Atypical hemolytic uremic syndrome: when pregnancy leads to lifelong dialysis: a case report and literature review

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Atypical hemolytic uremic syndrome (aHUS), a challenging disorder, commonly caused by inherited defects or regulatory processes of the complement alternative pathway. There are multiple causes, including pregnancy. Pregnancy provokes life-threatening episodes, preeclampsia, hemolysis elevated liver enzymes low platelets, microangiopathic hemolytic anemia (MAHA) and end-stage renal disease. Additionally, complement dysregulation and, with aHUS, affects fetal and maternal outcomes. Pregnancy-associated aHUS results in a poor prognosis with irreversible renal damage. Likewise, it is imperative to know that MAHA can provoke endothelial disruption, destruction of red cells and thrombocytopenia. We present a case of a young 18-year-old woman with MAHA and aHUS, requiring emergent cesarean section at 34 weeks of gestation and hemodialysis, secondary to complications from a recent pregnancy. Elevated blood pressure readings, rising creatinine levels, as well as her mother being on dialysis after pregnancy raised suspicion for thrombotic microangiopathy and aHUS. She was subsequently managed with plasma exchange, steroids, eculizumab and hemodialysis. Thus, plasma exchange should be initiated, with pending additional workup. Upon a definitive diagnosis of aHUS, eculizumab would be warranted to mitigate immune dysregulation. Understanding thrombotic microangiopathies diagnosis, and recognizing concomitant consequences, is vital. Having better insights into endothelial injuries can prevent unfortunate outcomes. *Cardiovasc Endocrinol Metab* 10: 225–230 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Hemolytic uremic syndrome (HUS) is characterized by a triad of nonimmune intravascular hemolytic anemia, thrombocytopenia and acute kidney injury (renal failure) [1,2]. Whereas HUS is categorized as typical, from Shiga toxin-producing *Escherichia coli* infection, atypical HUS is from uncontrolled complement activation or secondary HUS with a coexisting disease [2]. Atypical HUS (aHUS) encompasses various causes, including *Streptococcus pneumoniae*, viral (HIV and influenza) infections, autoimmune diseases (systemic lupus erythematosus and antiphospholipid syndrome), medications (calcineurin inhibitor, chemotherapy, antiplatelet agents, oral contraceptives), pregnancy and cobalamin deficiency [1]. Several genetic mutations, which involve complement factors H, B and I and membrane cofactor protein, have been identified in both familial and sporadic aHUS cases [1]. Pregnancy presents a challenge for the maternal immune system because of the need to protect the fetus from pathogens while preventing alloimmune injury by facilitating tolerance to paternal antigens [3]. The challenge is within the feto-maternal interface in the placenta and requires control of adaptive and innate immunity, including the complement system, as exemplified by women with aHUS. Atypical HUS is a disorder most caused by inherited defects of the alternative pathway of the complement or the process that regulates it, and pregnancy can provoke life-threatening episodes [4,5]. Pregnancy-related aHUS affects 1 in 25 000 pregnancies in the general population, which contrasts with an incidence of 20% in women with preexisting aHUS to cause significant maternal mortality and morbidity [6,7]. Preeclampsia, eclampsia and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome are strongly linked to complement dysregulation and consequently to aHUS, which complicates fetal outcomes [4].

Case presentation

An 18-year-old African American woman was admitted to medical ICU (MICU) for hypertensive urgency after she missed her hemodialysis session, where she was found to have blood pressure 202/141 mmHg. Her medical history includes epilepsy, hypertension, atypical hemolytic uremic syndrome and end-stage kidney disease, currently receiving dialysis via subclavian catheter. She reported no symptoms; physical examination was unremarkable.

Nifedipine drip and hydralazine were initiated for hypertensive urgency in the MICU. The hospital's nephrology service was consulted to evaluate the patient and resume hemodialysis. Her blood pressure was normalized after a single dialysis session. She was later transferred to the pediatric floor and soon discharged to a new local dialysis center for continued management.

