Case report

Diagnostic dilemma in a patient presenting with thrombotic microangiopathy in the setting of pregnancy

Mohamed Zakee Mohamed Jiffry[1,*], Mohammad Aimal Ahmed-khan[1], Felipe Carmona Pires[1], Nkechi Okam[1], Mahnoor Hanif[2]

[1]Department of Internal Medicine, Danbury Hospital, Danbury, CT, USA; [2]CMH Lahore Medical College, Lahore, Punjab, Pakistan

Abstract

We report a case of thrombotic microangiopathy in a postpartum female for which considerable diagnostic uncertainty existed initially regarding the etiology. This case highlights the limitations surrounding PLASMIC scoring criteria for the diagnosis of thrombotic thrombocytopenic purpura (TTP). A 32-year-old woman presented to maternofetal medicine in her third trimester of pregnancy at 32 weeks for a routine follow up and was subsequently found to have elevated blood pressures with proteinuria, and was diagnosed with pre-eclampsia. Worsening anemia and thrombocytopenia prompted a blood smear which showed schistocytes, concerning for a thrombotic microangiopathy. Creatinine was also elevated with normal liver enzymes being noted. A PLASMIC score of 4 placed her in the low-risk category for severe ADAMTS13 deficiency whilst she fulfilled criteria for partial HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome per Tennessee classification. Despite delivery, her symptoms persisted with subsequent ADAMTS13 assay confirming acquired TTP, subsequently requiring repeated plasmapheresis and rituximab to achieve disease control. Thrombotic microangiopathy remains a diagnostic challenge especially in the peripartum population, and scoring systems such as PLASMIC score and Tennessee classification may be of limited utility.

Keywords: *thrombotic microangiopathy; thrombotic thrombocytopenic purpura; hemolysis; elevated liver enzymes; low platelets; atypical hemolytic uremic syndrome; PLASMIC score; pregnancy; ADAMTS13*

Introduction

The importance of distinguishing between thrombotic thrombocytopenic purpura (TTP) and HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome in the workup of thrombotic microangiopathy becomes obvious when considering the divergent management strategies employed. The cornerstone of management in HELLP syndrome is delivery, which is the only effective treatment. Conversely, TTP is not managed by delivery, and plasma exchange is indicated urgently in the initial treatment of this condition.

Scoring systems such as the PLASMIC score can aid in the diagnosis of TTP, and have been validated as a predictive tool with good sensitivity for severe TTP (<10% activity) with scores of 5 or more [1]. However, the score cannot be used to definitely exclude or confirm the diagnosis, and is not a substitute for clinical judgement, as our case demonstrates [2-4].

We report a case of a 34-year-old female with acquired TTP who was initially misdiagnosed as having partial HELLP syndrome.

Case report

A 34-year-old female with no significant past medical history presented to maternal-fetal medicine for routine 32-week growth ultrasound, indication being pregnancy

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*Corresponding author: Mohamed Zakee Mohamed Jiffry, Department of Internal Medicine, Danbury Hospital, 24 Hospital Avenue, Danbury, CT 06810, USA Email: mohamedzakee.mohamedjiffry@nuvancehealth.org

affected by maternal obesity. The patient was noted to have elevated blood pressure ranging from 130/90 mmHg to high of 170/100 mmHg. The patient did not endorse headache, visual changes, epigastric/right upper quadrant pain, or shortness of breath. The patient reported good fetal movement, no contractions, no leakage of fluid, no vaginal bleeding. A review of symptoms was unrevealing.

This was the patient's second pregnancy, with her first being uneventful. The patient does not have any significant past medical or surgical history.

Physical examination revealed a female with a class II obesity, having a BMI of 38.5 Kg/m2. The patient was otherwise well-appearing, and system examination was unremarkable. Fetal heart rate was at 145 bpm with moderate variability and accelerations. No decelerations were present. Tocometry showed contractions every 4 to 15 minutes.

Following initial diagnostic assessment, she was found to have elevated creatinine, anemia, elevated bilirubin and thrombocytopenia with liver enzymes being only mildly elevated. Liver function tests (LFT) were significant for an elevated bilirubin of 2.1 mg/dL with mildly elevated ALT and AST of 50 IU/L and 55 IU/L respectively. Complete blood count (CBC) revealed a hemoglobin of 7.9 g/dL with mean corpuscular volume (MCV) of 97.2 fL with platelets less than 10,000/uL (Figure 1). Initial creatinine was elevated at 1.2 mg/dL (Figure 2), and a urine protein/ creatinine ratio was elevated at 0.88 suggesting proteinuria. A peripheral blood smear showed schistocytes present with marked thrombocytopenia (7,000/uL).

