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CASE REPORT

# Diapers and Dialysis: A Case Report on Postpartum Atypical Hemolytic Uremic Syndrome

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## Abstract

**Background:** While thrombotic microangiopathy (TMA) syndromes such as thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS) and atypical hemolytic uremic syndrome (aHUS) present similarly with hemolytic anemia, thrombocytopenia, and renal injury, their etiology and treatment differs. This poses challenges to prompt diagnosis and treatment. This becomes increasingly difficult in the peripartum setting due to considerable overlap between TMA and hypertensive disorders of pregnancy, and delays can ultimately have profound adverse effects on long-term outcomes.

**Case:** We describe a woman who was diagnosed with atypical hemolytic uremic syndrome in the postpartum period six days after hospital admission and was started on eculizumab. While she was eventually scheduled for outpatient eculizumab infusions, she left against medical advice on hospital day seven before her renal function and hemolysis labs improved.

**Conclusion:** This case demonstrates the importance of timely diagnosis for TMA syndromes such as aHUS. In order to promptly treat patients, delays in diagnostic criteria should be minimized to optimize patient outcomes.

## Introduction

Microangiopathic hemolytic anemia (MAHA) is a term that describes non-immune hemolytic disorders that occur in conjunction with small vessel disease [1]. Thrombotic microangiopathies (TMA) are characterized by MAHA in addition to thrombocytopenia and thrombotic lesions in small vessels causing ischemic injury [1,2]. The three most common microangiopathies are thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and atypical HUS (aHUS) [3]. While these syndromes present similarly with a common triad of hemolytic anemia, thrombocytopenia, and renal injury, the etiology and treatment of each differs. TTP is due to a severe deficiency of the enzyme ADAMTS-13, and it is treated with plasma exchange [1]. HUS occurs following infection with Shiga toxin-producing *Escherichia coli*, and it is treated by supportive care measures including fluids. aHUS is associated with deregulated complement systems, and is treated with eculizumab, a terminal C5 complement inhibitor [1,2].

While aHUS occurs in 0.23 to 1.9 per million in the general population, the most recent estimates for pregnancy-associated aHUS are from 1998, reporting an incidence of 1 in 25,000 pregnancies and commonly occurring after obstetric complications [4-6]. The pathogenesis of pregnancy-associated aHUS associated with defects in complement regulatory systems, which may be unmasked during pregnancy, a compliment-amplifying state [5,7]. aHUS frequently progresses to end-stage renal disease (ESRD), and is important to diagnose and treat early to maximize renal recovery

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and prevent long-term dialysis or kidney transplant [5]. Here we present a case of aHUS in a patient one week after Cesarean delivery and highlight the challenges of diagnosis and treatment, especially in postpartum patients.

## Case Description

A 27-year-old G7P1224 with a reported history of preeclampsia in prior pregnancy and poor prenatal care presented to the emergency department with shortness of breath, nausea, and vomiting on post-operative day 9 status post primary Cesarean delivery. This pregnancy was complicated by poor prenatal care, and her labor course was complicated by breech presentation at 32 weeks' gestation. She developed post-operative ileus and left against medical advice on post-operative day 4. She had not had a bowel movement or been able to tolerate a diet since before her Cesarean delivery. In the emergency department her labs were notable for hemoglobin 2.5 g/dL (reference range 12.3-15.3 g/dL), platelets 15 k/mcL (reference range 145-445 k/mcL), and creatinine 14.72 mg/dL (reference range 0.5-0.9 mg/dL), uric acid 16.7 mg/dL (reference range 2.4-5.7 mg/dL), reticulocytes 6.47% (reference range 0.5-2.0%), urine protein-to-creatinine ratio 2.67 mg/mg creatinine (reference range < 0.18 mg/mg creatinine), PT 17.0 seconds (reference range 11.8-14.3 seconds), INR 1.4 (reference range 0.9-1.1), LFTs within normal limits. Patient was tachycardic but otherwise hemodynamically stable. She received blood and platelet transfusions with a rise in hemoglobin to 6.0 g/dL and platelets to 62 k/mcL. She endorsed small blood clots in her emesis and normal postpartum bleeding, filling only one pad per day. She denied hematuria, rectal bleeding, or large-volume vaginal bleeding. She did endorse lightheadedness, fevers, and chills. She had no recent diarrheal illness and no previous acute renal injury, renal failure, or chronic renal disease. Her most recent creatinine six days prior to this admission at 0.54 mg/dL.