Medical records from previous admissions showed the patient was diagnosed with aHUS, possibly due to genetic factors and prior pregnancy complications. This patient is a G1P1 with a pre-term delivery at 34 weeks gestational age, secondary to preeclampsia and HELLP syndrome, which required emergent cesarean section. Postpartum, she was diagnosed with MAHA and aHUS, with ADAMTS13 level 75%. At that time, she declined plasmapheresis and discharged with pulse-dose steroids, with a creatinine of 2 mg/dl. Her family history is notable for her mother, who had preeclampsia/HELLP spectrum illness and required dialysis postpartum.

As per hospital notes, approximately 5 weeks after discharge from that admission, she again had recurrent MAHA with thrombotic microangiopathy manifested by acute renal failure with peaked creatinine of 18.85 mg/dl. Uremic symptoms persisted with nausea and vomiting. She was started on plasma exchange with two sessions of PLEX and treated with eculizumab. A total of three units packed red blood cells were given during admission to normalize hemoglobin 8.6 mg/dl. Of the immunology workup, ANA (antinuclear antigen)was positive (Table 1). Renal ultrasound revealed the medical renal disease. No other pathology was identified. Eculizumab was continued with biweekly hemodialysis.

Discussion

This unique case demonstrates the importance of understanding thrombotic microangiopathies (TMA) as a diagnosis while also recognizing concomitant consequences during pregnancy. Pregnancy is a critical condition for women with aHUS because of its well-documented ability to trigger episodes of TMA with irreversible renal failure [3]. While the presence of endothelial cell injury is important in all subtypes of aHUS, the mechanisms linking etiological triggers and mutations affecting complement proteins are poorly understood, which makes it an active focus for many researchers [8]. This implies there may be more than one mechanism, likely involving the alternative complement pathway, classical pathway, and mannose-binding lectin/mannose-binding lectin associated serine protease pathway [8]. For example, vascular injury and renal thrombotic microangiopathies are seen associated with connective tissue disorders, including systemic lupus erythematosus, antiphospholipid syndrome, anti-endothelial cell antibodies, humoral rejection of renal allografts, viral and bacterial infections [8].

Table 1 Results of factors

Tested for:	Result
ADAMTS13 activity	Negative
ANA (antinuclear antibody)	Positive
ANCA (anti-neutrophil cytoplasmic antibody)	Negative
Anticardiolipin antibody	Negative
Anti-SCL 70	Negative
Beta 2 glycoprotein	Negative
C3	Negative
C4	Negative
Dilute Russel viper	Negative
G6PD	Negative
Lupus anticoagulant	Negative
RF (rheumatoid factor)	Negative
RNA polymerase	Negative
TT inhibitor	Negative

TMA syndromes, such as typical HUS, aHUS, TTP and ITP, share specific clinical characteristics, which include microangiopathic hemolytic anemia (MAHA), thrombocytopenia and pathologic endothelial cell damage, resulting in ischemic end-organ injuries [9]. Genetic or acquired regulation defects of the alternative complement pathway result in aHUS [5]. Manifestations range from mild hematologic abnormalities to severe (life-threatening) end-organ damage (gastrointestinal bleeding, seizure, blindness, or acute kidney injury) [10]. Secondary TMA syndromes may be characterized by clinical manifestations like those of aHUS, with specific causes [10]. Distinguishing between aHUS and secondary TMA syndromes remains challenging, with similar manifestations but different treatment strategies [10].

Thrombotic thrombocytopenic purpura (TTP) is a systemic disease characterized by platelet aggregation into widespread platelet thrombi and resulting occlusion of the body's microvasculature [11]. This disease is closely related to and overlaps with hemolytic uremic syndrome within the broader definition of TMAs [9]. Historically, TTP has had mortalities as high as 90% when left untreated [12]. Prompt recognition and initiation of early therapy have drastically reduced that mortality rate to 10–20% [13,14]. Although the timing may be variable, the onset of the disease is often sudden and can be preceded by a prodromal episode of flulike symptoms [15,16]. The classic pentad of fever, hemolytic anemia, thrombocytopenia, renal impairment and neurologic manifestations is not universal, stressing the importance of high clinical vigilance in recognizing and treating this disease [12–16]. Given presentations that are well short of the classically described pentad of symptoms, a more accurate definition for TTP is MAHA and thrombocytopenia without other explanation [16,17]. Hemolytic anemia may cause jaundice or darkened urine, whereas thrombocytopenia may result in ecchymosis, petechiae, purpura or other forms of bleeding [18]. Depending on the organs affected, patients can present with neurologic deficits, signs of heart failure or abdominal tenderness [18]. The cascading pathophysiology of TTP is related to the deficiency of a von Willebrand factor (vWF) cleaving protease known as ADAMTS13, which regulates the cleaving of