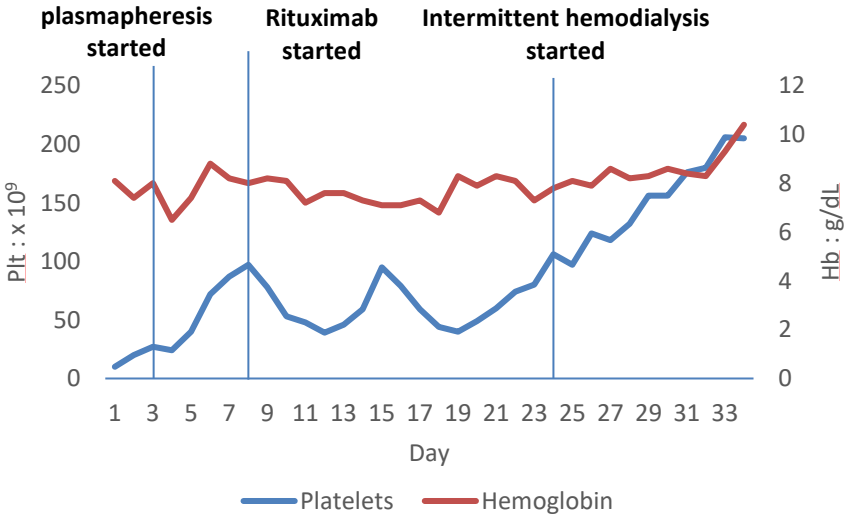

Fig. 1. A graphic representation of our patient's platelet counts and hemoglobin with important timestamps during her clinical course being highlighted by the drop arrows. Almost a month elapsed since initiation of daily plasmapheresis prior to normalization of the platelet counts.

With regard to her PLASMIC score, based on her laboratory results and absence of active cancer, solid organ or stem cell transplant, she scored 4 points which placed her in the low-risk group for severe ADAMTS13 deficiency, defined by activity level less than 15% according to this scoring system.

Initial suspicion was subsequently for a partial HELLP syndrome, and the patient underwent labor induction and uncomplicated vaginal delivery. However, persistence of her laboratory derangements post-delivery i.e. elevated creatinine, anemia and thrombocytopenia necessitated revision of the diagnosis and further work-up was done to rule out other thrombotic microangiopathies i.e. atypical hemolytic uremic syndrome (HUS), acquired or genetic TTP, or antiphospholipid antibody syndrome.

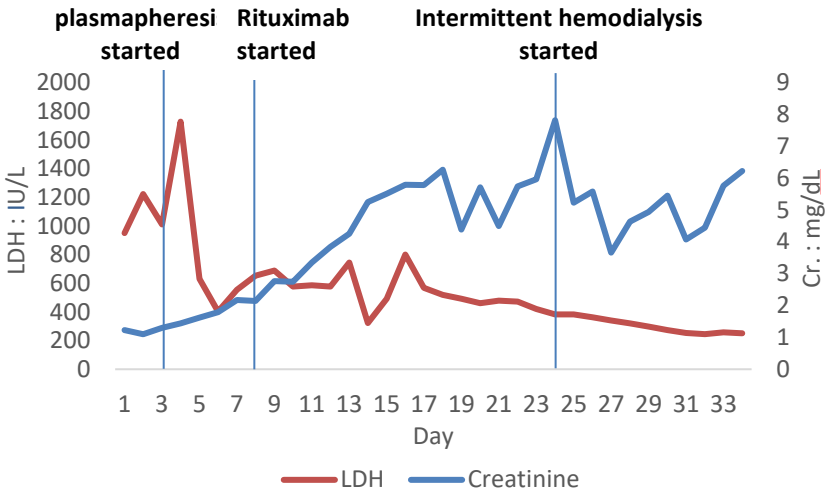

Fig. 2. A graphic representation of our patient's LDH and creatinine levels with important timestamps during her clinical course being highlighted by the drop arrows. Of note, despite resolution of hemolysis, her dialysis requirement persisted with subsequent kidney biopsy confirming chronic kidney failure secondary to thrombotic microangiopathy.

Work-up for antiphospholipid antibody included a negative diluted Russell viper venom test, and a negative lupus sensitive APTT. Beta-2 glycoprotein 1 IgM, IgG and IgA were negative at 1.2 mg/dL, <1.4 mg/dL and less than 0.6 mg/dL respectively. Anticardiolipin antibody IgM and IgG were negative at 0.8 U/mL and less than 1.6 U/mL respectively.

CH 50 complement level was 59 U/mL, within reference range. An atypical HUS panel was ordered which included genetic testing for ADAMTS13, C3, CD46, CFB, CFD, CFH, CFHR1, CFHR3, CFHR5, CF1, DGKE, PLG and THBD which were all negative.

An ADAMTS13 activity assay yielded the diagnosis with activity being found to be 12%.

She was subsequently initiated on daily plasmapheresis treatment and corticosteroids, with the addition of weekly rituximab infusions to her regimen one week later.

Over the next few weeks her platelet counts improved gradually, with her counts sustaining greater than 150,000/uL for three consecutive days prior to hospital discharge. Persistent derangement in her kidney functions necessitated regular hemodialysis thrice weekly. Rituximab infusions and low dose prednisone was continued as an outpatient.

A kidney biopsy was obtained to evaluate her persistent renal dysfunction with findings of thrombotic microangiopathy involving the glomeruli and blood vessels.

