Pregnancy-Associated Atypical HUS Treated Successfully With Eculizumab

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Abstract

P-aHUS is a rare complement-mediated disorder with pathophysiology based on complement dysregulation. Without prompt diagnosis and treatment, the disease can be life-threatening. We present a case of a 29-year-old gravida 1 woman at 41 weeks' gestation who developed severe renal impairment, thrombocytopenia, and neurologic symptoms. When she progressed to end-stage renal disease and required dialysis, suspicion arose for thrombotic thrombocytopenic purpura or hemolytic uremic syndrome (HUS), so specific ADAMTS13 testing was ordered. Empiric treatment with eculizumab was started, and clinical improvement was noted. Genetic testing later confirmed the diagnosis of pregnancy-associated HUS with 2 mutations in areas necessary for complement regulation (Factor H and MCP/CD46). This case demonstrates the importance of early initiation of anti-complement therapy to prevent irreversible renal damage and possibly death.

Case Description

A 29-year-old gravida 1 woman at 41 weeks' gestation presented for late-term induction. She had no past medical history and the pregnancy had been uncomplicated. Early in her induction, she had elevated blood pressures (BPs) between 140/90 and 160/110, which improved with oral labetalol. The initial HELLP labs were normal with the exception of low platelets (aspartate transaminase (AST) 30 U/L, alanine transaminase (ALT) 28 U/L, creatinine 0.72 mg/dL, platelets 107 Th/mm³, lactate dehydrogenase (LDH) 261 U/L.

During her induction, the patient continued to have severe BPs and reported an intermittent headache. She was treated with intravenous (IV) magnesium sulfate and labetalol, as needed. Her physical exam remained benign.

The patient progressed to complete dilation with persistent occiput posterior presentation, despite attempted manual rotation. Labs were drawn before her cesarean delivery for arrest of second stage: platelets 80 Th/mm³, fibrinogen 280 mg/dL, international normalized ratio (INR) 1.4. She was transfused 1 unit of fresh frozen plasma (FFP). Delivery was complicated by a postpartum hemorrhage, due to uterine atony, and was treated with hemabate, pitocin, and massage. Estimated blood loss was 1000 cc. The newborn's Apgar scores were 9 and 10.

In the recovery room, the patient became profoundly hypotensive and tachycardic, and was empirically transfused with 2 units of platelets, 1 unit of FFP, and 1 unit of packed red blood cells (PRBCs). Stat labs were ordered: platelets 33 Th/mm³, hemoglobin 9 g/dL, creatinine 1.43 mg/dL,
AST 880 U/L, ALT 578 U/L. Urine output (UOP) was 24 cc/hr. The composite clinical picture was thought to be secondary to acute blood loss anemia in the setting of HELLP syndrome.

The patient had a second postpartum hemorrhage associated with hypotension, wherein 300 cc of clot and blood were evacuated with fundal massage. While hypotensive, the patient became confused, stating, “I am ready to have this baby.” She was reminded that she had already delivered her baby, the details of which she recalled once her BP normalized. The neurologic exam findings were normal, but the labs at this time remained abnormal (platelets 70 Th/mm³, LDH 3044 U/L).

Over the next 48 hours, the patient had periods of oliguria interspersed with low–normal UOP. During this time, her creatinine increased to 1.88 mg/dL, 2.26 mg/dL, then 2.54 mg/dL, despite a transfusion of 2 units each of PRBCs and FFP. She continued to have intermittent periods of confusion, complaining of “red spots and words” in her field of vision, “like laser pointers.”

On the evening of postoperative day (POD) 2, the patient complained of chest tightness. Crackles were present in bilateral lung fields, and furosemide was ordered because of concern for pulmonary edema. Severe BPs were noted, requiring treatment with IV hydralazine. When the patient’s nurse returned to the bedside to administer the furosemide, she found the patient with all IV sites, cuffs, and sensors removed. The patient was breathing but unresponsive to verbal stimuli. The physician was notified and, once at the bedside, saw that the patient was responsive and appropriately oriented, though frightened.

As a result of acute neurologic change, a stat computed tomography (CT) was ordered to rule out hemorrhagic stroke, which was negative for any acute intracranial abnormality. Repeat labs on POD2 returned creatinine 4.1 mg/dL, platelets 30 Th/mm³, and hemoglobin 9.5 g/dL. Nephrology was consulted and a renal ultrasound was ordered. The ultrasound demonstrated echogenic kidneys, consistent with medical renal disease. Hyponatremia was noted and 3% normal saline (NS) started.

The neurology service was consulted, and the service suspected encephalopathy secondary to posterior reversible encephalopathy syndrome (PRES). Magnetic resonance imaging (MRI) and an electroencephalogram (EEG) were ordered; unfortunately, the patient was unable to remain still long enough for an MRI.

On POD3, the patient’s creatinine was 5.89 mg/dL, and new-onset hyperkalemia was noted, prompting initiation of hemodialysis. The previously ordered EEG was read as abnormal but nonspecific. Platelets were noted to be 44 Th/mm³. Nephrology believed that the acute kidney injury was secondary to acute tubular necrosis in the setting of acute blood loss anemia.