large vWF multimers into smaller proteins [18]. Without ADAMTS13, the accumulation of vWF attracts and binds platelets, which results in widespread platelet aggregation with thrombi in the microvasculature of the body and leads to end-organ damage [19]. Pregnancy is a known precipitant of TTP and can potentially unmask hereditary TTP [20]. TTP can present at any time in the prepartum period but is more common in the second and third trimesters. After considering preeclampsia, eclampsia and hemolysis, elevated liver enzyme levels, low platelet count (HELLP) in the perinatal mother, the evidence support a similar treatment approach in pregnancy [21]. Plasma exchange remains the standard treatment, and delivery should be considered early [22].

Immune thrombocytopenic purpura (ITP) is an acquired immune-mediated syndrome characterized by isolated thrombocytopenia and increased risk of bleeding [18]. It is classified as primary ITP, a diagnosis of exclusion without an inciting cause or secondary ITP with an underlying condition or medication that drives the immunologic response resulting in platelet degradation [18]. Although highly variable, mucocutaneous bleeding is the most common clinical presentation, with petechial or purpuric rash on lower extremities with areas of constriction that are common and tend to appear and recede over days [23]. In one study of 245 ITP patients, 28% were asymptomatic, 60% had purpura and 12% presented with gross bleeding [24–26]. In chronic ITP, patients report fatigue because of increased inflammatory cytokines, anemia and steroids used in treatment [18]. Paradoxical thrombosis is also a potential presentation for chronic ITP [18]. The loss of platelets is due to increased platelet destruction and inhibition of megakaryocyte platelet production [27]. It is mediated by specific IgG autoantibodies from B lymphocytes against platelet membrane proteins (GPIIb/IIIa) [18]. Bleeding and infection represent the most serious complications [24]. Intracranial hemorrhage and gastrointestinal bleeding are most significant and, although platelet counts do not directly correlate with bleeding, most spontaneous life-threatening bleeding occurs when platelet counts are less than 10 000/mm^3 [18]. The mortality from hemorrhage is approximately 1% in children and 5% in adults if left untreated [18].

Disseminated intravascular coagulation (DIC) is an acquired systemic process of overstimulation of the coagulation pathway resulting in thrombosis, followed by consumption of platelets and coagulation factors and ending in hemorrhage [18]. DIC can be acute and decompensated when the generation of clotting factors cannot match excessive consumption, or chronic and compensated when clotting factor consumption is matched by production [18]. Acute DIC has a rapid onset of bleeding in more than 64% of cases [28]. Bleeding from more than three unrelated sites is highly suggestive of DIC [29]. Acute renal failure, jaundice, acute respiratory distress, thromboembolism, coma, delirium, headache, neurologic deficits and shock can be present. DIC is a clinical diagnosis, but laboratory data can aid in the presumptive diagnosis [18]. Platelets, fibrinogen and antithrombin III will be decreased, while fibrin degradation products, D-dimer, partial thromboplastin time and prothrombin time will be elevated [29]. The prognosis for those with DIC is poor, and up to 50% of patients will die [18]. DIC from sepsis has a significantly higher death rate than DIC associated with trauma [18]. Acute DIC requires admissions, aggressive resuscitation, and treatment of the underlying cause [18].