The patient was admitted to internal medicine, and further work-up revealed LDH 3421 U/L (reference range 110-216 U/L), haptoglobin < 10 mg/dL (16-200 mg/dL), negative DAT, and marked schistocytes on blood smear. LFTs were within normal limits. There was no overt bleeding noted on exam. C3 was 138.9 mg/dL (reference range 85.0-193.0 mg/dL), C4 was 27.3 mg/dL (reference range 12.0-36.0 mg/dL). Further work-up including blood cultures, anti-neutrophil cytoplasmic antibodies panel, serum B12 level, anti-parietal antibody, intrinsic factor, cardiolipin antibody, phosphatidylserine antibodies, beta-2 glycoprotein antibodies, hepatitis B surface antigen, hepatitis B core antibody, DRVVT, and hexagonal phospholipid panel were all unremarkable. Given evidence of hemolysis and marked renal injury, there was concern for a diagnosis of TMA. PLASMIC score was calculated at 6, and ADAMTS-13 activity level was ordered to evaluate for TTP.

On hospital day two the patient was started on empiric plasma exchange and steroids while ADAMTS-13 activity levels were pending. Her creatinine remained elevated, and she was persistently oliguric and uremic, therefore hemodialysis (HD) was initiated. Subsequently, it was noted her nausea and vomiting had resolved. Additionally, the patient developed new hypertension and was started on amlodipine and carvedilol.

The patient's hemoglobin and platelet values continued to downtrend throughout her hospitalization despite plasmapheresis and she continued to require regular packed red blood cell (pRBC) and platelet transfusions to maintain hemoglobin > 7 mg/dL and platelets > 10 k/mcL. LDH down-trended but haptoglobin remained persistently < 10 mg/dL despite plasmapheresis. On hospital day six, the patient underwent renal biopsy which revealed arteriolar thrombosis with segmental necrosis and moderate arteriolar hyaline arteriolosclerosis, consistent with a TMA syndrome. Given the patient's marked renal injury, new-onset hypertension, and continued hemolysis despite plasmapheresis, the patient was diagnosed with aHUS. Plasmapheresis was discontinued. On hospital day six, ADAMTS-13 activity level resulted at 56.8% (reference range > 66.8%), confirming the diagnosis of aHUS. Meningococcal vaccines were administered, the patient was started on penicillin prophylaxis, and the patient received one eculizumab treatment for aHUS.

Due to a lack of renal recovery, a tunneled dialysis catheter (TDC) was inserted and outpatient dialysis was arranged. On hospital day seven, the patient left against medical advice (AMA) prior to her second dose of eculizumab despite ongoing HD due to symptomatic improvement and a desire to return home with to her children. She continued outpatient HD twice weekly with markedly improved renal function. Nineteen days after discharge she developed gram positive bacteremia and her TDC was removed without need for further HD. She was treated with IV vancomycin and cefepime for six days then discharged with oral linezolid. At the time of this case report, the patient is status post three eculizumab treatments and has achieved partial hematologic remission with hemoglobin 8.7 mg/dL, platelets 356 k/mcL, LDH 334 U/L, and haptoglobin 102 mg/dL.

## Conclusions

This case is interesting because it highlights the challenging diagnosis of a TMA syndrome, especially in a postpartum patient. There is considerable overlap between hypertensive disorders of pregnancy and TMA. While she was reportedly normotensive during this pregnancy, our patient had poor pre-natal care and did report a history of pre-eclampsia in previous pregnancies for which she was on magnesium sulfate for

seizure prophylaxis. Indeed, the clinical picture of new-onset hypertension, proteinuria, renal insufficiency, and thrombocytopenia in a postpartum patient is concerning for pre-eclampsia, which can confound the TMA triad of renal insufficiency, thrombocytopenia, and hemolytic anemia [8].