On PODs 4 and 5, the patient’s creatinine remained stable between 5 and 6 mg/dL. An MRI was negative for any acute structural abnormality of the brain. Repeat EEG was mildly abnormal, suggestive of residual encephalopathy. Platelets were 107 Th/mm³, AST 92 U/L, ALT 232 U/L, and LDH 1233 U/L. The patient’s mental status had improved, but she still had intermittent confusion. An ADAMSTS13 level was ordered, with a concern for TTP.

On POD6, the patient’s creatinine worsened to 7.15 mg/dL, hemoglobin to 7.6 g/dL, and platelets to 78 Th/mm³. Hematology was consulted to test for plasmapheresis, which was performed. The precipitate was not phenotypically consistent with TTP.

On POD7, ADAMSTS13 resulted as mildly reduced, which was nondiagnostic for TTP and more consistent with atypical HUS. With TTP ruled out, a diagnosis of atypical HUS was highly suspected, and eculizumab was ordered. In the setting of progressively deteriorating labs, a single injection of eculizumab medication was administered, after which the patient demonstrated slow but consistent improvement in renal and hematologic parameters. After a complete work-up, her final diagnosis was autosomal recessive atypical hemolytic uremic syndrome (aHUS) associated with mutations in complement factor H-related 1 (CFHR1) protein, as well as membrane cofactor protein (MCP) CD46.

The patient was discharged home on POD13 with a plan for indefinite continuation of eculizumab injections every 2 weeks. At her 3-month follow-up appointment, a levonorgestrel intrauterine device was placed to prevent contraception. She is doing well and continues to be followed by hematology/oncology.

Discussion

Hemolytic uremic syndrome is a type of TMA that develops from congenital, infectious, or acquired causes. While the more common type of HUS is Shiga toxin-mediated, aHUS is a complement-mediated disorder with pathophysiology based on complement dysregulation.2,3
This dysregulation occurs after a genetic or acquired defect causes complement activation to go unchecked, creating membrane attack complexes. The membrane attack complex causes an inflammatory response in the endothelium leading to the clinical manifestations of renal impairment, hemolytic anemia, thrombocytopenia, and, at times, neurologic involvement.2,4

In the setting of pregnancy, symptoms of aHUS may overlap with symptoms of preeclampsia, HELLP, or eclampsia. Even so, accurate and timely diagnosis of these disorders is vital. Factors that may aid in the diagnosis include timing of onset, severity of renal impairment, severity of thrombocytopenia, and presence of neurologic involvement.2

Nearly 80% of P-aHUS cases occur postpartum, while preeclampsia and HELLP are primarily seen after 20 weeks’ gestation during the pregnancy. Only about 5% of preeclampsia occurs in the postpartum setting.1

The renal dysfunction found in P-aHUS is severe.1,2 Unregulated complement causes tissue damage such as renal impairment by inducing endothelial cell activation and producing procoagulative factors. Thrombocytopenia is the result of platelet activation by membrane attack complexes leading to platelet degranulation and aggregation. Neurologic symptoms are likely caused by reduced blood flow to the brain secondary to multiple microthrombi as well as uremia from kidney dysfunction.1,2,4

This patient had mutations in both CFHR1 protein, as well as MCP CD46. This combination of mutations has been described in only 1 other case of P-aHUS, which was successfully treated with eculizumab.1 Factor H and MCP CD46 are proteins central to the regulation of complement activation.1,2,4,5 They protect the endothelium and prevent events that can cause platelet aggregation and eventually consumptive thrombocytopenia.2

The frequency of factor H mutation in aHUS is 24% to 28%.2 Within 3–10 years after onset of aHUS, 70% to 80% of patients with factor H mutation experience death or end-stage renal disease.1 Isolated mutations in MCP CD46 occur at a frequency of 7% to 8% and in combination with other complement gene mutations at a frequency of up 22%.7 The 3–10 year occurrence of death or end-stage renal disease is less than 20%.1

Eculizumab is a monoclonal antibody directed against the complement component C5. It prevents the cleavage of C5, further reducing the production of C5a and the membrane attack complex. It has been shown to be superior to plasma therapy in inducing remission in patients with acute aHUS.4 We found 8 case reports of P-aHUS treated by eculizumab after 2013.1,2,3

With the inclusion of our case, 6 of the 9 patients required dialysis due to the development of end-stage renal disease. The timing of disease onset ranged from 17 weeks’ gestation to postpartum day 7, with only 1 case occurring during pregnancy. The average platelet nadir was 41Th/mm3. Six of the 9 P-aHUS cases occurred in the patient’s first pregnancy.

Although renal recovery with eculizumab was noted in 7 of the 9 cases, duration between onset of disease and initiation of therapy ranged from 3 days to 26 weeks.1 Earlier initiation of anti-complement therapy is associated with improved renal outcomes,1,6 which further supports the importance of timely diagnosis and treatment.

Conclusion

P-aHUS is a rare but life-threatening disease that is often delayed in recognition and treatment. Because P-aHUS frequently occurs in a patient’s first pregnancy without any associated history, these patients are not identified as high risk—and no protocol for screening exists. With the inability to predict who will develop this disease, we must be diligent in our efforts to diagnose and treat P-aHUS effectively. Our understanding of this disease is improved with the availability of case reports with various presentations and outcomes. Prompt diagnosis and initiation of therapy in this patient likely prevented irreversible renal damage and possibly death.

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References


