

Case reports

Atypical Complement-Mediated Hemolytic Uremic Syndrome Triggered by Molar Pregnancy

Robert Pell, MD¹, Cindy Iwuagwu, DO², Drake Dixon, MD¹, Marinna Panting, DO³, Shayne Gue, MD, MSME¹ 

¹ Emergency Medicine, UCF/HCA Florida Healthcare GME (Greater Orlando/Osceola), ² Internal Medicine, UCF/HCA Florida Healthcare GME (Greater Orlando/Osceola), ³ Obstetrics & Gynecology, UCF/HCA Florida Healthcare GME (Greater Orlando/Osceola)

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Complement-mediated hemolytic uremic syndrome (CM HUS) is a rare but potentially devastating disease that results in intravascular hemolysis and thrombocytopenia, precipitating severe end-organ damage. CM HUS is a specific disorder under the collective group of thrombotic microangiopathies along with thrombotic thrombocytopenic purpura (TTP).

Pregnancy itself can be a precipitant of CM HUS, although rare, due to dysregulated complement activation. Typical pregnancy induces elevated complement activation in effect with equal elevation of inhibitory factors to protect the fetus. In a susceptible individual, pregnancy itself may contribute to complement dysregulation resulting in CM HUS. A high index of suspicion is required to differentiate the true cause of the presentation, as there is no specific testing for CM HUS. A devastating result of CM HUS is complete renal failure.

Management strategies may include plasma exchange and anti-complement immunotherapies. In this report, we will present a case of postpartum precipitated CM HUS complicated by acute kidney injury requiring hemodialysis and anti-monoclonal therapy.

INTRODUCTION

Thrombotic Microangiopathy (TMA) includes a group of disorders caused by platelet microthrombi formation in the small vessels, characterized by microangiopathic hemolytic anemia and thrombocytopenia, and leads to end organ damage.^{1,2} Specifically in pregnancy, there tends to be two categories of TMA, related and associated.³ Pregnancy-related TMA's, or inherent to pregnancy itself, include examples such as pre-eclampsia and hemolysis, elevated liver enzymes, and low platelets (HELLP). Pregnancy-associated TMA's, or those precipitated by pregnancy include CM HUS, TTP, and lupus. In regards to pregnancy-associated TMA, TTP appears to be predominant in the third trimester whereas CM HUS predominates the postpartum period. The clinical course of CM HUS is not affected by delivery and, in fact, the postpartum period may have the greatest risk potential for the initiation of CM HUS.¹ The clinical presentation of CM HUS is very similar to TTP, although the renal system is more commonly affected than the brain and heart, as seen in TTP.¹ A third TMA, Shiga toxin-mediated, or "typical" hemolytic uremic syndrome (ST HUS), is more so an infectious disease-mediated disorder associated with recent bloody diarrheal illness and new-onset acute kidney injury.⁴ The incidence of pregnancy-associated TMA's is suggested to be approximately 1 in 25,000 although may be

more as there have been many recent advances in diagnostic technologies resulting in a higher index of suspicion.^{1,5}

CM HUS, also known as "atypical HUS," is a disorder in which patients have defective complement regulation precipitated by a trigger, with pregnancy being a well-known cause.^{3,6,7} The complement cascade, including activators C3 and Factor B, is a part of the innate immune system responsible for the lysis of target cells by ultimately forming destructive pores in the cell membrane. Complement regulators, such as Factor H, Factor I, and a membrane cofactor CD-46, are responsible for inhibiting this cascade to its own cells and preventing microvascular and end-organ damage.^{1,7} Genetic mutations of the complement system, comprising up to 40% of cases, and autoantibodies against factors can lead to dysregulation and downstream effects.^{8,9} The complement cascade is regulated with high redundancy, and therefore, many abnormalities can be tolerated until the balance is upset by particular triggers.¹⁰

