Atypical Presentation of Pregnancy-Related Hemolytic Uremic Syndrome

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The cause of acute kidney injury during pregnancy and in the postpartum period can be particularly challenging to diagnose, especially when it is necessary to differentiate among preeclampsia; eclampsia; hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome; and thrombotic microangiopathies (TMAs). All these disease entities can present with kidney failure, microangiopathic hemolytic anemia, and thrombocytopenia. We present a teaching case of atypical hemolytic uremic syndrome in the postpartum period in a young woman who was found to have mutations of uncertain clinical significance in the complement cascade, including in *C3*, *CFH*, and *CFI*. We use this as an opportunity to review the clinical presentation and pathophysiology of preeclampsia, eclampsia, and the TMAs. We focus on diagnostic challenges, especially because many patients with TMA do not present with thrombocytopenia, which can delay diagnosis. We additionally review the clinical settings in which administration of eculizumab, a C5 membrane attack complex inhibitor, is appropriate.

Complete author and article information provided before references.

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Introduction

Evaluation of pregnancy-related acute kidney injury (AKI) is a challenging clinical problem because the physician must consider additional causes apart from those encountered in the general population. For example, decreased kidney perfusion can be caused by hyperemesis gravidarum and uterine hemorrhage, whereas intrinsic causes include acute pyelonephritis, septic abortion, and bilateral renal cortical necrosis.[1] Additionally, obstructive AKI can rarely be caused by ureteral obstruction by the gravid uterus.[2] Other conditions during pregnancy and the immediate postpartum period may also occur, including preeclampsia; eclampsia; hemolysis elevated liver enzymes and low platelets (HELLP) syndrome; and thrombotic microangiopathies (TMAs), such as thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (aHUS). We present a case of AKI in the postpartum period that illustrates the diagnostic challenges the clinician faces when considering preeclampsia, eclampsia, HELLP syndrome, and TMAs.

Case Report

Clinical History and Initial Laboratory Data

A 23-year-old woman required a cesarean section at 38 weeks of gestation for severe preeclampsia and breech presentation at an outside institution. She had had no other pregnancies, was a nonsmoker, and there was no known family history of eclampsia. She was discharged from the outside hospital on treatment with oral labetalol and experienced a seizure at home 2 weeks later. Upon representation to the outside hospital, systolic blood pressure was >180 mm Hg. She was treated with intravenous (IV) lorazepam and an IV magnesium bolus of 6 g and started on a 2-g/h magnesium drip. The patient was transferred to our institution for further care.

Upon transfer to our institution, the patient could not recall her seizure and reported blurry vision and feeling "foggy." Blood pressure was 160/120 mm Hg and she was tachycardic to a heart rate of 110 beats/min. Physical examination findings were notable for diminished deep tendon reflexes diffusely and following commands slowly. The uterine fundus was palpable below the umbilicus and there was trace pitting edema in the lower extremities. Laboratory findings were notable for serum creatinine concentration of 1.3 mg/dL, normal liver test results, mild anemia without thrombocytopenia, and lactate dehydrogenase concentration > 2,000 U/L (Table 1). No baseline serum creatinine measurements were available. Magnetic resonance imaging of the brain showed increased T2/fluid-attenuated inversion recovery (FLAIR) signal in the bilateral posterior parietal, occipital, temporal lobes, deep gray nuclei, and periventricular white matter, consistent with posterior reversible encephalopathy syndrome (Fig 1).

Severe eclampsia was diagnosed, and the obstetric team managed the patient's blood pressure with a nicardipine infusion and provided IV crystalloid for management of the AKI. The patient was continued on an IV magnesium

Teaching Cases focus on interpretation of pathology findings, laboratory tests, or imaging studies to educate readers on the diagnosis or treatment of a clinical problem.

Table 1. Relevant Laboratory Data

Laboratory Test	Admission (day 0)	Renal Consultation (day 5)	Kidney Biopsy (day 12)	Dialysis Initiated (day 17)	Dialysis Stopped (month 4)
Serum creatinine, mg/dL	1.35	1.96	4.04	5.45	1.4
Magnesium, mg/dL	5.9	2.2	2.0	2.4	
Hemoglobin, g/dL	11.0	10.0	8.2	8.6	10.2
Platelets, $\times 10^3/\mu L$	176	261	177	254	201
Lactate dehydrogenase, U/L	2,107	1,160	952	662	527
Alanine aminotransferase, U/L	20	26	28		
Aspartate aminotransferase, U/L	41	28			
Total bilirubin, mg/dL	0.8	0.3	0.4		
Direct (conjugated) bilirubin, mg/dL	0.2		0.2		
Alkaline phosphatase, U/L	78	55	60		
Haptoglobin, mg/dL		76			

infusion for 24 hours, which was titrated to a serum magnesium concentration of 4 to 6 mg/dL (3.3-4.9 mEq/L). The patient's serum creatinine concentration continued to worsen and by day 5 after admission, serum creatinine concentration had increased to 2 mg/dL (Table 1).

