

## **Atypical hemolytic uremic syndrome in the postpartum period: a case series**

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**Keywords:** Atypical hemolytic uremic syndrome; pregnancy complications; renal disease; maternal morbidity

### **Abstract**

*Background: Atypical hemolytic uremic syndrome (aHUS) may present in either the antepartum or postpartum period and is often indistinguishable from other pregnancy-associated diseases. Timely recognition and appropriate treatment can greatly reduce maternal morbidity and mortality.*

*Cases: This case series describes two cases of aHUS in the post-partum period, the difficulty in distinguishing the diagnosis, and the implementation of appropriate treatment with eculizumab, a terminal complement inhibitor.*

*Conclusion: As a terminal complement inhibitor, eculizumab, has been shown to significantly improve clinical and long term renal outcomes, early diagnosis of aHUS is increasingly important. These two cases of aHUS demonstrate the path of accurate diagnosis and timely initiation of therapy to maximize the possibility of patient recovery.*

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### **Introduction**

This case series describes atypical hemolytic uremic syndrome (aHUS), a rare complication in the post-partum period, which may lead to lifelong complications or even maternal mortality. Clinical signs and laboratory findings may make the diagnosis difficult due to similarities with other post-partum processes such as acute fatty liver of pregnancy (AFLP), hemolytic anemia, elevated liver enzymes, and low platelets (HELLP) syndrome and thrombotic thrombocytopenic purpura (TTP). The importance of placing aHUS on the differential in the antepartum and postpartum period is paramount for obstetricians, and care of these patients requires a multi-disciplinary approach. Newer therapies and possible genetic variants contributing to aHUS have improved outcomes and directed further care for patients. Expedient diagnosis and implementation of therapy or referral to a center that can provide care can be the difference between life or

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death for these patients.

**Case 1:**

A 30 year old G1P0 was admitted to the labor and delivery unit for a scheduled cesarean section at 39w0d gestation due to breech presentation. The patient underwent an uncomplicated procedure and delivered a healthy female infant.

The patient had an uncomplicated postpartum course until post-operative day (POD) 3. On POD3 she had general malaise, body aches, nausea and an episode of emesis. Vital signs were unremarkable. Later that day, she became acutely jaundiced. Laboratory tests revealed a white blood count (WBC) of 29.4 K/mm<sup>3</sup> and elevated total bilirubin of 25.9 mg/dL. The remainder of her liver panel laboratory values were hemolyzed on multiple draws. Peripheral blood smear was also concerning for hemolysis with many schistocytes present. Hemoglobin dropped from 11.7 to 10.4 g/dL and platelets decreased from 154 to 89 K/mm<sup>3</sup>. Her PT was 30 seconds, INR 3.1, PTT 45 seconds, and fibrinogen 67 mg/dL. LDH was 6600 U/L. She was also noted to have acute kidney injury with a creatinine (Cr) of 2.3 mg/dL. Due to concern for acute liver failure and disseminated intravascular coagulation (DIC), the patient was transferred to the Surgical and Neurosurgical Intensive Care Unit. A right upper quadrant ultrasound revealed mildly elevated extrahepatic biliary dilatation and mild hepatosplenomegaly. The initial differential diagnosis included AFLP, HELLP syndrome, atypical TTP-HUS or an infectious process. She was started on magnesium sulfate for seizure prophylaxis, which was shortly

thereafter stopped due to hypermagnesemia from decreased renal excretion. She was empirically started on piperacillin/tazobactam and acyclovir as the etiology of her disease process remained unknown and infectious causes remained in the differential diagnosis. Two units of fresh frozen plasma, two units of packed red blood cells, and one unit of cryoprecipitate were administered to correct her DIC. PRBCs were given as needed to keep her Hgb above 7.0 g/dL.

The patient was anuric over the next 24 hours and also developed encephalopathy with symptoms of fatigue, lethargy, and confusion. She was initiated on hemodialysis on POD5 due to encephalopathy, metabolic acidosis, hypervolemia, and hypermagnesemia in the setting of anuric renal failure.

