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Case Report

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HELLP Syndrome at 17 Weeks Gestation: A Rare and Catastrophic Phenomenon

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Abstract

HELLP syndrome is a collection of symptoms described as hemolysis, elevated liver enzymes and low platelets. HELLP syndrome complicates 0.01-0.6% of pregnancies and can be considered a severe variant of preeclampsia. The occurrence of HELLP syndrome diagnosed before the 20th week of gestation has been most commonly reported in association with antiphospholipid antibody syndrome (APS) or triploid chromosomal anomalies. A 41-year-old primigravida was admitted at 17 weeks and 6 days gestation with hypertension, proteinuria, hemolytic anemia and acute renal injury. She was diagnosed with HELLP syndrome, and subsequently suffered from an intrauterine fetal demise. After delivery, the clinical manifestations of HELLP syndrome resolved within 7 days with the exception of her acute renal failure. Interdisciplinary teams of physicians were able to exclude other imitators of preeclampsia, such as hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), APS, lupus and acute fatty liver of pregnancy. This case is difficult to diagnose, given the similar presentation of several microangiopathic hemolytic anemias. The clinical manifestations and laboratory findings of HELLP and its mimicking conditions seem as if they are mirror images of each other. However, the discrete differences in our patient presentation, clinical findings, laboratory results and overall postpartum course leave HELLP syndrome as the most consistent diagnosis. It is imperative to investigate for all possible etiologies as HELLP syndrome at 17 weeks gestation is extremely rare and mimicking conditions may require alternative management strategies.

Keywords: Pregnancy; HELLP; Antiphospholipid antibody syndrome; Second trimester

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Introduction

HELLP syndrome is a collection of symptoms described as hemolysis, elevated liver enzymes and low platelets. HELLP syndrome complicates 0.01-0.6% of pregnancies and can be considered a severe variant of preeclampsia [1]. The occurrence of HELLP syndrome diagnosed before the 20th week of gestation has been most commonly reported in association with antiphospholipid antibody syndrome (APS) or triploid chromosomal anomalies [2-6]. We present a case of atypical HELLP syndrome at 17 weeks and 6 days gestation with subsequent placental abruption and fetal demise. A review of the literature was performed and several impersonators of preeclampsia will be discussed and utilized in comparison to our patient clinical course and outcome.

Case Report

A 41-year-old Caucasian primigravida at 17 weeks and 6 days presented to a regional community hospital with complaints of progressive nausea, vomiting, diarrhea and right upper quadrant pain. Her blood pressures were mild range at 150 systolic and 90 mm Hg diastolic. She denied any history of hypertension prior to pregnancy and denied any visual disturbances, chest pain or palpitations. She reported a history of iron deficiency anemia, and a surgical history notable for gastric bypass surgery and cholecystectomy. The present pregnancy was conceived with her current husband and she denied any drug allergies or contributory family history. She denied use of tobacco or illicit substances. The physical examination revealed hypertension, mild tachycardia, severe jaundice, icteric conjunctivae bilaterally and no evidence of purpura or petechia. Her exam revealed no evidence of neurologic abnormalities or edema, and she was able to converse at her baseline mental status. Her deep tendon reflexes were normal. Fetal cardiac activity was appreciated by ultrasound examination. The laboratory studies were notable for an alanine aminotransferase (ALT) 1,411 units/L and aspartate aminotransferase (AST) 4,211 units/L. The urinalysis studies revealed a +3 proteinuria, creatinine level of 0.56 mg/dL, platelet count 234,000 per µL, INR 1.4 and hematocrit 33%. She was placed on magnesium seizure prophylaxis at 2 g/h.

The evening of her presentation she was transferred to a tertiary care facility for comprehensive maternal and fetal

evaluation where intrauterine fetal demise was confirmed with ultrasound findings consistent with placental abruption. Her blood pressures remained moderately elevated 140 - 160/90 mm Hg and her laboratory studies were then notable for a hematocrit of 24%, fibrinogen levels 200 mg/dL, lactate dehydrogenase (LDH) level of 3,070 U/L, a significant decline in her platelet count to 37,000 per µL and an increase in creatinine to 3.0 mg/dL. The heightened suspicion for atypical HELLP syndrome, early disseminated intravascular coagulopathy (DIC) or a similarly presenting microangiopathic hemolytic anemia remained paramount. She was transfused with two units of fresh frozen plasma and one unit of packed red blood cells, and subsequently underwent a dilation and evacuation (D and E) procedure on the same day of transfer to our institute. D and E was complicated by uterine atony requiring multiple uterotonic medications with an estimated blood loss of 500 mL. The operative findings were consistent with placental abruption, as the placenta was detached from the uterine wall on ultrasound prior to procedure and independently delivered prior to the fetus during the procedure.

