Pregnancy-Associated Atypical Hemolytic-Uremic Syndrome

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Précis

Introduction Early diagnosis of atypical uremic–hemolytic syndrome may be challenging during the puerperium period. Correct diagnosis and timely management are crucial to improve outcomes.

Background Pregnancy-associated atypical hemolytic-uremic syndrome (p-aHUS) is a rare condition characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Triggered by pregnancy, genetically predisposed women develop the syndrome, leading to a disastrous hemolytic disease characterized by diffuse endothelial damage and platelet consumption. This disease is a life-threatening condition that requires prompt diagnosis and therapy.

Case A 19-year-old G1P1 Caucasian female with suspicion of HELLP syndrome was treated at our facility for severe thrombocytopenia and acute kidney injury. A diagnosis of atypical uremic–hemolytic syndrome was later confirmed. The patient's condition improved with normalization of platelets and improvement in kidney function after 14 days of plasmapheresis. She was subsequently treated with eculizumab, a monoclonal antibody against C5. The patient tolerated well the therapy and is currently in remission.

Conclusion Diagnosis of p-aHUS is challenging, as it can mimic various diseases found during pregnancy and the postpartum. Plasma exchange should be promptly initiated within 24 hours of diagnosis. Eculizumab has risen to become an important tool to improve long-term comorbidities and mortality in this group population.

Keywords
- atypical hemolytic-uremic syndrome
- eculizumab
- pregnancy
- management

Atypical hemolytic-uremic syndrome (aHUS) is a rare life-threatening disease characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury that is not related with *Escherichia coli* 0157:H7 infections. aHUS accounts for 5 to 10% of hemolytic-uremic syndrome cases. When pregnancy triggers the thrombotic microangiopathy (TMA), the disease is referred to as pregnancy-associated atypical hemolytic-uremic syndrome (p-aHUS). It affects 1 out of every 25,000 pregnancies, mostly in the postpartum period, and it is associated with poor maternal outcomes.[1,2] The clinical course of aHUS can be severe, with most patients suffering neurologic injury, renal impairment, and multiorgan failure.[2,3] In a French cohort, 60 to 70% of aHUS developed end-stage renal disease (ESRD).[4]

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The pathogenesis of the disease involves unregulated activation of the alternate complement pathway, resulting in diffuse endothelial damage, platelet activation, and ultimately TMA with multiorgan failure secondary to distal ischemia. The excessive activation of the complement pathway results from dysfunction of regulatory proteins secondary to mutations in the CFH, MCP, CFI, or C3 genes.[4]

The mainstay of therapy involves replacing the mutant dysfunctional forms of proteins with normal regular proteins by plasma exchange (PE). Despite initial PE with recovery of platelet counts, a significant percentage of patients do not recover kidney function and eventually develop ESRD.[4]

Uncontrolled alternative complement pathway activation in p-aHUS supports the use of anti-C5 therapy (eculizumab) to induce terminal complement blockade and reverse this condition.[5] Eculizumab is a humanized monoclonal antibody that binds to complement component C5 to inhibit its cleavage to C5a and C5b.[6] Outcomes have improved since the introduction of eculizumab for the treatment of aHUS.[6,7] Although this condition can be effectively treated with eculizumab, there is no evidence to guide treatment.[6,7] Here, we present the case of a patient who presented with apparent HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome after spontaneous vaginal delivery who was later determined to have p-aHUS. She was subsequently treated with PE followed by eculizumab.

Case

A 19-year-old G1P1 woman was admitted to our facility for induction of labor at 39 weeks of gestation. At admission, she denied neurological symptoms and had normal range blood pressures. On hospital day 1, she was diagnosed with preeclampsia based on elevated blood pressures and a protein-to-creatinine ratio of 1.0. The patient underwent an uncomplicated spontaneous vaginal delivery. On postpartum day 1, the patient developed severe thrombocytopenia, hemolytic anemia, elevated liver enzymes, and acute kidney injury. She was subsequently treated for suspected HELLP syndrome.

Laboratory investigation revealed serum creatinine of 2.38 mg/dL, hemoglobin 5.3 g/dL, lactate dehydrogenase (LDH) >6,450 U/L, serum aspartate aminotransferase 114 IU/L, total bilirubin 2.2 mg/dL, platelet count 50,000/mm^3, and undetectable haptoglobin levels. Peripheral smear revealed marked schistocytosis. The patient's condition did not improve during the first 24 hours postpartum. With the presence of TMA, ADAMTS13 levels were sent and the patient was initiated on daily PE with concomitant prednisone therapy (1 mg/kg/day). Throughout the therapy, hemoglobin levels were maintained above 7.0 g/dL with transfusion of packed red blood cells as needed. On hospital day 6, her creatinine peaked at 3.9 mg/dL and the platelet decreased to 22,000/mm^3. After six cycles of PE, the laboratory values started to improve. On hospital day 9, the ADAMTS13 activity was reported as normal at 96%. Complement tests revealed alternative pathway dysregulation with low plasma levels of C3 at 74 mg/dL (86–184 mg/dL) and low levels of C4 11 mg/dL (20–59 mg/dL). Classical and alternative pathway activity was normal given a CH50 of 69 CAE units (60–144 CAE units).

