdiagnosis, thereby affecting treatment and clinical outcomes.[2] The finding of 2 or more schistocytes in a microscopic field with a magnification 100 suggest of MAHA.[5] Accurate description of different morphological features of schistocytes should be practiced when reporting blood film.

The Schistocyte Working Group of the ICSH has prepared specific recommendations to standardize schistocyte identification, enumeration, and reporting in peripheral blood film.[2] Schistocytes are estimated as a percentage after counting at least 1000 red blood cells. A schistocyte count has a definite clinical value for the diagnosis of TMA in the absence of additional severe red cell shape abnormalities, with a confidence threshold value of 1%. Therefore, the presence of schistocytes on blood film should be reported in terms of their number and described according to this recommendation, which allows the diagnosis of possible TTP or other TMAs until proven otherwise. Discriminating features between TMAs was outlined in the recent guideline.[4] However, there are times when the presentations or laboratory results are not compatible with any specific condition, and, hence, the diagnosis is made through clinical experience and based on predominant features.

In case number 1, it was quite clear that this patient had TTP in view of insidious onset of thrombocytopenia and the fluctuating neurological symptom (fainting episode). The finding of schistocytes in her initial blood film had triggered the possibility of TTP, and, interestingly, her blood film had many spherocytes, which was obvious on serial blood film. She was unfortunate as her presentation with thrombocytopenia was initially diagnosed and treated as

immune thrombocytopenia. She deteriorated rapidly leading to delaying a decision for therapeutic PE.

SLE with hematologic complications such as Evan syndrome (ie, a combination of autoimune hemolytic anemia [AIHA] and thrombocytopenia) might be another diagnosis to consider. However, as the DAT was negative in this patient, it is difficult to include this diagnosis, although negative DAT had been reported in AIHA. Unlike in this patient, SLE with hematologic manifestations usually improved after IVIG treatment. Negative DAT excludes AIHA, and, hence, the presence of microspherocytes is not related to autoantibody to the red cells.

The diagnosis of HELLP is unlikely in case 1 due to normal blood pressure recording. Catastrophic APS would be another possibility, which usually presents as multiorgan failure and rapid deterioration similar to the events in this case. It is also an autoimmune disorder; however, no specific laboratory results (such as lupus anticoagulant or anticardiolipin antibodies) to support this condition in her. Therefore, this patient ws likely to have had TTP, which was secondary to SLE or APS, based on the results of autoimmune profile.

For case 2, the diagnosis of TTP was challenged by initial DIC, which developed as a result of retained placenta. TTP was suspected when the hemoglobin and platelet counts did not improve in parallel with the clinical and coagulation test results. There was no obvious reason for persistent worsening of thrombocytopenia and ongoing hemolysis at that time. The unexplained dropping of her platelet count to a very low level (12×10^3/uL) together with features of ongoing hemolysis triggered the possibility of TTP. Her blood film showed a significant number of schistocytes as evidence of MAHA. She also had features of renal impairment. Slow recovery of DIC could be another possible diagnosis to consider. However TTP was presumed in this case in view of the persistent abnormal laboratory findings despite adequate DIC treatment.

Lastly, for case 3, there was a lengthy discussion on the diagnosis of TTP. The fact that schistocytes were only occasionally seen in the blood film and the patient had severe preeclampsia, a diagnosis of HELLP syndrome was more appropriate based on her clinical presentation. In addition, the platelet count rapidly improved and sustained steadily after 2 sessions of PE. The beneficial effect of PE may take a longer time in a typical TTP. Hence, a diagnosis of TTP should be reviewed critically and take into account various aspects, including trends of the relevant laboratory results.

The revised criteria for TTP did not give much help, and, therefore, justification of the diagnosis was made based on the clinical ground when no other reason could explain the feature of thrombocytopenia and MAHA. In this case 3 for example, TTP was likely at that stage as LDH level was very high with a reducing trend of platelet count despite adequate blood pressure control.

It is known that the diagnosis of TTP especially in pregnancy may overlap with other pregnancy TMA conditions. No specific test is available routinely in medical laboratories to aid the diagnosis such as ADAMTS 13 assay. Hence, there is a tendency to over-diagnosed TTP in order to avoid delaying in giving timely PE.