As her clinical picture evolved, it appeared to be more consistent with aHUS due to progressively worsening renal failure and persistently severe thrombocytopenia. C3 complement levels were also collected and were noted to be mildly low at 83 mg/dL. She was started on eculizumab, a complement inhibitor, on POD6 as treatment for presumed aHUS. Her platelets began to rise after eculizumab initiation and recovered from 36 to 190 k/mm<sup>3</sup> within 72 hours. She was started on prophylaxis for meningitis with penicillin VK due to the complement blocking effects of the eculizumab and the complement mediated immune response required for defense from encapsulated organisms. She also received vaccinations for hemophilus influenzae, meningococcus, and pneumococcus. Eculizumab was started

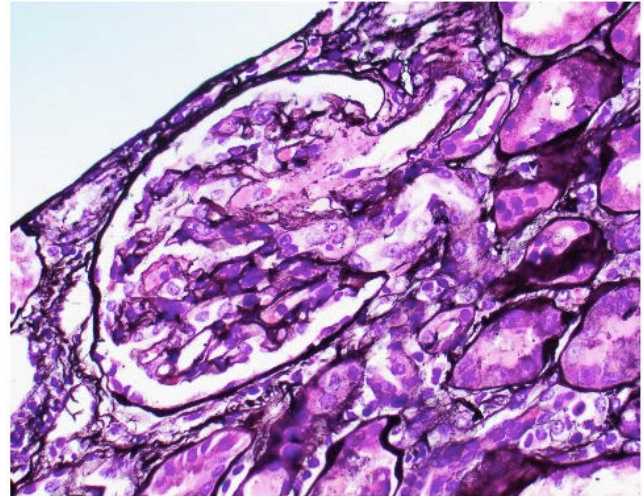
at 900 mg intravenously weekly for four weeks and then increased to 1200 mg intravenously every 2 weeks.

The hepatology service was consulted and completed an extensive work up for liver failure, which returned negative for all infectious, autoimmune, and drug related causes. ADAMST13 returned normal, ruling out TTP. Her AST/ALT reached maximum on POD4 to 1311/244 U/L and then trended downwards.

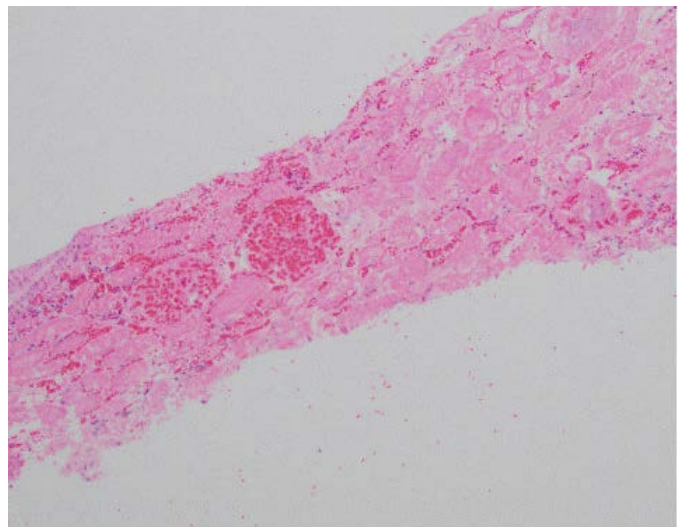
A renal biopsy confirmed the diagnosis of aHUS with findings consistent with changes of acute thrombotic microangiopathy including areas of acute tubular necrosis, fibrin thrombi in capillary loops, and cortical necrosis (Figure 1). Glomerular staining was negative for IgG, IgA, IgM, C3 and C1q, ruling out other etiologies of immunopathologic glomerulonephritis.

The patient continued to be anuric at discharge and remained on dialysis three times a week. She continued eculizumab therapy as an outpatient.

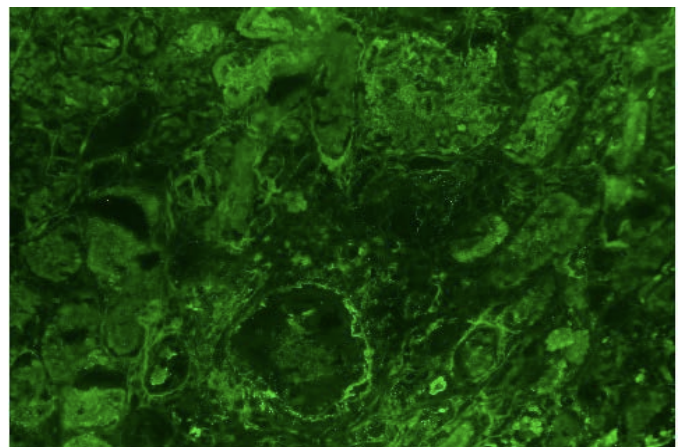
She underwent genetic testing and was not found to have a classic gene mutation for aHUS, including complement factor H (CFH), membrane cofactor protein (MCP), factor I (IF), and auto-antibodies against CFH-Ab. Her renal function did not improve with eculizumab therapy and she underwent a renal transplant six months after her initial presentation and is doing well. She continues on eculizumab therapy.