After regular hemodialysis for 6 months with little to no improvement of kidney function, the decision to seek a kidney transplant was made, which she is now awaiting.

Discussion

This case demonstrates the marked heterogeneity of the presentation of TTP. The classic pentad of TTP, namely fever, anemia, thrombocytopenia, renal failure and neurologic dysfunction occur in only roughly 20-30% of patients with the disease, and the diagnostic difficulty is compounded by the relatively long turnaround times for diagnostic confirmation with the ADAMTS13 activity assay. In fact, as a consequence of these issues, the British TTP guidelines recommend initiation of plasmapheresis even with thrombocytopenia and MAHA (evidenced by elevated LDH, schistocytes and indirect hyperbilirubinemia) in the absence of a more likely cause to explain said presentation [4].

Similarly, HELLP syndrome is also recognized to have significant variation in

clinical manifestations, and partial HELLP syndrome is a recognized clinical phenomenon [5, 6]. The Tennessee classification system recognizes both complete and partial HELLP syndrome variants. Complete HELLP syndrome is characterized by a platelet count of 100,000/μL or less, AST or ALT levels of 70 IU/L or more and LDH (or bilirubin) (with hemolysis as evidenced on abnormal peripheral smear) levels of 600 IU/L (≥0.2 mg/dL) or more. On the other hand, partial HELLP syndrome can be diagnosed based on the findings of severe pre-eclampsia plus only one of either ELLP (Elevated liver enzyme levels, thrombocytopenia, no hemolysis), EL (Mildly elevated liver enzyme levels, no thrombocytopenia, no hemolysis), LP (Thrombocytopenia, no hemolysis, normal liver enzyme levels) or HEL (Hemolysis, liver dysfunction, no thrombocytopenia) [7].

Yet other authors use different criteria, including biochemical evidence alone, or severe pre-eclampsia substantiated by biochemical evidence [8].

Another complicating issue in this case was the Plasmic scoring system which placed her at low risk for severe ADAMTS13 deficiency. With regard to her Plasmic score, the patient scored one-point for platelet count less than 30 x 109, one point for hemolysis evidenced by reticulocyte count greater than 2.5% and elevated total bilirubin of 2.1, one point for absence of active cancer, and one point for absence of history of solid organ or stem cell transplant, totaling 4 points which placed her in the low risk group for severe ADAMTS13 deficiency, defined by activity level less than 15% according to this scoring system, which stands in contrast to her reported ADAMTS13 activity assay of 12%. The Plasmic model has been externally validated as having a relatively good sensitivity (90%) and specificity (92%) with a positive predictive value of 72% and, significantly, a negative predictive value of 98% [9].

Our patient's progressive renal failure, persisting for greater than 6 months following the initial diagnosis, is also very atypical for TTP. Despite microthrombi being found throughout the kidney, as evidenced on our patient's kidney biopsy, TTP is unique among the primary thrombotic microangiopathies for minimal abnormalities of kidney function [10]. The severity of our patient's renal manifestations was such that kidney transplant evaluation is being considered owing to her persistent renal dysfunction and dialysis requirement.

Ascertaining the correct diagnosis becomes all the more important in this context when considering that the only treatment available for a diagnosis of HELLP syndrome is immediate delivery, with its attendant increased risk of morbidity of the newborn [11]. As outlined, currently available scoring systems, although validated, may be unreliable in ascertaining the diagnosis in patients presenting with an atypical clinical picture.

Conclusions

This case demonstrates the difficulties encountered when differentiating between the thrombotic microangiopathies with sufficient reliability as to make a firm diagnosis and institute appropriate management. Notably, currently available scoring systems, such as the Plasmic model for TTP diagnosis and the Tennessee classification system for the diagnosis of HELLP, may be of limited clinical utility, especially in the presence of atypical disease manifestations such as the unusually severe kidney dysfunction observed in our patient with TTP. The importance of making an accurate diagnosis in the antepartum setting cannot be overstated when considering the divergent management strategies employed for the management of TTP and HELLP syndrome.

Abbreviations

TTP – thrombotic thrombocytopenic purpura
HELLP – Hemolysis with elevated liver enzymes and low platelets
PLASMIC score - Platelet count; combined hemolysis variable; absence of Active cancer; absence of Stem-cell or solid-organ transplant; MCV; INR; Creatinine

ADAMTS13 - a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13
ALT – Alanine aminotransferase
AST – Aspartate aminotransferase
CBC – Complete blood count
MCV – Mean corpuscular volume
CH50 – 50% hemolytic complement, total
CFB – complement factor B
CFD – complement factor D
CFH – complement factor H
CFHR1 – complement factor H related 1
CFHR3 – complement factor H related 3
CFHR5 – complement factor H related 5
CF1 – complement factor 1
DGKE – Diacylglycerol kinase epsilon
PLG – plasminogen
THBD – thrombomodulin

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Author's contributions
The authors meet the ICMJE authorship criteria. MAAK, FCP and NO managed the patient and collected the data. MH wrote the manuscript. MZMJ supervised and approved the final version of the work to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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