She was transferred to the surgical intensive care unit where she remained intubated for 30 h and magnesium seizure prophylaxis continued for 24 h after the procedure given in small boluses of 1 - 2 g to keep the magnesium level in low therapeutic range (4 - 6 meq/L). She was extubated on postoperative day 1 and complained of headache and transient shortness of breath. Radiologic imaging with CT and MRI were performed and were normal. A radiograph of the chest was notable for a small left pleural effusion. She underwent an echocardiogram confirming normal left ventricular ejection fraction and mild pulmonary hypertension. Her abdominal ultrasound was consistent with a normal liver without evidence of hematoma or abdominal ascites. Her headache resolved with fioricet and regular dietary intake. Her AST and ALT drastically decreased after the D and E procedure to 597 and 1,110 units/L respectively. The platelet count increased to 61,000 per µL, INR was 1.0, and hemoglobin and hematocrit were 8.6 g/dL and 24% respectively. Additional workup was done to r/o other possible causes including daily peripheral smears to look for shistocytes and helmet cells but these were seen rarely on the smears. Also, ADAMTS 13 was 37%, slightly reduced.

Throughout the remainder of her hospital course, she weaned off oxygen support, returned to regular ambulation and her laboratory abnormalities returned to normal without requiring plasmapheresis. Her AST and ALT were 19 and 57 units/L respectively and platelet count was 121,000 per µL with exception of her renal function, as her creatinine continued to climb to a peak of 6.0 mg/dL. She required three hemodialysis sessions throughout her 9-day hospital course and remained anuric with less than 50 mL of urine output daily. She was discharged home to outpatient hemodialysis treatment and her renal function completely recovered 4 weeks after hospital discharge without evidence of long-term renal injury.

Discussion

This patient presented during her mid trimester with a profound and progressive clinical syndrome that resembled a number of different diagnosis. A review of the literature was remarkable for several case reports and case series in women with similar presentations but the subtle differences in their presentation, laboratory findings, radiologic findings and long-term outcomes set them apart from each other. There are several microangiopathic disorders diagnosed in pregnancy presenting obstetricians with a daunting diagnostic challenge. Additionally, preeclampsia may be superimposed on any one of these disorders, making an already difficult diagnosis seem almost impossible. Traditionally, the definition of preeclampsia is well known and is diagnosed in 5-8% of pregnancies. Identifiable risk factors for preeclampsia include African-American race, nulliparity, extremes of age, multifetal gestations, chronic hypertension, diabetes mellitus, connective tissue disease and preexisting APS [7, 8].

HELLP syndrome is defined as the combination of hemolysis with a microangiopathic blood smear, increased liver associated enzymes and low platelets in pregnancy. Approximately, 5-10% of women with preeclampsia develop HELLP syndrome. However, it has been postulated that as many of 15-20% of HELLP syndrome patients do not have antecedent preeclampsia. Patients with HELLP syndrome commonly present with complaints of nausea, vomiting, and epigastric pain similarly described by our patient. Hypertension and proteinuria are evident in up to 85% of HELLP cases, but the pathogenesis of HELLP is not fully understood. Several hypotheses include the alteration in maternal-fetal immune balance, creating a maternal immune rejection of a genetically foreign fetus. Others have proposed that HELLP is an acute inflammatory condition instigated by the placenta [9]. Evidence has shown a role for the complement system in preeclampsia and HELLP syndrome, and murine models demonstrated that complement activation and subsequent dysregulation of angiogenic factors such as vascular endothelial growth factor increase in spontaneous abortion and intrauterine growth restriction [9, 10]. In addition to several proposed pathogenic mechanisms of HELLP, it has a strikingly similar presentation and possibly common pathogenic link to another thrombotic microangiopathy we know as hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP).

HUS and TTP are two microangiopathic disorders described in case reports and small case series with estimated incidence of 1 in 100,000 pregnancies. The triad of HUS has been classically described as thrombocytopenia, microangiopathic hemolytic anemia and renal dysfunction. The addition of fever and neurologic symptoms makes the classic pentad of TTP. The underlying pathologic disturbance is demonstrated as systemic or intrarenal aggregation of platelets within arterioles and capillaries in association with endothelial cell injury due to elevated levels of large von Willebrand factor multimers [9]. TTP is associated with either a familial or acquired idiopathic etiology, and studies have shown that many patients with acute, severe TTP have significant reduction of a von Willebrand factor-cleaving metalloprotease known as ADAMSTS-13. The cleavage of large von Willebrand factor multimers is prevented and platelets aggregate in various organs with resultant thrombocytopenia and erythrocyte injury. Studies have shown approxi-

mately 33% of severe TTP patients have significant reduction of ADAMSTS-13 activity to < 5%. In contrast, a patient with HELLP syndrome will have normal levels of von Willebrand factor multimers and ADAMSTS-13 activity is normal (> 65%) or mildly decreased [7, 11, 12]. ADAMSTS-13 was slightly reduced to 37% in our case. Additionally, ADAMSTS-13 antibodies are absent. Renal involvement manifests with hematuria and proteinuria, demonstrating tea-colored urine, and laboratory studies often reveal platelet count less than 20,000 per μL. The patient will demonstrate marked LDH level elevations and severe anemia with hematocrit less than 25%. The presence of shistocytes will be evident on peripheral smears, which our patient did not display upon several peripheral smear examinations during her course [7, 13]. Additionally, plasma exchange therapy is the treatment of choice in TTP, and delay in early therapy increases the mortality rate in these patients. Our patient improved clinically and laboratory wise drastically after the D and E and without plasmapheresis.

