A Complicated Case of Thrombotic Thrombocytopenic Purpura in Pregnancy with Superimposed Pre-Eclampsia

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Abstract

TTP (thrombotic thrombocytopenic purpura) is a rare life-threatening thrombotic microangiopathy which mimics HELLP syndrome (Hemolysis, elevated liver enzymes, low platelet count) and HUS (Hemolytic Uremic Syndrome), to differentiate between them can be extremely difficult and challenging due to the immense overlap in clinical and laboratory manifestations. A lady in 30's, presented with severe unexplained thrombocytopenia with signs and symptoms of severe pregnancy induced hypertension with HELLP syndrome at 26 weeks of gestation. It was a diagnostic challenge to the attending obstetricians who were unable to differentiate between severe HELLP and TTP while planning her delivery. The patient's condition was deteriorating rapidly, it was difficult to decide about the delivery, especially since platelet transfusion, which is necessary to correct thrombocytopenia due to HELLP, could aggravate her TTP. Timely decisions and multidisciplinary care are essential to ensure a safe outcome for mother and baby.

Keywords: Obstetrics and gynecology, Thrombotic Thrombocytopenic purpura, pre-eclampsia.

Introduction

Approximately 1 in 25,000 to 1 in 100,000 pregnancies worldwide are complicated by thrombocytopenic purpura (TTP). TTP-like syndrome occurs in critical illnesses due to complement activation, both conditions share the same underlying pathology and difficult to be differentiated.(1) They are characterized by hemolytic anemia, thrombocytopenia, and multi-vascular thrombi formation. Associated with high maternal and perinatal mortality, TTP can cause acute renal insufficiency, ischemic heart disease, altered mental status and end organ damage in mother and can lead to miscarriage and intrauterine fetal death.(2,3)

Hereditary or acquired deficiency of the Von Willebrand Factor (VWF) cleaving protease ADAMTS-13 (A Disintegrin and Metalloproteinase with Thrombospondin type 1 motif, member 13) activity of less than 10% causes TTP. The autoantibodies against ADAMTS-13 are responsible of causing 95% of the acquired TTP, which is commonly seen in 3rd and 4th decade of life. Hereditary TTP (<5%) usually presents during initial years of life, however, it can also have a delayed presentation in adulthood. Hereditary TTP, manifesting for the first-time during pregnancy, is challenging to diagnose due to its similarities with other thrombotic microangiopathy (TMA) () such as

Hemolytic Uremic Syndrome(HUS), Anti-Phospholipid Syndrome (APLS), systemic lupus erythematosus(SLE) and Hemolysis, Elevated Liver enzymes, Low Platelet (HELLP) syndrome.(4,5)

Plasmapheresis, the cornerstone for treatment of TTP, has reduced mortality of pregnancy associated TTP from 58.10% (in 1980) to 9% (in 1996).[6] Management of TTP in pregnancy is by plasma therapy with continuation of pregnancy, but in cases of superimposed severe preeclampsia, it mandates delivery. TTP with superimposed preeclampsia has higher maternal mortality (44.4%) compared to TTP in pregnancy alone (21.8%).[5] These challenges the managing team to make the right decision in cases where undiagnosed TTP presents for the first time in preterm pregnancy with superimposed preeclampsia.

Our case highlights the importance of multidisciplinary teams to exclude other causes of thrombocytopenia in pregnancy. High index of suspicion for TTP, early plasmapheresis, and timely obstetric decision for delivery can save both mother and fetus.

Case Report

A lady in 30's, gravida 2, para 1, with no living child, with severe thrombocytopenia at 26 weeks of gestation, was referred to hematology and obstetrics care at our tertiary hospital.

During her last pregnancy, at 24 weeks she had fever, body ache, joint pain, hematuria, subconjunctival hemorrhage, and epistaxis. Her blood pressure (BP) was high, hemoglobin 6.2 g/dL and platelet 11,000/dL with intra uterine fetal demise. She was stabilized in ICU, received blood and blood products, induced with Misoprostol, and delivered a still born fetus with birth weight around 500g. The blood parameters improved, and she was discharged within 6 days. Post-delivery nephrology review was done, as her blood indices returned to normal no further analysis done. She was on natural methods of barrier contraception for 9 years due to the bad experience.

