Multidisciplinary team approach for an atypical presentation of postpartum thrombotic thrombocytopenic purpura and severe preeclampsia in the Intensive Care Unit

ABSTRACT
Thrombotic thrombocytopenic purpura (TTP) is a rare hematologic syndrome during pregnancy with overlapping features of severe preeclampsia and is associated with high morbidity and mortality. We present a case of postpartum TTP, associated with severe preeclampsia. Therapeutic approach for this case included corticosteroids, plasma exchange therapy, and immunomodulatory therapy. We describe the pathophysiology of TTP in pregnancy and its similarities with other disorders that constitute the thrombotic microangiopathy syndrome, as well as other clinical factors which made the final diagnosis challenging. In addition, we highlight the value of a multidisciplinary team care approach to assure an optimal outcome for this clinical scenario.

Key words: Multidisciplinary team approach; plasma exchange therapy; severe preeclampsia; thrombotic thrombocytopenic purpura

Introduction
Thrombotic thrombocytopenic purpura (TTP) is a rare, life-threatening disorder, presenting with thrombocytopenia, microangiopathic hemolytic anemia, and microvascular thrombosis leading to renal dysfunction and neurological symptoms. A severe functional deficiency of a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13 (ADAMTS13), the specific von Willebrand factor-cleaving protease, causes accumulation of hyperadhesive platelets and unusually large von Willebrand factor multimers that lead to the spontaneous formation of microthrombi within the microcirculation. TTP has a female predominance (2:1), an incidence of 4–10 cases/million people/year, and the global mortality rate is approximately 20% despite plasma exchange therapy (PLEX), which remains the gold standard therapeutic intervention. The time during pregnancy with greatest risk for the development of TTP is near term and during the postpartum period. Furthermore, severe preeclampsia, TTP, and systemic lupus erythematosus (SLE) may all present with hypertension, proteinuria, increased creatinine levels, thrombocytopenia, and seizures.

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Case Report

A 31-year-old female with a medical history of chronic hypertension, SLE on hydroxychloroquine, and previous episodes of deep venous thrombosis on long-term enoxaparin therapy presented to the emergency department with heavy vaginal bleeding 4-day postpartum. Her obstetric history is significant for three term pregnancies with one episode of postpartum transient ischemic attack, one preterm pregnancy due to severe preeclampsia, two spontaneous abortions, and one ectopic pregnancy. Her most recent pregnancy course was remarkable for preeclampsia (diagnosed by week 27) controlled by labetalol, followed by an uneventful vaginal delivery at 35 weeks.

Further evaluation in the emergency department revealed tachycardia, hypotension, fever, anemia (hemoglobin 6.9 g/dl), and thrombocytopenia (34,000/µL). Liver function tests, fibrinogen, and renal function were within normal limits on initial workup. The patient initially received intravenous fluid resuscitation, red blood cells and platelet transfusions, and broad-spectrum antibiotics for possible sepsis. Enoxaparin and hydroxychloroquine were discontinued, and the patient was admitted to the surgical Intensive Care Unit with immediate consultation with the obstetric service, who emergently performed intrauterine balloon tamponade in the operating room under general anesthesia, after which the vaginal bleeding ceased, and her hemodynamics improved. Posteriorly, the platelet count continued to decrease to a nadir of 17,000/µL with associated anemia despite several units of red blood cells and platelet transfusions. A hemolytic panel was positive only for the presence of schistocytes, with normal haptoglobin, bilirubin, and reticulocyte count.

On hospital day 3, an autoimmune panel evaluation was obtained including complement levels, cardiolipin antibodies, antinuclear antibody, anti-Smith, dsDNA, SSA/SSB, ADAMTS-13 activity and antibodies, antibodies against hydroxychloroquine, and heparin-induced thrombocytopenia panel. In addition, the patient developed persistent-elevated blood pressure (average 160/100 mmHg) with concomitant epigastric pain and acute kidney injury (creatinine 2.75 mg/dl). Magnesium sulfate was initiated due to concerns of worsening preeclampsia. A microscopic urinalysis revealed granular casts suggestive of acute tubular necrosis, proteinuria, and absent dysmorphic red blood cells. No renal replacement therapy was initiated, as the patient continued to have adequate urine output. Detailed graph of platelet count, hemoglobin, and creatinine levels is shown in Figures 1 and 2.

During hospital day 5, the patient developed acute aphasia and altered mental status. Further workup was negative for stroke, and neurologic symptoms resolved in several hours. A multidisciplinary team conference was held the same day gathering input from intensive care, nephrology, obstetrics and gynecology, rheumatology, transfusion medicine, and hematology services. The consensus was to initiate daily PLEX while waiting for the final results of the autoimmune panel, which was unremarkable, except for severe deficiency of ADAMTS13 activity (<5%, reference range >67%), thus confirming the diagnosis of TTP.

PLEX was initiated on hospital day 6, with a significant clinical improvement within 72 h. Interestingly, despite daily PLEX, thrombocytopenia was refractory to therapy, thus prompting initiation of additional immunosuppressive treatment with methylprednisolone (hospital day 14), rituximab (hospital day 18), and vincristine (hospital day 22), followed by improvement on the platelet count she was eventually discharged to rehabilitation.

Discussion

Multiple changes of the hemostatic system during pregnancy occur at term and at the time of placental separation with inherent risk for other pregnancy-related syndromes, such as preeclampsia, eclampsia, and hemolysis, elevated liver enzymes and low platelets syndrome. ADAMTS13 activity progressively decreases during the course of pregnancy, a phenomenon possibly related to the physiologic increase of von Willebrand factor concentration, as ADAMTS13 activity inversely correlates with plasma von Willebrand factor concentrations, therefore pregnancy itself may trigger an acute episode of TTP in the peripartum period.\(^\text{[3,4]}\)

PLEX: Plasma exchange therapy

Figure 1: Platelet count variation during hospital admission. The graph also depicts the platelet count changes after PLEX started and PLEX combined with other immunomodulatory therapies. RTX: Rituximab, VCR: Vincristine, PLEX: Plasma exchange therapy

The association between SLE and TTP is infrequent and constitutes a difficult diagnosis. In a large population-based
cohort of patients with TTP (Oklahoma TTP-Hemolytic Uremic Syndrome Registry), of the 283 patients with TTP, only 21 (7.4%) were associated with SLE, 2 of these (10%) having severe deficiency of ADAMTS13 activity. Furthermore, this study showed that idiopathic cases of TTP with severe deficiency of ADAMTS13 (<10%) were younger and had lower platelet counts upon diagnosis, an elevated risk of renal involvement, required additional PLEX sessions, and had a higher recurrence risk.

The case presented a significant diagnostic challenge based on the acuity of its presentation, superimposed preeclampsia and SLE, no signs of hemolytic disease, and persistent initial clinical deterioration. The presence of schistocytes on the peripheral smear raised suspicion to investigate disorders related to thrombotic microangiopathy disorders. The authors emphasize the importance of a multidisciplinary team approach, and the initiation of PLEX which benefitted the patient and changed her clinical course. However, this decision was made based merely on clinical observation, given the rapid deterioration for this patient. The authors also highlight the importance of early introduction of PLEX therapy since early initiation of PLEX in patients with TTP has been shown to decrease mortality to <20%, and a delay in diagnosis may result in devastating consequences. Finally, our case exemplifies that even with the gold standard therapy for TTP (PLEX), patients may require further escalation of care with immunomodulation (rituximab and vincristine) to assure the best possible outcome, as well as emphasizing timely utilization of appropriate hospital resources is paramount in the management of similar life-threatening clinical conditions.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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