Unlike other forms of TMA in pregnancy, such as TTP with a laboratory-tested deficiency in ADAMTS13,^{10,11} differentiating features of CM HUS are often clinical including the presence of rapidly increasing serum creatinine leading to severe kidney injury, typically requiring hemodialysis. There is high mortality in the acute phase, up to 15% if delay in diagnosis and treatment, and as many as 50% of cases remain in end-stage renal disease on hemodialysis.¹² To prevent rapid renal deterioration to end-stage kidney disease, anti-complement monoclonal therapy, Eculizumab,

should be initiated promptly when CM HUS is suspected. This is thought to improve kidney function and platelet count and decrease the need for prolonged hemodialysis.¹

CASE PRESENTATION

This is a case of a 34-year-old G6P2032 female at 12 weeks (estimated gestational age), with a past medical history of hypothyroidism, who presented to the hospital for a scheduled suction dilation and curettage after being diagnosed with molar pregnancy. The planned procedure was performed with approximately 800 milliliters of intraoperative blood loss. Soon after the procedure, while in the post-anesthesia care unit, the intensive care unit team was alerted for an extended episode of hypotension and bradycardia. The patient was placed in Trendelenburg with no change in hemodynamic status. Due to concerns of persistent bleeding, 2 units of packed red blood cells, tranexamic acid, and methergine were given. Laboratory values were later found to be significant for hemoglobin of 8.4 g/dL (reference range: 11.2-15.7), down from preoperative hemoglobin of 12.7 g/dL. All other laboratory values at that time remained unremarkable. The patient thereafter became hemodynamically stable with improvement in hemoglobin to 11.1 g/dL after transfusion. The patient was advised to stay in the hospital overnight under close observation. Within twenty-four hours, the patient's hemoglobin again dropped to 7.8 g/dL, platelets decreased from 124 to 29. D-dimer elevated to 17,560 ng/mL (reference range: 0-529) and fibrinogen levels decreased to 156 mg/dL (reference range: 207-493). PT was mildly elevated at 13 seconds (reference range: 10-12.8) and PTT was normal at 28 seconds (reference range: 25-38). Creatinine increased from 0.95 to 3.43 mg/dL (reference range: 0.55-1.3). A peripheral blood smear was assessed which showed the presence of schistocytes, increasing the concern of disseminated intravascular coagulation (DIC). The patient was given further blood transfusion but displayed no clinical signs of DIC such as mucosal bleeding or bruising. Nephrology was consulted as creatinine continued to rise the next day to 7.3 mg/dL. After a renal ultrasound was found to be unremarkable, the patient consented to initiation of hemodialysis.

Hematology was also consulted and requested further studies such as ADAMTS13, haptoglobin, LDH, C3, and C4. High-dose methylprednisolone was initiated with a plan to start plasmapheresis. Computerized Tomography (CT) of the abdomen and pelvis was completed due to persistent abdominal pain and worsening hemoglobin despite transfusions which revealed extensive hematometra. The patient was taken back to the operating room for evacuation of hematometra and implantation of a Cook balloon to serve as a uterine tamponade. Plasmapheresis did not impact the patient's clinical course. The patient's ADAMTS13 level returned at 62.3 % (reference normal: 66.8%). As CM HUS was a considerate differential, and after all other laboratory testing was unremarkable for underlying high-risk infections, eculizumab therapy was initiated. Being a specialty pharmaceutical, eculizumab was shipped from the drug manufacturer after contacting the physician resource sup-

port group. The medication arrived within 10 hours and the patient was immediately initiated on an eculizumab course at 900 mg IV infusion every 7 days for the first 4 weeks, followed by a single dose of 1,200 mg IV infusion 7 days after the fourth dose, and then 1,200 mg IV infusion every 14 days. The patient thereafter had improvement in the hospital course and was ultimately discharged off hemodialysis and advised to continue outpatient infusions. A two-week course of amoxicillin for meningococcal prophylaxis, initiated prior to eculizumab therapy, was also continued.¹³