HUS commonly develops after a prodromal diarrheal illness associated with Shiga toxin producing *E. coli* (STEC) and *Shigella dysenteriae* type 1 [9, 12, 14]. HUS presents as a close relative of the TTP spectrum and is extremely rare in pregnancy with almost all cases being described in the postpartum period ranging from 48 h to 10 weeks after delivery. Postpartum HUS was first described in 1968 as the presentation of Coombs test negative hemolytic anemia, acute renal failure and renal thrombotic microangiopathy [15]. It is only described in case reports and case series in the obstetrical literature due to its rare presentation. A review of 11 cases of HUS/TTP occurring in 1988 - 1996 showed that only three of the 11 patients were diagnosed prior to fetal viability, with most patient presenting in the third trimester or peripartum period [16]. Patients usually present with edema, hypertension, bleeding manifestations or severe renal failure with most patients being left with some form of residual renal deficit. Historically, the maternal mortality rate was estimated 50%; however, recent advancement in treatment options has shown to decrease this rate to 10% in more recent case series with a 20% fetal loss rate [16, 17]. In contrast to HELLP syndrome delivery is not a cure, nor is it absolutely indicated with an HUS/TTP diagnosis [7, 18]. Preeclampsia rarely causes acute renal failure (ARF) but can occur due to severe hemorrhage, such as with placental abruption. When acute renal failure occurs in a patient with severe preeclampsia, expedited delivery is recommended because this enhances the recovery of maternal condition. Most ARF from preeclampsia or eclampsia is reversible and has excellent prognosis even if these patients required temporary dialysis support. In patients requiring long-term dialysis, likely pregnancy or preeclampsia has unmasked the underlying chronic renal disorder or there has been some degree of renal cortical necrosis which requires chronic hemodialysis. Long-term renal function depends on the extent of cortical necrosis. Our patient required hemodialysis for approximately 1 month and thereafter, regained normal renal function and urine output.

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by antigen-antibody complexes deposited in capillaries and various visceral organs that can manifest as nephritis, pleuritis, hepatic and even brain involvement. Severe lupus flares occur in 25-30% of pregnancies and may develop in the first time during the pregnancy and postpartum period [7]. Antiphospholipid antibodies have been shown to be present in 30-40% of patients with systemic lupus and these patients are at increased risk for thrombotic microangiopathy, resulting in a similar clinical picture to that seen in HELLP syndrome and HUS/TTP [1, 7]. The catastrophic antiphospholipid syndrome occurs in less than 1% of patients with antiphospholipid antibodies, and most commonly affected organs are kidneys, cardio-respiratory and the central nervous system which manifests with similar symptoms and laboratory findings as HELLP syndrome and HUS/TTP [7]. However, our patient tested negative for antiphospholipid antibodies, complement factors and lupus associated antibodies, thus making this an unlikely diagnosis.

Acute fatty liver of pregnancy is a rare and potential fatal fetal complication most often presenting in the third trimester, with an incidence of 1 in 10,000 - 15,000 deliveries. The onset of clinical symptoms has been reported to range from 27 to 40 weeks gestation with an average age of 36 weeks gestation. Patients complain of a 1 - 2 week history of anorexia, nausea, vomiting, right upper quadrant pain and headache. However, approximately 15-20% of patients present with none of the above described symptoms. The laboratory studies usually reveal hemoconcentration, leukocytosis and normal to low platelet count. Liver enzymes will be elevated and a coagulopathy will manifest with a prolonged PTT and low fibrinogen levels. Ammonia levels are increased, especially in late stage of the disease [7, 10]. In contrast, patients with HELLP syndrome present most commonly with hypertension and proteinuria. HELLP patients will have severely decreased platelet count as seen in our patient, as well as a normal ammonia level. Furthermore, this diagnosis becomes less likely as our patients presentation occurred in early second trimester.

In conclusion, this case was difficult to diagnose given the similar presentation to several other microangiopathies. The clinical manifestations and laboratory findings of HELLP syndrome, HUS/TTP, APS and acute fatty liver of pregnancy are significantly similar to one another, and at times seem as if they are mirror images. However, the discrete differences with regards to our patient presentation, physical exam findings, laboratory results, and overall clinical course leave HELLP syndrome as the most consistent final diagnosis. The only aspect of this patient's course rather atypical for an HELLP syndrome patient is acute tubular necrosis requiring hemodialysis for 1 month after diagnosis until she regained normal renal function. However, all of these disease presentations carry the risk for renal insufficiency. It is imperative to investigate for all possible imitators of preeclampsia as described in this case; however, each syndrome has distinguishing clinical features and laboratory findings that make the correct diagnosis important in promoting the optimization of maternal and fetal outcome.

Declaration

The views expressed herein are those of the authors and do not reflect the official policy or opinion of the Department of Defense or the United States Navy.

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