Heparin-induced thrombocytopenia (HIT) occurs after the initiation of heparin and is divided into two distinct processes [18]. Type 1 is clinically benign, nonimmune-mediated and a direct medication mediated effect [18]. Type 2 is a life-threatening and limb-threatening immune-mediated process with the formation of antibodies against heparin platelet factor 4 complex (PF4) [30]. Patients are often asymptomatic with unexplained thrombocytopenia 4–10 days after heparin exposure [18]. Spontaneous bleeding is unusual, but paradoxical venous thrombosis with thrombocytopenia is described [31]. The overall incidence is less than 3% and increases with the duration of heparin exposure [18]. If heparin treatment is greater than 4 days, the incidence increases to 15%, whereas the incidence is 0.2% if heparin treatment is less than 4 days [30]. Diagnosis begins with a history of heparin exposure, thrombocytopenia or decrease in platelet count greater than 50% from baseline preceding heparin use [18]. Supporting laboratory data include the gold standard serotonin release assay, an ELISA immunoassay for PF4, particle gel assay or heparin-induced platelet aggregation assay [18,32].

HELLP and preeclampsia in pregnancy are also common microangiopathies [33]. HELLP is a syndrome of MAHA, elevated liver enzymes and low platelet counts during the third trimester of pregnancy [33,34]. Preeclampsia occurs as new onset of hypertension with either proteinuria or end-organ dysfunction after 20 weeks gestation in a previously normotensive woman [33,34]. Signs and symptoms include severe hypertension, persistent/severe headache, visual disturbance, epigastric pain, nausea, vomiting and altered mental status [33,34]. MAHA and thrombocytopenia are severe complications [33–36].

In acute aHUS, as diagnosed in this case, the pathologic picture is capillary thrombosis [37,38]. Glomerular capillary wall thickening is from endothelial cell swelling and accumulation of flocculent material within endothelial cells and basement membrane [37,38]. Platelet and fibrin thrombi occlude glomerular capillaries [37,38]. Fibrinoid necrosis of the afferent arteriole with thrombosis may be seen [37,38]. Mesangiolysis occurs early in the disease process and subsequently replaced by sclerotic changes [37,38]. Early arterial changes are variable, ranging from mild endothelial swelling to fibrinoid necrosis with occlusive thrombi formation [37,38]. There is mucoid intimal hyperplasia with vessel lumen narrowing

[37,38]. Complement, fibrin, and immunoglobulin deposits are found in glomeruli, mesangium and capillary loops, respectively [37–41].

The pathogenesis of all subtypes of aHUS reflects increased production of the terminal complement components, C5a, C5b and subsequently C5b-9, from enhanced alternative pathway activation by defective regulation or excess activation [8,33]. This has been supported by one study evaluating the elevated soluble C5adesArg and C5b-9 in serum of patients with active aHUS. In rats, CD59, the inhibitor of C5b-9, protected glomerular endothelial cells from immune-mediated TMA [8]. To demonstrate the histologic and phenotypic simulation of human HUS, increased platelet and fibrin deposition secondary to neutralization of CD59 in rats with goat anti-rat IgG antibody resulted in endothelial cell injury and reduced renal function [42].

Endothelial damage caused by TMA can induce elevated blood pressure. Severe hypertension, such as in the case presented, can result in progressive endothelial damage and renal vasculature dysfunction, with fibrinoid necrosis of arterioles and glomerular capillary tufts [43,44]. Patients with hypertension-associated TMA should undergo aggressive blood pressure control and supportive treatments to resolve TMA and prevent further kidney injury [45]. Here, the patient received nifedipine drip and continuous blood pressure monitoring. Additionally, in a retrospective case series study, genetic predisposition of the alternative complement pathway was identified in hypertensive patients with TMA [10,43,46].

The goal, as presented in this case, is to manage aHUS in pregnancy by the ability to minimize TMA risk and mitigate further injury [3]. Although both secondary TMA and aHUS require the removal of triggering factors, aHUS need correction of complement dysregulation [10]. Without appropriate treatment, patients can develop ESRD despite blood pressure control secondary to dysregulation of the alternative complement pathway, which can cause renal impairment in patients with malignant hypertension [10,43]. Current treatment protocols for aHUS are based on plasma exchange/infusion [10]. Two approaches have been suggested: prophylactic infusions of fresh frozen plasma (FFP), coupled with plasma exchange recommended for patients with TTP or expectant management with immediate treatment with eculizumab due to its safety, especially in those with paroxysmal nocturnal hemoglobinuria and in small number of patients with pregnancy-associated aHUS [47–58].