Furthermore, it can be difficult to distinguish between TTP and aHUS, and prompt, diagnosis-specific treatment is essential to maximize long-term outcomes. To help address this, the PLASMIC score was developed. The PLASMIC score evaluates a number of criteria including thrombocytopenia, hemolysis, and creatinine to predict severe ADAMTS-13 deficiency, thus identifying patients who could benefit from empiric plasma exchange therapy [9]. Our patient's PLASMIC score was 6, indicating high risk for TTP. While we did initially favor aHUS over TTP due to our patient's marked renal injury and new-onset hypertension, it was appropriate to start empiric treatment with plasma exchange therapy while results were pending. While it is important to start eculizumab promptly when a diagnosis of aHUS is established, aHUS remains a diagnosis of exclusion and TTP should be ruled out with ADAMTS-13 activity levels first [10].

Delays in initiating the correct treatment can be devastating, leading to ESRD, dialysis, and kidney transplant. While aHUS is similar in presentation to TTP, it's pathophysiology, and thus its treatment, vastly differs. TTP is caused by an inherited mutations of the ADAMTS-13 gene or acquired anti-ADAMTS-13 antibodies. The resulting enzyme deficiencies cause large von Willebrand factor multimers to form, resulting in hemolytic anemia and ischemic tissue injury [2]. TTP benefits from therapeutic plasma exchange (plasmapheresis), which removes anti-ADAMTS-13 antibodies and replaces the ADAMTS-13 enzyme. In contrast, as a complement-mediated disorder, aHUS benefits from a different approach. Patients with aHUS typically have genetic or acquired defects in the alternative complement pathway (AP). The complement system is a group of proteins that, when activated, triggers a cascade of reactions, including the formation of C5 convertase (C3bBbC3b) [11]. C5 convertase then generates C5a and C5b, and C5b ultimately binds to complement proteins C6, C7, C8, and C9 to create membrane attack complex (MAC), C5b-9. MAC then directly causes cellular lysis [11]. There are many genetic variants both related to aHUS, but they ultimately result in complement dysregulation and red blood cell hemolysis. aHUS is usually inherited in an autosomal dominant manner with incomplete penetrance of approximately 50%, which can explain the need for an environmental trigger such as infection, medications, or, as demonstrated in this patient, pregnancy [10]. In pregnancy, the complement system is up-regulated, and this may unmask defective complement regulation [8]. Originally designed to treat paroxysmal nocturnal hemoglobinuria, eculizumab is a human monoclonal antibody that inhibits the cleavage of C5 into C5a and C5b, thus preventing the formation of the C5b-9 MAC complex and ultimately preventing red blood cell hemolysis [12]. It is not surprising, then, that treatment of aHUS with plasmapheresis results in only minimal or transient resolution of hemolysis, as demonstrated by our patient. However, although eculizumab is now considered a first-line therapy, it was only recently FDA-approved for the treatment of aHUS in 2011, and pregnant women were excluded from clinical trials [5].

There are additional barriers to obtaining eculizumab. Most notably, it is expensive, and normal ADAMTS-13 levels are often required by insurance companies for coverage. This is exacerbated by turnaround times for ADAMTS-13 testing, which may be limited. Delays in ADAMTS-13 activity levels may drastically change patient outcomes, contributing to the need for lifelong HD or kidney transplant. Our patient's ADAMTS-13 levels, for example, were sent for analysis on hospital day two and did not result until hospital day six, in part because of a holiday weekend. This delayed both her diagnosis and the initiation appropriate treatment, which in addition to potentially worsening her prognosis, extended her hospital stay and contributed to her decision to leave AMA before we were able to see improvement in her hemolysis labs.

Recent insights into the pathophysiology of TMA syndromes such as TTP and aHUS have distinguished them as separate entities with distinct etiologies and treatments. However, the diagnosis of aHUS remains a challenge. It is rare, has overlapping features with TTP, and ultimately remains a diagnosis of exclusion. Because prompt treatment is crucial for long-term outcomes, a high suspicion for aHUS should be held for patients with TMA, especially in peripartum patients.

## Authors Contribution

All authors have contributed equally to the work.

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