Quiz

Severe thrombocytopenia and neurological symptoms in pregnancy: a diagnostic challenge between hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome and thrombotic thrombocytopenic purpura (TTP)- what is your diagnosis?

A 24-year-old primigravid woman at 35 weeks and 5 days of gestation presented to the emergency service with uterine contractions. Due to persistent contractions, she was admitted to the obstetrics and gynecology ward. Her medical history included hypothyroidism, for which she was taking levothyroxine and she had no prior surgical history.

On examination, her vital signs were stable: blood pressure was 128/78 mmHg; heart rate 84 bpm; and temperature 36.6 °C. Physical examination revealed 2+ pitting edema in both lower extremities. Obstetric ultrasonography showed a singleton live fetus in cephalic presentation with biometric measurements corresponding to 36-37 weeks of gestation and an amniotic fluid index of 16 cm. Non-stress testing revealed irregular uterine contractions, and the cervical length was measured at 33 mm.

Initial laboratory tests demonstrated a hemoglobin level of 8 g/dL, hematocrit 24%, platelet count of 6,000/μL, aspartate aminotransferase 77 IU/L, alanine aminotransferase 31 IU/L, creatinine 1.25 mg/dL, urea 63 mg/dL, lactate dehydrogenase 1407 U/L, and 2+ proteinuria on urinalysis.

Answer

These findings led to a presumed preliminary diagnosis of hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome. The patient was referred to hematology due to severe thrombocytopenia. As a result of the peripheral smear analysis performed by hematology, the platelet value was consistent with the whole blood result, erythrocytes were evaluated as hypochromic microcytic, and schistocytes were not observed. During the physical examination of the patient, petechiae in the places under pressure, laboratory values upon the follow-up of mucosal bleeding and immune thrombocytopenic purpura (ITP) were considered as a differential preliminary diagnosis. Given the absence of schistocytes or abnormal cells on peripheral blood smear, bone marrow examination was deferred. No evidence of infection, drug-induced thrombocytopenia, or autoimmune disease was identified. This supported the preliminary diagnosis of ITP.

With the recommendation of hematology, the patient started treatment with intravenous immunoglobulin (IVIG) at 40/mg/kg/day for 5 days and a single dose of 80 mg of methylprednisolone. After platelet elevation elective birth induction was planned.

On the second day of hospitalization, the patient developed sudden-onset aphasia. Due to concerns of worsening preeclampsia or HELLP syndrome with neurological involvement, an emergency Cesarean section was performed. Preoperative platelet count was 20,000/μL. A live infant weighing 2480 grams was delivered.

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Neurology consultation was obtained postoperatively. Brain magnetic resonance imaging (MRI) with diffusion sequences, electroencephalogram, and carotid Doppler ultrasound were all unremarkable. The patient's normal brain MRI ruled out the possibility of ischemic stroke, and the absence of hypertension or seizures ruled out the possibility of preeclampsia and eclampsia.

After five days of IVIG, platelet count increased to 58,000/μL. On postoperative day 5, the patient was discharged with low molecular weight Heparin and instructions for bleeding precautions.

At routine follow-up, she reported blurred vision. Laboratory testing revealed a platelet count of 17,000/μL. This time, the peripheral smear showed schistocytes. ADAMTS13 activity was found to be <10%, confirming the diagnosis of thrombotic thrombocytopenic purpura (TTP). Plasma exchange therapy was initiated immediately.

This case illustrates the diagnostic challenge of thrombocytopenia in pregnancy, where HELLP syndrome, ITP and TTP can present with overlapping features. Initially, HELLP syndrome was suspected due to the combination of hemolysis leading to anemia, elevated liver enzymes, and thrombocytopenia, but the presence of mucocutaneous bleeding and isolated severe thrombocytopenia without schistocytes made ITP more likely. However, the sudden onset of a focal neurologic deficit (aphasia) on the second day of hospitalization raised concern for TTP. An ischemic stroke was considered, but the brain MRI was unremarkable, and eclampsia was deemed less likely in the absence of severe hypertension or seizures. The diagnosis of TTP was confirmed when a repeat peripheral blood smear revealed schistocytes and ADAMTS13 activity <10%. This chronological evolution illustrates that TTP can initially mimic ITP or HELLP syndrome, and that the hallmark of TTP of microangiopathic features may only become evident over time.

HELLP syndrome is a pregnancy or postpartum condition characterized by hemolysis (with microangiopathic findings on peripheral smear), elevated liver enzymes, and thrombocytopenia (1). Although often considered a severe form of preeclampsia, about 15-20% of HELLP cases occur without prior hypertension or proteinuria, suggesting it may be a distinct disorder (2). There is no effective medical treatment to regress HELLP syndrome but delivery may be associated with improvement in clinical signs and symptoms over time. Maternal complications are often hemorrhagic and may include life-threatening hepatic hemorrhage (3). Neonatal outcomes are mainly related to gestational age at delivery, as HELLP frequently results in preterm birth (4).