Empiric plasma therapy is recommended while waiting for pending Shiga toxin, ADAMTS13, anti-CFH autoantibody, and genetic testing [59–61]. Plasma therapy can be administered via plasma infusion or plasma exchange [10]. Functional complement regulating proteins are supplied by plasma infusion with FFP [10]. The effect of plasma infusion is limited in a small number of patients with complement factor H deficiency [60]. Plasma exchange replaces absent or defective complement regulators and removes autoantibodies or mutated circulating complement regulators [62]. Prior to finalizing a diagnosis, plasma exchange is standard of care [10]. After ruling out TTP, Shiga toxin *E. coli*, HUS and secondary TMA syndromes, treating patients with eculizumab is recommended. However, if eculizumab is unavailable, plasma exchange is an alternative treatment option [10]. The American Society for Apheresis adjusted the category for therapeutic apheresis from category II (second-line therapy) to category III (nonestablished role for apheresis) for patients with complement factor gene mutations [61,63]. A 1.5 plasma volume, equivalent to 60–70 mL/kg per session, should be exchanged for FFP [64]. Plasma exchange must be performed daily for 5 days, then five times daily for 2 weeks, and subsequently three times weekly for 2 weeks [64,65]. Long-term maintenance therapy can be weekly to every 2–4 weeks [64,65]. The absence of response from plasma exchange is either an absence of normalization of platelet count or absence of reduction in plasma creatinine level less than/equal to 25% of patients without severe chronic damage on biopsy or renal imaging after five consecutive days of plasma exchange [59,64,65]. The number of sessions and duration of plasma exchange for aHUS are controversial [10]. Decisions concerning duration or discontinuation should be made based upon patient's response and underlying condition [61]. This has significantly improved morbidity and mortality in individual cases but not formally evaluated in clinical trial [8]. It may beneficially supplement levels of deficient complement components in plasma (i.e. Factors H or I) [8]. It also removes mutated proteins that exert a negative effect on complement regulation [66]. Pathogenic autoantibodies may also be removed [8]. However, it is not uniformly effective, as it is time-consuming and there is significant procedure-related morbidity (access-related infections) [8].

As mentioned in the case, this patient received eculizumab during her hospital stay to further prevent renal damage. Lately, there have been reports of effectiveness with renal improvement and overall patient survival, including for patients with plasma-sensitive and plasma-resistant aHUS, including posttransplant recurrence [66,67]. Eculizumab, a recombinant, humanized monoclonal immunoglobulin, targets complement component 5 (C5) and hinders cleavage of C5 to C5a and C5b as first-line treatment compared to plasmapheresis [27].

Eculizumab is a humanized murine mAb against C5. This prevents C5 cleavage and limits C5a and 5b production by any of the three complement pathways [8]. Early initiation of eculizumab has been effective for minimizing renal damage [8]. Dosage and schedule should be adjusted according to body weight [68]. Patients should receive meningococcal vaccination 2 weeks prior to the first dose because the drugs increase the risk of meningococcal

infections [69]. If initiated less than 2 weeks after vaccination, patients should receive additional prophylactic antibiotics until 2 weeks after vaccination [70].

Ravulizumab, a long-acting C5 inhibitor approved by the FDA for treating adult and pediatric patients (<1 month of age) with aHUS, inhibits complement-mediated TMA [10]. A minimum duration of 6 months should be maintained [10]. Extension beyond 6 months should be based upon an individual basis [10]. Ravulizumab reduces treatment burden, with infusions once every 4 or 8 weeks, depending on body type [10]. Further studies are needed regarding use in pregnancy [70].

Conclusion

Pregnancy-associated aHUS results in a poor prognosis, with irreversible renal failure if left untreated. Although many reports have discussed the pathogenesis of this disease, particularly with endothelial cell damage and renal (glomerular) damage, there is still ongoing research to understand more about the mechanisms and effective treatment modalities. More studies, that is, in vivo, must be made to highlight the importance of appropriate management to mitigate the progression of the disease in this patient population to reduce morbidity and mortality. Developing a deeper appreciation of the pathophysiological background about aHUS focuses upon each regulator involved in organ damage for greater consideration of such rare anomalies. Having better insights into various endothelial injuries results in the best approaches to prevent unfortunate outcomes.

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Conflicts of interest

There are no conflicts of interest.

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