In her present unplanned pregnancy, all her antenatal checkups were normal till she reached 24 weeks and 5 days when her blood pressure was found to have increased. Her body mass index was 25.58kg/m2. She started on antihypertensive medications. A week later, she presented to the emergency at a peripheral maternity hospital with high blood pressure, low platelet count and proteinuria. She was treated as a case of early onset severe pre-eclampsia with the possibility of HELLP syndrome. She received magnesium sulphate for severe pre-eclampsia and steroid cover for fetal lung maturity, preparing her for delivery. The fetal parameters were corresponding to 25 weeks gestational age with expected weight of 800 gm with normal doppler. Due to severe thrombocytopenia, she was started on IV methylprednisolone and received platelets transfusion. However, despite the platelet transfusion her platelet dropped to 15,000/dL.

Patient developed hematuria and platelet count dropped further to 13000/ dL with normal liver function tests, so the diagnosis of HELLP syndrome was doubted. In view of her past obstetric history, other causes of thrombocytopenia such as TTP, HUS and SLE were considered. The multidisciplinary team consisting of nephrologist, hematologists, rheumatologist, and obstetricians discussed her possible differential diagnosis. The blood film showed schistocytes, which raised the possibility of TTP. The confirmatory test of thrombotic thrombocytopenic purpura ADAMTS-13 was sent.

Patient transferred to HDU in our institute, started on plasmapheresis (PTX), as a part of management of TTP. Three days later, her platelet dropped to 12,000/dL. She was transfused with fresh frozen plasma and 2 units packed RBCs, repeated platelet was 25,000/dL, so PTX was restarted. Meanwhile, the patient had symptomatic severe pre-eclampsia, with headache, epigastric pain, and chest pain with desaturation. Cardiologist advised ECG and bedside echo-cardiography, both were normal, but her troponin was high (20 ng/L).

She received IV bolus labetalol two times and started on labetalol infusion in view of her very high blood pressure readings. To consider delivery at this stage was very difficult. Hematologists preferred continuation of pregnancy with plasmapheresis, obstetricians considered delivery in view impending eclampsia, neonatologists were worried about extreme prematurity and anesthetists were reluctant to provide anesthesia due to very low platelets. The crucial decision about continuation or termination of pregnancy was difficult to make.

Unable to confirm TTP (awaiting ADAMTS-13 result), unable to exclude severe pre-eclampsia and with patient condition rapidly deteriorating, the obstetrician decided for immediate delivery by cesarean section at 26 weeks of

gestational age. The patient's platelet count was 46,000/dL at the time of delivery. A live baby girl weighing 730g, with normal cord pH was delivered.

After the delivery, the patient was monitored in a high dependency unit, on magnesium sulphate and labetalol infusion. Methylprednisolone was continued. Labs improved dramatically, her platelets rose to 110,000/dL in 48-hours post-delivery, without plasmapheresis. Her final diagnosis was severe preeclampsia with HELLP syndrome, however, TTP could not be ruled out and ADAMTS-13 (confirmatory test) was still pending at the time of discharge. Patient discharged home in good condition on day 4 of delivery, on oral labetalol 200 mg twice per day, oral prednisolone, and Clexane for thromboprophylaxis.

She followed the hematologist ten days after delivery. Her platelet count had dropped to 18000d/L, she received 3 sessions of fresh frozen plasma therapy within the next two months by which time her steroids were tapered and stopped. Currently she is not on any medications. Her daughter was discharged from the neonatal intensive care unit after two months from the delivery, with weight of 3.4 kg in good condition, without any neurological sequelae.

On admission to our institute, the patient's hemoglobin was 7.4 g/dL, she received 2 units packed RBCs, hemoglobin was 9.0g/dL at discharge. Her platelet count and lactate dehydrogenase (LDH) are shown in figure 1. Her creatinine and glomerular filtration rate were always within the normal range. Her liver function tests showed alkaline phosphatase 82 U/L (normal range: 35-104 U/L), Aspartate Serum Transferase (AST) 32 U/L (normal range: 0-31 U /L), Alanine Serum Transferase (ALT) 20 U/L (normal range: 0-31U/L). Our patient's LDH/AST ratio was 21.68 which is one of the supportive labs for diagnosis of TTP. [7]