DISCUSSION

Thrombotic microangiopathies all have the same underlying target of the endothelial cell, although each disorder may affect through its own particular mechanism. CM HUS, in particular, is a disorder of the complement system causing anemia, thrombocytopenia, and renal injury.¹⁴ As seen above, pregnancy is a well-known trigger of CM HUS due to a dysregulated complement system. This was determined largely in part by the efficacy of anti-complement therapies, such as eculizumab as of recent.¹⁵

Although CM HUS may be considered a diagnosis of exclusion, it is highly recommended to start eculizumab as soon as possible, to prevent chronic sequela.¹⁶ As discussed above, this condition may arise from a trigger in a genetically susceptible individual. It was seen in a prior study of pregnant females, the risk being highest while in their second pregnancy.¹⁷ In patients that developed CM HUS, approximately 71% required hemodialysis due in part to significant renal injury.¹⁸ Although our patient was discharged without the need for chronic hemodialysis, a study conducted showed that on a 7 year follow-up in patients that did not receive anti-complement treatment, 53% developed end-stage renal disease, 19% chronic kidney disease, and 28% had a CM HUS relapse.¹⁸ In a study of 10 patients who received anti-complement treatment, none developed end-stage renal disease at follow-up.¹⁹ Eculizumab, the monoclonal antibody therapy for CM HUS, works by targeting the complement protein C5. This ultimately prevents the formation of the terminal complement complex C5b-C9 and endothelial damage.²⁰ A complication of anti-complement therapy is the risk of contracting high-risk encapsulated organisms. Therefore, pre-therapy studies are performed to ensure the patient is not in a carrier state. Along with this, prophylaxis treatment and meningococcal vaccine should be routinely administered prior to initiation of anti-complement therapy. In the pregnant patient, an obstetrics team should be consulted for continued fetal assessments and monitoring.¹

CONCLUSIONS

This case demonstrates an unlikely culprit of postpartum complications. Although rare, CM HUS can be the underlying cause of clinical deterioration and laboratory abnormalities resulting in hemolytic anemia, thrombocytopenia, and renal injury. If left untreated, this can ultimately result in renal failure and even death. The underlying pathogene-

sis of CM HUS is a dysregulated complement system, leading to overactivation and targeting of the endothelium. Unfortunately, CM HUS is largely a diagnosis of exclusion as there is no definitive test for confirmation. The first step is to maintain a high level of suspicion while simultaneously ruling out other causes. This condition may require a multi-disciplinary approach including members from intensive care, obstetrics and gynecology, nephrology, hematology, and even infectious disease. Treatment is centered on providing the novel monoclonal antibody, eculizumab, which counteracts excessive C5 complement and in effect terminates the formation of terminal complement complex. Eculizumab is a rather expensive and often unavailable therapy, and thus, care must be taken to expedite arrival so as not to delay care. Of importance to note is that eculizumab therapy also makes the individual susceptible to high-risk encapsulated organisms; thus, care must be taken to provide proper prophylactic vaccinations and antibiotic regimens. If CM HUS is suspected in a patient displaying likely clinical signs and symptoms, and if therapies are initiated promptly, the patient is more likely to make an uneventful recovery without long-lasting effects, including permanent renal failure and relapse.

LIST OF ABBREVIATIONS

CM HUS – Complement-mediated hemolytic uremic syndrome; TTP – thrombotic thrombocytopenic purpura; TMA – Thrombotic Microangiopathy

ETHICS APPROVAL

Consent was obtained or waived by all participants in this study. HCA Centralized Algorithms for Research Rules on IRB Exemptions (CARRIE) issued approval 2024-1083.

COMPETING INTERESTS

The authors declare that they have no competing interests

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COVER IMAGE ATTRIBUTION

Image from JetEM, <https://doi.org/10.21980/J82W7T>.

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