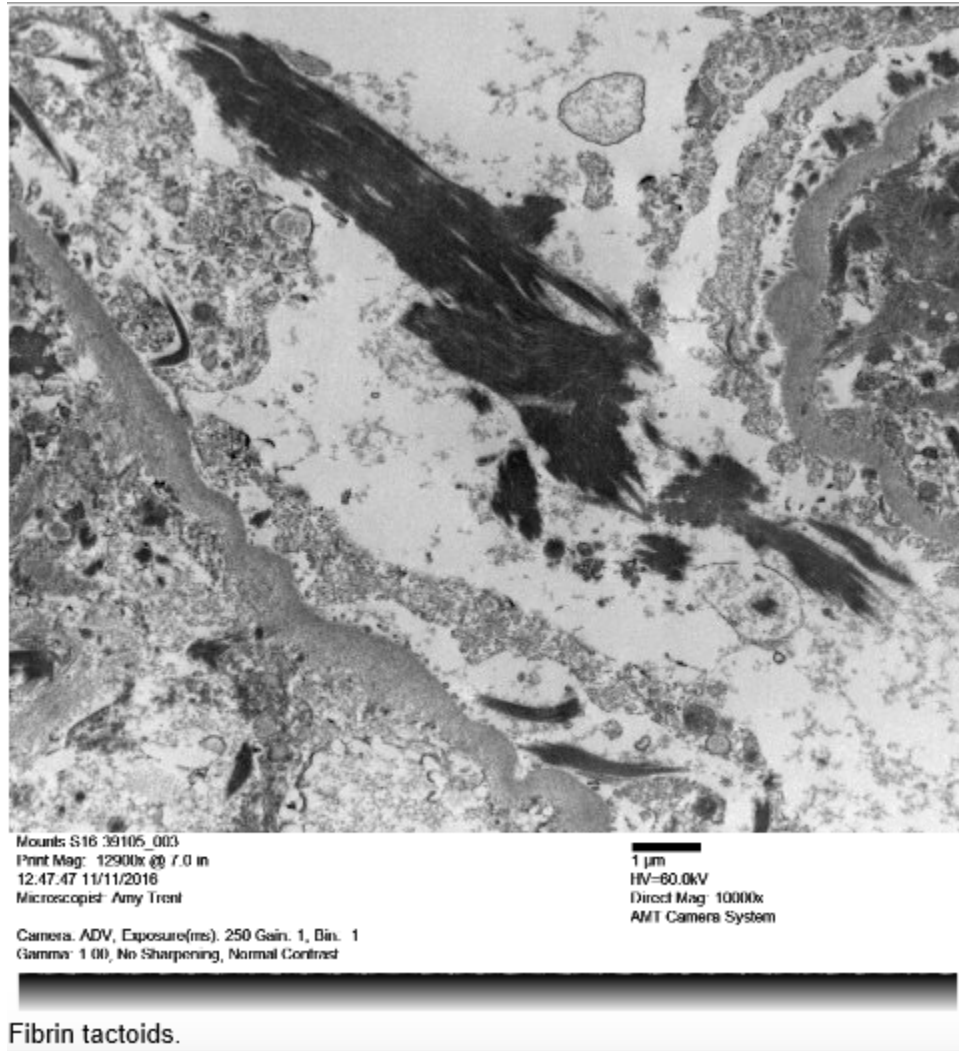
JMS: Fibrin thrombi in capillary loops.



H+E: Cortical necrosis.



Fibrin leak into vessel wall.



**Figure 1. Renal biopsy results revealing changes consistent with acute thrombotic microangiopathy and areas of cortical necrosis and acute tubular injury/necrosis.**

**Case 2:**

A 30 year old G1P0 at 34w4d presented to the labor and delivery unit due to concern for preeclampsia. She had a diagnosis of gestational hypertension and had completed a 24 hour urine protein which returned at 798 mg. She was admitted for observation due to a diagnosis of preeclampsia without severe features. At 34w6d, she had severe range blood pressures as well as elevated AST/ALT of 41/41 U/L, meeting criteria for preeclampsia with severe features. She underwent an induction of labor and was started on magnesium sulfate for seizure prophylaxis.

During her induction course, she developed epigastric pain and increasing AST/ALT of 156/147 U/L. Other HELLP laboratory values remained stable at this time with platelets  $206 \text{ K/mm}^3$  and Cr 0.7 mg/dL. The decision was made to proceed with delivery via cesarean section due to worsening preeclampsia with severe features remote from delivery. She underwent an uncomplicated procedure, producing a healthy male infant.