Rapid diagnosis and early treatment are critical to reduce the morbidity and mortality of TTP. PE remains the treatment of choice, and plasma infusions used if there is a delay in PE. It is recommended that treatment with PE should be initiated as soon as possible, within 4 to 8 hours if a patient presents with MAHA and thrombocytopenia in the absence of another identifiable cause.[4]

An unusual clinical presentation might also influence the decision in making the diagnosis in order to avoid a delay in management. As seen in case 3 above, HELLP syndrome was recognized, but the diagnosis of TTP was considered relevant at that time. A similar report to case 3 had been published previously whereby an initial diagnosis of HELLP syndrome was changed to TTP, and, in that case, it was supported by an ADAMTS13 test.[7]

TTP has been reported to be predominantly in women, and about 12% to 31% are pregnant or postpartum.[8] There may be obstetrical complications for fetal growth as a result of underlying TTP. It was noted that a continued risk may be seen in future pregnancies. The role of ADAMTS13 to support the clinical diagnosis is unclear, but persistent low levels may indicate a higher risk of relapse.[9] Management of women who develop TTP during pregnancy includes non-estrogen containing contraception as estrogen may precipitate TTP episodes.[4]

ADAMTS13 assays are not available in most routine medical laboratories worldwide. It is not recommended for the initial diagnosis of TTP. ADAMTS13 antigen and activity assays together with autoantibody detection could assist in the diagnosis and monitoring of patients.

It is important to stress that TTP is a diagnosis made by exclusion of other related conditions supported with clinical and routine laboratory parameters. An initial schistocyte count of greater than 1% strongly suggests a diagnosis of TTP in the absence of other known causes of thrombotic microangiopathy.[10] Spherocytes in TTP are part of schistocytic changes, which should not be confused with other conditions and could be a prominent feature as seen in case 1 here.

Conclusion

Diagnosis of TTP is challenging especially in obstetrical practice, as many other TMA conditions are peculiar during pregnancy. In our cases, TTP was presumed by the pentad of anemia, thrombocytopenia, negative DAT, schistocytosis, and elevated LDH. The threshold for the number of schistocytes in blood film is very low, and, hence, its presence mandates a suspicion of TTP in unexplained anemia and thrombocytopenia. Effective discussion is required between the clinician and hematopathologist to review any diagnosis of TMAs critically. Lastly, it is recommended that ADAMTS 13 assays should be offered in local referral laboratories especially to evaluate difficult cases as these are not available routinely.

Author Contributions

Conceived and designed the experiments: WWAR, WZA, MNH. Analyzed the data: WWAR. Wrote the first draft of the manuscript: WWAR, WZA. Contributed to the writing of the manuscript: WWAR, WZA, MNH. Agree with manuscript results and conclusions: WWAR, WZA, RM, SA, MNH, AH. Jointly developed the structure and arguments for the paper: WZA, MNH. Made critical revisions and approved final version: WWAR, WZA, RM, SA, MNH, AH. All authors reviewed and approved of the final manuscript.

Funding

Authors disclose no funding sources.

Competing Interests

Authors disclose no potential conflicts of interest.

Disclosures and Ethics

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

References

1. Moake JL. Thrombotic microangiopathies. *N Engl J Med*. 2002;347:589–600.
2. Zini G, d'Onofrio G, Briggs C, et al. ICSH recommendations for identification, diagnostic value, and quantitation of schistocytes. *Int J Lab Hematol*. 2012;34:107–16.
3. Cohen JA, Brecher ME, Bandarenko N. Cellular source of serum lactate dehydrogenase elevation in patients with thrombotic thrombocytopenic purpura. *J Clin Apheresis*. 1998;13:16–9.
4. Scully M, Hunt BJ, Benjamin S, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *Br J Haematol*. 2012;158:323–35.
5. George JN. Clinical practice. Thrombotic thrombocytopenic purpura. *N Engl J Med*. 2006;354:1927–35.
6. Moschowitz E. Hyaline thrombosis of the terminal arterioles and capillaries: a hitherto undescribed disease. *Proc NY Pathol Soc*. 1924;24:21–4.
7. Gerth J, Schleussner E, Kentouche K, Busch M, Seifert M, Wolf G. Pregnancy-associated thrombotic thrombocytopenic purpura. *Thromb Haemost*. 2009;101:248–51.
8. Mc Minn JR, George JN. Evaluation of women with clinically suspected thrombotic thrombocytopenic purpura-hemolytic uremic syndrome during pregnancy. *J Clin Apheresis*. 2001;27:641–6.
9. Ducloy-Bouthors AS, Caron C, Subtil D, et al. Thrombotic thrombocytopenic purpura: medical and biological monitoring of six pregnancies. *Eur J Obstet Gynecol Reprod Biol*. 2003;111:146–52.
10. Burns ER, Lou Y, Pathak A. Morphologic diagnosis of thrombotic thrombocytopenic purpura. *Am J Hematol*. 2004;75:18–21.