Nephrology was consulted for management of the worsening AKI and requested further investigations. Urine analysis showed 2.4 g of protein on a spot collection and 3+ blood, and urine microscopy demonstrated nondysmorphic red blood cells. A peripheral smear showed 2 to 3 schistocytes/high-power field. Serologic workup showed ADAMTS13 (von Willebrand factor protease) activity of 40% and normal complement concentrations. A uterine ultrasound did not show retained products of conception.

Additional Investigations

Despite supportive care, the patient's kidney function deteriorated, so kidney biopsy was performed. Light microscopic sections demonstrated TMA with thrombosis of afferent arterioles (Fig 2). Marked subendothelial edema and mucointimal hyperplasia caused near-occlusive narrowing of the small arteries. Ischemia to glomeruli was manifested by mesangiolysis, endothelial cell swelling, lifting of the endothelium from the basement membrane with deposition of subendothelial flocculent material, and formation of basement membrane double contours. There was no endocapillary proliferation. Immunofluorescence studies showed no deposition of immunoglobulin G (IgG) or C3. There was nonspecific capillary wall staining for IgM and IgA, which did not have any correlation on electron microscopy. Electron microscopy showed the ischemic changes mentioned; there was no evidence of an immune complex process on electron microscopy.

Genetic testing was performed for mutations in several genes associated with complement-mediated HUS, including *CFH*, *CD46* (the gene encoding membrane cofactor protein [MCP]), *CFI*, *C3*, *CFG*, *CFHR1*, *CFHR3*, *CFHR4*, *CFHR5*, *THBD* (encoding thrombomodulin), *PLG* (encoding plasminogen), and *DGKE* (encoding diacylglyercol kinase epsilon), and 3 mutations were detected. The first was a heterozygous missense variant in exon 17 of C3 (the cytosine at nucleotide 2,203 substituted by thymine, predicted to lead to the arginine at amino acid 735 being replaced by a tryptophan [p.Arg735Trp]); the

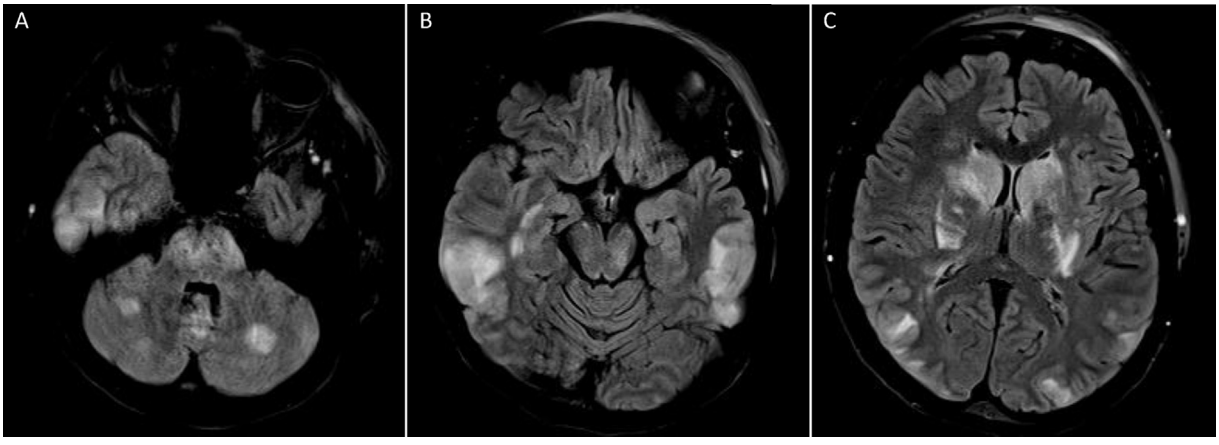

Figure 1. Magnetic resonance image of the brain shows increased T2/fluid-attenuated inversion recovery (FLAIR) signal in the (A) cerebellum, (B) bilateral posterior parietal, and (C) periventricular white matter, consistent with posterior reversible encephalopathy syndrome.