Urinary micro-albumin creatinine ratio (normal range: <20 mg/g) initially was 780mg/g it increased 3470 mg/g on the day of cesarean delivery, supporting the diagnosis of worsening pre-eclampsia. Her prothrombin (PT, normal range: 9.7 to 11.8secs) was normal throughout her hospital stay. Activated plasma thromboplastin (APTT, normal range: 25.1 to 37.7 secs) was within normal limits on admission, APTT increased to >160 sec after fresh frozen plasma (FFP) returning to normal post-delivery. Similarly on admission the normal fibrinogen (normal range: 200-400mg/dL) admission increased to 630 mg/dL after FFP transfusion, returning to normal post-delivery. The various laboratory parameters comparing TTP, HELLP and our patient are shown in table1.

Her ultrasound on admission showed single active fetus in transverse lie with fetal parameters of 25 weeks 4 days, expected fetal weight of 799 grams, normal amniotic fluid volume with normal umbilical artery doppler study (PI 0.9), Normal MCA-PSV (33 in maximum at 1.1 MOM) and normal ductus venosus study. The results of ADAMTS-13 (A Disintegrin and Metalloproteinase with Thrombospondin type 1 motif-member 13) test, done on frozen citrated plasma of patient came back after 1 month of delivery, it showed no ADAMTS-13 antibodies at 4.8 U/ml (normal <12U/ml). It showed low ADAMTS-13 activity at 0.09IU/ml (normal range: 0.40 to 1.30 IU/ml) and low ADAMTS-13 antigen of 0.03IU/ml (normal range:0.41 to 1.41 IU.ml) **confirming congenital TTP.**

Table 1: Differences between thrombotic microangiopathies in pregnancy.

	TTP	**Preeclampsia/ HELLP**	**Our patient**
Pregnancy specific	no	yes	yes
Thrombocytopenia	very low platelets	low platelets	Very low platelets
Hemolysis on peripheral blood smear	schistocytes ++	schistocytes ++	schistocytes ++
ADAMTS-13 levels	severely reduced	slightly reduced to normal	severely reduced
Liver enzymes	normal	high	normal
PT/PTT	normal	high	normal

Fibrinogen	normal	decrease	normal
Treatment	plasmapheresis	delivery	***both***

Discussion

During the last decade, there has been a marked increase in the knowledge and the understanding of the pathogenesis of TTP. TTP diagnosis is difficult if occurred in pregnancy, as there is a clinical overlap with spectrum of pregnancy-related problems, such as severe pre-eclampsia (PE), HELLP syndrome, gestational thrombocytopenia and with hemolytic uremic syndrome (HUS). [8] Co-existence of PE/ HELLP with TTP was estimated by Martin et al [6] to occur in about 17% in his series of 166 patients, and this carried higher maternal mortality rate when compared with cases with pure TTP (44% vs. 21%), possibly due to a delay in diagnosis or in the initiation of plasmapheresis.

Hereditary TTP is rare 1 in 100,000, accounting for less than 5% of total TTP. When TTP manifests first time during pregnancy the likelihood of having hereditary TTP is much higher (24% in the French TMA National Registry and 66% in the UK TTP Registry). [9,10] Hereditary TTP has always been associated with serious complications in pregnancy. [11] The maternal and perinatal prognosis of hereditary TTP in pregnancy continues to be poor. [12] Kasht et al in their review found 97% of these patients had serious complications during one or more pregnancy, with mean gestational age at presentation 22 weeks and maternal mortality of 16% and stillbirth rate of 32 to 44%. [13,6]

Our patient had a good outcome in comparison to those reported in the literature. She had presented with features of TTP in her first pregnancy and had a bad perinatal outcome, which went unrecognized. In the present pregnancy, she manifested the features of TTP at around the same weeks of gestation (around 25 weeks). Hereditary TTP occurring first time in pregnancy has a high rate of stillbirth (approximately 70%), especially if it occurs before 28 weeks of gestation. [9] If we had failed to recognize TTP along with the superimposed pre-eclampsia in this pregnancy, she would have had a catastrophic result.

Disclosure

Ethical approval was not required for this article in accordance with the Institutional Ethics Committee. Written informed consent was obtained from the patient for publication of this case report after full explanation regarding her case being published for academic interest. The authors have no conflicts of interest to declare.

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