TTP is a rare, life-threatening thrombotic microangiopathy caused by ADAMTS13 deficiency, which cleaves von Willebrand factor. The traditional diagnostic pentad of fever, thrombocytopenia, microangiopathic hemolytic anemia, neurologic symptoms, and renal failure is now considered outdated, as fewer than 10% of acute cases present with all five features (5). Nearly all patients show severe thrombocytopenia ($<30\times10^3/\mu$L) and microangiopathic hemolytic anemia with schistocytes on peripheral smear. Common symptoms include mucocutaneous bleeding, fatigue, and dyspnea (6).

Symptoms related to organ ischemia or infarction are most commonly neurologic. About 60% of patients present with neurological manifestations, ranging from headache and confusion to stroke, coma, or seizures (7). Furthermore, renal involvement usually manifests as isolated proteinuria or hematuria with acute renal failure being uncommon in TTP, and serum creatinine is typically below 2 mg/dL at presentation. However, acute renal injury does not exclude a diagnosis of TTP. Some studies have reported severe TTP with ADAMTS13 activity <10%, acute kidney injury in 10-27% of patients (8).

HELLP syndrome and TTP are two important conditions that must be considered in the differential diagnosis of preeclampsia, although they have distinct clinical and

Table 1. Comparison of clinical features

Feature/condition	Preeclampsia	HELLP syndrome	TTP	ITP	Present case
Timing	>20 weeks of gestation	Usually 3rd trimester or postpartum	Rare in pregnancy, often postpartum	Can occur anytime	35+5 weeks at admission, diagnosis postpartum
Blood pressure	Elevated (≥140/90 mmHg)	May be elevated; 15-20% normotensive	Usually normal	Normal	128/78 mmHg (normal)
Proteinuria	Present	Often present	Possible (minimal)	Absent	2+ proteinuria

Table 1. Continued

Feature/condition	Preeclampsia	HELLP syndrome	TTP	ITP	Present case
Neurological symptoms	Eclampsia (seizures)	Rare, severe cases	Common (~60%): headache, confusion, stroke	Very rare	Aphasia developed
Treatment	Antihypertensives, $MgSO_4$, delivery	Urgent delivery	Plasma exchange, steroids	IVIG, steroids	Started on IVIG + steroids; plasma exchange added
Postpartum course	Usually resolves	Improves after delivery	Requires continued postpartum treatment	May persist or recur	Initially thought ITP, ultimately TTP confirmed

TTP: Thrombotic thrombocytopenic purpura, ITP: Immune thrombocytopenic purpura, IVIG: Intravenous immunoglobulin, HELLP: Hemolysis, elevated liver enzymes and low platelets

Table 2. Comparison of hematological and laboratory features

Feature/condition	Preeclampsia	HELLP syndrome	TTP	ITP	Presented case
Thrombocytopenia	Mild to moderate	Marked (<100,000/μL)	Severe (<30,000/μL)	Severe (<20,000/μL)	6,000 → 58,000 → 17,000/μL
Hemolysis (anemia)	Rare	Microangiopathic hemolysis (schistocytes)	Severe MAHA (schistocytes, ↑LDH)	Rare; autoimmune if present	Initially no schistocytes → later positive; Hb: 8 g/dL
Liver enzymes	Normal or mildly elevated	AST, ALT, LDH significantly ↑	LDH ↑; AST/ALT usually normal	Normal	AST: 77 IU/L, ALT: 31 IU/L, LDH: 1407 U/L
Renal function	Mild to moderate impairment	Can be impaired	Creatinine <2 mg/dL typical	Normal	Creatinine: 1.25 mg/dL, Urea: 63 mg/dL
Peripheral smear	Usually normal	Schistocytes (+)	Schistocytes (+)	No schistocytes	Initial smear: no schistocytes → later positive
ADAMTS13 activity	Normal	Normal	<10%	Normal	<10% → TTP diagnosis

HELLP: Hemolysis, elevated liver enzymes and low platelets, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, TTP: Thrombotic thrombocytopenic purpura, ITP: Immune thrombocytopenic purpura

laboratory features. HELLP is typically associated with elevated liver enzymes, hypertension, and proteinuria, whereas TTP is characterized by severe hemolytic anemia, marked thrombocytopenia, neurological symptoms, and ADAMTS13 deficiency. Differentiating between the two is essential for accurate diagnosis and timely intervention. While HELLP syndrome usually resolves after delivery without requiring additional treatment, TTP necessitates continued therapy in the postpartum period (9).

Diseases that should be considered in differential diagnosis are compared in Tables 1 and 2.

As demonstrated in the present case, TTP should remain a consideration in pregnant patients who develop neurological symptoms, even an isolated deficit such as aphasia, since such a presentation might otherwise be attributed to eclampsia or stroke. Accurate differentiation between conditions with similar clinical features is essential to ensure timely initiation of appropriate treatment.

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Footnotes

Conflict of Interest: *No conflict of interest is declared by the authors.*

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