A diagnosis of aHUS was considered due to an atypical presentation for thrombotic thrombocytopenic purpura (TTP) but with improvement in secondary plasmapheresis therapy. Further genetic workup revealed the patient to be a heterozygous carrier for a CD46 (MCP membrane cofactor protein) sequence variant (p.T383I; c.1148C > T). Mutations in CFH, CFB, C3, and CFI genes were excluded.

On hospital day 14, the decision was made to discontinue plasmapheresis based on the patient's platelets remaining greater than 150,000/mm^3 for 2 consecutive days with near-normal LDH and stable hemoglobin levels. The patient did not require dialysis and was discharged 19 days after admission with a creatinine value of 1.4 mg/dL and a platelet count of 180,000/mm^3. The patient received vaccination against *Neisseria meningitides*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* before being discharged in anticipation of Eculizumab administration. Eculizumab was started 27 days after discharge at a dose of 900 mg intravenously per week for 4 weeks with a maintenance regimen of 1,200 mg at week 5 followed by 1,200 mg every 2 weeks for 26 weeks. The drug was well tolerated, without developing the associated side effects of headache, leukopenia, or allergic reactions. Currently, the patient, in clinical remission, is on eculizumab treatment and doing well.

Discussion

P-aHUS is a severe systemic disease associated with uncontrolled alternative complement pathway activation. Hyperactivation of complement results in diffuse endothelial injury with subsequent formation of fibrin and platelet microthrombi in the vasculature leading to hemolysis, thrombocytopenia, and end organ dysfunction from ischemia (mostly in the form of acute kidney injury). Most cases of p-aHUS occur during the postpartum period.[4] Patients with mutations in genes encoding complement proteins are predisposed to dysregulation of the alternative complement pathway during this period. Several factors such as inflammation, drugs, cancer, preeclampsia, maternal–fetal hemorrhage, and infections may act as a trigger for complement activation in an already genetically susceptible individual.

The diagnosis of p-aHUS can be challenging, as this condition mimics several other diseases that must be ruled out when making a diagnosis. Common features such as acute renal failure, thrombocytopenia, and microangiopathic hemolytic anemia seen in p-aHUS are also observed in severe preeclampsia with HELLP syndrome, TTP, and acute fatty liver of pregnancy. Although it is sometimes difficult to distinguish between these syndromes, it is imperative to make the right diagnosis in a timely manner to treat patients appropriately. HELLP syndrome typically resolves after delivery and hemolysis is less severe; note that it may act as a stimulus for the development of the p-aHUS in genetically predisposed patients. While some of the clinical features of these different syndromes overlap, different laboratory studies can help guide the clinician to the right diagnosis (►**Table 1**).

Table 1 Clinical imitators of p-aHUS

	HELLP	AFLP	TTP	aHUS
Time of onset	3rd trimester	3rd trimester	2nd and 3rd trimesters	Postpartum
Recovery after delivery	1 wk	1–2 d	No recovery	No recovery
Primary/unique clinical manifestation	Hypertension and proteinuria	Nausea, vomiting, malaise	Neurological symptoms	Renal involvement
DIC (%)	Less than 20	50–100	Rare	Rare
Acute kidney injury	Mild/moderate	Moderate	Mild/moderate	severe
Lab findings				
Hemolytic anemia	+	0/+	++	+
Partial thromboplastin time increase	0/+	+	0	0
Hypoglycemia	0	+	0	0
Thrombocytopenia ($<$100,000/mm^3)	More than 20,000	More than 50,000	20,000 or less	More than 20,000
LDH (IU/L)	600 or more	Variable	More than 1,000	More than 1,000
Elevated ammonia	0/+	+	0	0
Elevated bilirubin	0/+	+	+	NA
Liver transaminase increase	+	++	0	0
vWF multimers	0	0	+	+
ADAMTS13 $<$10%	0	0	++	+
Clinical signs/symptoms				
Purpura	0	0	+	0
Fever	0	0	+	0
Neurological findings	0	0	+	0
Hypertension	+	0/+	0/+	+
Jaundice	0/+	++	0/+	0/+
Nausea and vomiting	0/+	0/+	+	+
Abdominal pain	0/+	0/+	+	+

Abbreviations: ++, always present; +, usually present; 0/ + , occasionally present; 0, absence; AFLP, acute fatty liver of pregnancy; p-aHUS, pregnancy-associated atypical hemolytic-uremic syndrome; DIC, disseminated intravascular coagulation; HELLP, hemolysis, elevated liver enzymes, and low platelet count; LDH, lactate dehydrogenase; NA, not available; TTP, thrombotic thrombocytopenic purpura.