She was continued on magnesium sulfate for 24 hours after delivery. She continued to have severe range blood pressures, which were responsive to antihypertensive medications. HELLP laboratory values were trended every 6 hours with liver function tests reaching a maximum of AST 2993 U/L, ALT 1600 U/L. Her platelets additionally dropped to a nadir of  $40 \text{ k/mm}^3$  and her Cr rose to 1.4 mg/dL, accompanied by oliguria. Due to lower extremity numbness and a magnesium level of 8.6 mg/dL, magnesium sulfate was discontinued. Her hemoglobin also dropped from 10.1

to 7.7 g/dL, despite being given 1 unit of packed red blood cells in the interim. A RUQ ultrasound was obtained without any evidence of liver hematoma or other abnormalities.

Nephrology was consulted on POD2 due to continued rise of Cr to 3.0 mg/dL, hyperkalemia, and decreased UOP. Due to concern for TTP versus aHUS versus HELLP, complement levels, haptoglobin, LDH, ADAMTS13, and urine studies were obtained. Complement levels returned low, LDH was elevated, and haptoglobin was undetectable, concerning for thrombotic microangiopathy secondary to aHUS. The decision was made to start eculizumab therapy. ADAMTS13 did return normal at 81% (normal  $>60\%$ ), ruling out the diagnosis of TTP.

The patient's renal function continued to decline and decision was made to start dialysis due to electrolyte abnormalities. Over the next few days, her platelets significantly improved from 80 to  $105 \text{ K/mm}^3$  suggesting therapy with eculizumab was effective. She was discharged on POD8 with plans for outpatient hemodialysis twice weekly and weekly eculizumab infusions.

As an outpatient, she continued dialysis, eculizumab infusions, and follow up with Nephrology. Her creatinine improved, platelets returned to normal range, and her C3 normalized to  $>100 \text{ mg/dL}$ . Dialysis was eventually stopped due to renal recovery. She underwent genetic testing which returned negative for any causative variants for aHUS. She currently continues on eculizumab treatment.

## **Conclusion**

aHUS has death rates as high as 25% and progression to end stage renal disease (ESRD) as high as 50%.<sup>1</sup> As the two above case reports demonstrate, these outcomes make it important to recognize aHUS early, so the appropriate interventions can be made (Table 1). aHUS can be very difficult to differentiate from other diseases such as HELLP, AFLP, and TTP due to a significant overlap in symptoms and laboratory abnormalities.<sup>2</sup> Of these diagnoses, TTP is unique in that it can often be differentiated, as it is generally related to an ADAMTS13 deficiency and most commonly occurs in the 2nd trimester.<sup>3</sup>

Thrombotic microangiopathy (TMA) describes the process of endothelial cell injury and thrombus formation in the microvasculature. This leads to hemolytic anemia, non-immune thrombocytopenia, and organ failure.<sup>3</sup> TMA has been shown to occur in 1 per 25,000 pregnancies and is a classic feature associated with HUS.<sup>4</sup> Classically, HUS is associated with bacterial infections with Enterohemorrhagic Escherichia Coli (EHEC). All non-EHEC-associate HUS is referred to as atypical HUS (aHUS).

aHUS is often expressed in the setting of genetic or autoimmune defects in the complement system in combination with underlying complement amplifying conditions, including pregnancy and its complications. This is referred to as the 'multiple-hit' hypothesis.<sup>3</sup> In the postpartum period, complement may be activated by maternal circulation of fetal cells, infection, hemorrhage, preeclampsia, and/or HELLP.<sup>4</sup>

Underlying mutations in complement regulators or activators such as complement factor H (CFH), membrane cofactor protein (MCP), factor I (IF), and auto-antibodies against CFH-Ab are associated with aHUS.<sup>1,5</sup> CFH, the main mediator of the alternative pathway of complement, is the most common genetic mutation in aHUS.<sup>3,5,6</sup> Patients with an underlying complement defect are more susceptible to developing TMA.<sup>1</sup>