Owing to the high prevalence of complement gene mutations in the population, we recommend a comprehensive genetic and molecular study of the alternative complement pathway to confirm the diagnosis.

Physicians also should be aware that complement gene mutation carriers, such as our patient, have penetrance of only 40 to 50%, and confer predisposition rather than causality. Hence, detection of these mutations should not be used to predict future recurrence of the syndrome but rather to emphasize physicians for close monitoring during pregnancy and the postpartum period.

Owing to its devastating nature, we recommend starting PE within 24 hours of diagnosis without waiting for the aforementioned genetic testing or other testing (e.g., ADAMTS13), as genetic/confirmatory testing takes usually weeks before they are available. PE should be performed daily as soon as possible. We also recommend using pooled plasma from male donors to decrease the chances of transfusion-related lung injury. A multidisciplinary team consisting of maternal–fetal medicine specialists, intensivists, hematologists, and transfusion medicine pathologists should be involved in the management and long-term therapy of this patient population. Duration of PE is usually individualized on the basis of the patient's response and should be continued until complete normalization of the blood parameters (platelets $>$ 150,000/mm^3 for 2 consecutive days and normalization of LDH). In general, failure of PE is considered when there is persistent thrombocytopenia or worsening clinical status despite intervention.

Despite the initial success of PE in maintaining normal platelets counts and LDH, the abnormal pattern of complement activation and TMA are likely to persist with the risk of irreversible organ damage, primarily renal, in the subsequent weeks to months. Moreover, within 1 year of diagnosis, more than 60% of patients with acute kidney injury

Table 2 Proposed initial management of atypical HUS

Proposed initial management of atypical hemolytic-uremic syndrome
Start plasma exchange ASAP (after obtaining all pertinent laboratories such as ADAMTS 13)
Avoid transfusion of platelets prior to central line placement
Consider high-dose steroids (prednisone 1 mg/kg/d)
Start renal replacement therapy as needed for hyperkalemia, pulmonary edema, metabolic acidosis, and uremia
Transfuse packed red blood cells as needed to keep hemoglobin level >7 g/dL
If diagnosis of atypical HUS confirmed, consider prolonged therapy with complement inhibitors (eculizumab)

Abbreviation: HUS, hemolytic-uremic syndrome.

secondary to p-aHUS will progress to ESRD or succumb to the disease (6).

Eculizumab is a humanized recombinant monoclonal antibody that inhibits the terminal pathway of complement activation by blocking the activation of complement protein C5. Recent evidence among patients with p-aHUS suggests that eculizumab increased platelet counts, improved renal function, decreased the need for renal replacement therapy, and improved overall quality of life (7). The latter has led the Food and Drug Administration (FDA) to approve eculizumab for the treatment for aHUS in the United States. We have summarized initial treatment of p-aHUS in ►**Table 2.**

The diagnosis of p-aHUS remains challenging, and management should involve a multidisciplinary team and includes prompt PE. Eculizumab has improved long-term outcomes in this group population and should be considered.

Teaching Points

- Early diagnosis of atypical uremic–hemolytic syndrome is challenging often mimicking other diseases that occur during pregnancy.
- Correct diagnosis and timely management are crucial to improve outcomes.
- Management involves a multidisciplinary team, prompt PE, and Eculizumab.

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References

1 Dashe JS, Ramin SM, Cunningham FG. The long-term consequences of thrombotic microangiopathy (thrombotic thrombocytopenic purpura and hemolytic uremic syndrome) in pregnancy. Obstet Gynecol 1998;91(5, Pt 1):662–668
2 Noris M, Remuzzi G. Hemolytic uremic syndrome. J Am Soc Nephrol 2005;16(4):1035–1050
3 Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. N Engl J Med 2009;361(17):1676–1687
4 Fakhouri F, Roumenina L, Provot F, et al. Pregnancy-associated hemolytic uremic syndrome revisited in the era of complement gene mutations. J Am Soc Nephrol 2010;21(5):859–867
5 Faguer S, Huart A, Frémeaux-Bacchi V, Ribes D, Chauveau D. Eculizumab and drug-induced haemolytic-uraemic syndrome. Clin Kidney J 2013;6(5):484–485
6 Legendre CM, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med 2013;368(23):2169–2181
7 Caprioli J, Noris M, Brioschi S, et al; International Registry of Recurrent and Familial HUS/TTP. Genetics of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome. Blood 2006;108(4):1267–1279