Caprioli et al. completed a study of genetic analysis for CFH, MCP, and IF in 156 patients with aHUS.<sup>5</sup> Approximately 56% of these patients did not have any of these three mutations. This study determined that screening for known mutations in patients with aHUS may determine the success of subsequent renal transplant if needed. Patients with MCP mutations were found to have a remission rate of 80-90% without treatment and to have the best prognosis.<sup>1</sup> MCP is a transmembrane protein highly expressed in the kidney, which supports the idea that renal transplant would cure the disease. In the case of CFH and IF, these factors are mostly synthesized in the liver and recurrence rate for aHUS with these mutations is very high, approaching 100%, suggesting that a renal transplant may not be successful. Caprioli et al. found that 6/7 patients with CFH and IF mutations had graft failure due to disease recurrence and 2/2 patients with MCP mutations had a successful renal transplant.<sup>5</sup> These data suggest that genetic screening in patients with aHUS may be important in counseling for recurrence and prognosis as well as determining successful renal transplant in those with ESRD. In our

cases, testing was completed at the Molecular Otolaryngology and Renal Research Laboratory at the University of Iowa. Both of the above patients underwent genetic testing and did not have evidence of a classical genetic mutation for aHUS. Therefore, for the patient in case 1, the recommendation was made for her to undergo renal transplantation from a non-related donor in the event there is an unknown genetic component to her aHUS.

Multiple studies have described the use of plasma exchange therapy immediately after diagnosis of aHUS until hematologic parameters stabilize, followed by eculizumab therapy with good overall outcomes and renal recovery.<sup>2,7</sup> It is thought that plasma exchange significantly increases survival rates by transiently correcting laboratory abnormalities, but ultimately complement inhibitors are necessary to improve renal recovery by inhibiting the underlying complement dysregulation.<sup>7</sup> Before the advent of eculizumab, plasma therapy was considered the mainstay of treatment with good survival rates but high rates of morbidity associated with end stage renal disease.<sup>1</sup> Eculizumab is a humanized monoclonal antibody that arrests complement activation and progression of TMA by binding with high affinity to human C5 complement protein and preventing pro-inflammatory complement formation. Use of this therapy can lead to recovery of renal function over time, with the possibility of discontinuation of dialysis and avoidance of renal transplant, as noted in case 2.<sup>8</sup> In a randomized control trial by Legendre et al. of 37 patients receiving eculizumab for aHUS, results

revealed that eculizumab was associated with significantly improved clinical outcomes and that the sooner eculizumab is started, the better the improvement in renal function.<sup>8</sup> This same study also found similar outcomes for patients regardless of treatment with plasma exchange.<sup>8</sup> In our cases, the patients were started on eculizumab at different times. The first patient was started on POD6, as soon as disease progression revealed that aHUS was the more likely process due to persistent thrombocytopenia and worsening of renal function. The second patient was started on eculizumab on POD2 due to early suspicion of aHUS. The different renal function outcomes for each patient may support that earlier initiation of eculizumab, despite an unclear clinical picture, can be beneficial to the patient. Though it is important to consider that eculizumab can be cost prohibitive, at around \$18,000 per dose, and has immunosuppressive properties, making correct diagnosis important.

aHUS in the post-partum period is associated with significant maternal morbidity and mortality. Early diagnosis can be difficult due to overlap with other disease processes. These case reports demonstrate the importance of early diagnosis of aHUS and early administration of eculizumab (Table 1). When aHUS is considered a possible diagnosis, it may be beneficial to begin eculizumab therapy as early initiation has been shown to significantly improve outcomes. Genetic testing can be helpful in determining recurrence risk as well as outcomes of renal transplantation and should be considered for all patients with aHUS. For these patients, future pregnancies

are not recommended as the recurrence of aHUS can be high.

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**Table 1: Clinical presentation**

Patient	Presentation	Liver function	Platelet nadir/recovery after treatment	Initial Hgb drop	Renal function	Complement Function	Treatment	Genetic testing
<b>30 yo G1P0 s/p PLTCS for breech presentation at 39w0d</b>	Acute jaundice on POD3	AST 1311 ALT 244	Plts 36 -> 190	Hgb 11.7 -> 10.4	<ul style="list-style-type: none"> <li>• Anuria</li> <li>• Electrolyte abnormalities</li> <li>• Renal biopsy with acute thrombotic microangiopathy</li> <li>• Dialysis</li> <li>• Renal transplant</li> </ul>	<ul style="list-style-type: none"> <li>• Complement mildly low</li> </ul>	Eculizumab started on POD6	Negative
<b>30 yo G1P0 s/p PLTCS for worsening PET at 34w6d</b>	PET -> worsening renal function on POD2	AST 2993 ALT 1600	Plts 40 -> 105	Hgb 10.1 -> 7.7	<ul style="list-style-type: none"> <li>• Low UOP</li> <li>• Electrolyte abnormalities</li> <li>• Dialysis</li> <li>• Full recovery</li> </ul>	<ul style="list-style-type: none"> <li>• Complement Low</li> </ul>	Eculizumab started on POD2 at initial suspicion	Negative