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Pregnancy-Associated Atypical Hemolytic Uremic Syndrome: A Case Report with *MCP* Gene Mutation and Successful Eculizumab Treatment

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Abstract

Pregnancy-associated atypical hemolytic uremic syndrome (P-aHUS) is a rare condition characterized by microangiopathic hemolytic anemia and kidney injury from thrombotic microangiopathy. P-aHUS occurs in approximately 1 in 25,000 pregnancies and is strongly related to complement dysregulation and pregnancy-related disorders, such as preeclampsia, eclampsia, and hemolysis, elevated liver enzymes, low platelet (HELLP) syndrome, resulting in adverse perinatal and fetal outcomes. Complement dysregulation in P-aHUS is commonly attributed to genetic mutations or autoantibodies affecting complement factors, including *CFH*, *CFI*, and *MCP*. We present a case of a 25-year-old primigravida who experienced severe preeclampsia and HELLP syndrome followed by the development of complicated P-aHUS during the early postpartum period. The patient exhibited severe clinical manifestations, including hypertensive emergency, central nervous system involvement, renal impairment, and microangiopathic hemolytic anemia. Timely initiation of eculizumab therapy resulted in successful disease remission. Further genetic analysis revealed a likely rare pathogenic *MCP* gene variant.

Keywords
- aHUS
- pregnancy
- thrombotic microangiopathy
- eculizumab
- HELLP syndrome

Pregnancy-associated atypical hemolytic uremic syndrome (P-aHUS) is a rare condition characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and acute kidney injury (AKI) with a thrombotic microangiopathy (TMA).[1] P-aHUS occurs in approximately 1 in every 25,000 pregnancies and has significant consequences on long-term patient mortality and morbidity.[2] Differentiating P-aHUS from other postpartum cases of MAHA and AKI is crucial as patients with P-aHUS often present with more severe renal dysfunction. Thus, a thorough evaluation of the patient presentation is essential to accurately diagnose P-aHUS while ruling out similar conditions such as hemolysis, elevated liver enzymes, low platelet (HELLP) syndrome and pre-eclampsia.[3–5]

Pregnancy is a known complement amplifying condition, and maternal exposure to semiallogenic fetoplacental

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material increases over gestation, with peak exposure at delivery.[3,5,6] Complement regulators in soluble and membrane-bound forms prevent overactivation of C3 convertase and inhibit the alternative complement cascade on endothelial surfaces.[3] Genetically susceptible individuals harbor mutations or develop autoantibodies to complement factors that regulate the alternative complement pathway.[5,7,8] Complement factor H (CFH), complement factor I (CFI), and membrane cofactor protein (MCP) are the most frequently affected proteins. Additionally, gain-of-function mutations of key complement component C3 and complement factor B (CFB) can also lead to an enhanced complement response and poorer outcomes in P-aHUS.[1,3,5,9]

P-aHUS is marked by a substantial risk of progressing to end-stage kidney disease (ESKD), with rates reaching up to 78% at 24 months' postpartum in the absence of eculizumab therapy.[10] Data from a retrospective analysis conducted on a cohort of 87 P-aHUS patients from a European aHUS registry revealed a ESKD rate up to 55% in the postpartum period.[8] Emerging evidence indicates that eculizumab treatment may mitigate the complications associated with P-aHUS. However, careful evaluation of its safety during pregnancy is warranted for optimal clinical decision-making.[5]

In this case study, we report a primigravida with complicated P-aHUS in the postpartum period associated to a rare *MCP* mutation and the successful course of eculizumab treatment.

Case Presentation

A 25-year-old primigravida was admitted to the medical intensive care unit with a diagnosis of hypertensive emergency following an emergency cesarean section at 32 weeks of gestation due to preeclampsia and HELLP syndrome. The patient presented with a sudden onset of severe pulsatile holocranial headache 12 hours prior to admission. No history of head trauma, seizures, or illicit drug use was reported. The patient had no prior history of any type of stroke, and there was no evidence of antiplatelet or anticoagulant medication use upon review of her medications. Additionally, there was no significant personal or family history of systemic diseases.

On admission, blood pressure was 220/120 mm Hg, pulse rate was 115 beats/min, respiratory rate was 19 cycles/min, and temperature was 37.3°C. She was obtunded with a Glasgow Coma Scale score of 14/15. The patient presented with mild kidney injury, anemia, thrombocytopenia, and mild transaminitis, as shown in ►**Table 1**. Emergency computed tomography of the head revealed a subcortical ischemic lesion in the left frontal region (►**Fig. 1**). A magnetic resonance imaging control was performed and revealed an acute evolving ischemic injury with hemorrhagic transformation in the left frontal region and perilesional edema (►**Fig. 2**). Within 72 hours, the patient developed anuric renal failure, hemodynamic instability, and neurological complications with decreased levels of consciousness, which required intubation, intravenous (IV) support, and hemodialysis. Despite intensive management, hemodynamic instability persisted, along with intravascular hemolysis indicated by elevated levels of lactate dehydrogenase and progressive thrombocytopenia (►**Table 1**). The patient received plasma exchange treatment on the first and second postpartum days and underwent a total of four hemodialysis sessions during her treatment (on postpartum days 2, 4, 6, and 8; ►**Fig. 3**).

Furthermore, laboratory tests were issued for differential diagnostic purposes of other diseases. The activity of ADAMTS13 was normal 72.6% (40–130%), which excludes thrombotic thrombocytopenic purpura (TTP). In the stool samples, the pathogens causing typical hemolytic uremic syndrome (HUS) tested negative. Serum complement C3 (0.65, 0.71–1.41 g/L) and C4 (0.09, 0.12–0.34 g/L) levels were low. Coombs test was negative. Antiphospholipid and antinuclear antibodies were not detected. Infection serology concerning Hepatitis B and C, and HIV was negative.

A presumptive diagnosis of P-aHUS was made 4 days after her presentation in the setting of neurological involvement, thrombocytopenia, MAHA, negative Shiga-toxin testing, and severe renal impairment. As a result, an initial dose of 900 mg IV of eculizumab was administered, followed by a series of four weekly doses of the same amount. Concurrently, the patient received pneumococcal vaccination and prophylactic penicillin treatment. She exhibited a prompt recovery and did not require further hemodialysis after the fourth session, which was conducted on the 8-day postpartum. Kidney function corrected gradually, platelet count elevated, and hemolysis resolved.

Two months following discharge from the hospital, her renal function had improved with and without neurological sequelae. At present, the patient continues to receive

Table 1 Patient parameter over the disease course

Parameter	Admission	D1	D2	1 wk	4 wk	8–12 wk
Hb (g/L; 115–165)	58	62	71	67	84	112
Platelets (150–400 $\times 10^9$/L)	21	32	28	75	198	245
Reticulocytes (50–100 $\times 10^9$/L)	205	162	143	86	73	78
Haptoglobin (0.3–2.15 g/L)	0.22	0.08	0.1	0.38	1.2	1.4
LDH (120–250 UL)	2,153	2,586	2,452	1,451	246	223
Creatinine (45–90 mmol/L)	182	224	183	432	376	134
eGFR ($>$ 90 ml/min 1.73 m^2)	28	31	45	23	28	32

Abbreviations: eGFR, estimated glomerular filtration rate; Hb, Hemoglobin; LDH, lactate dehydrogenase.

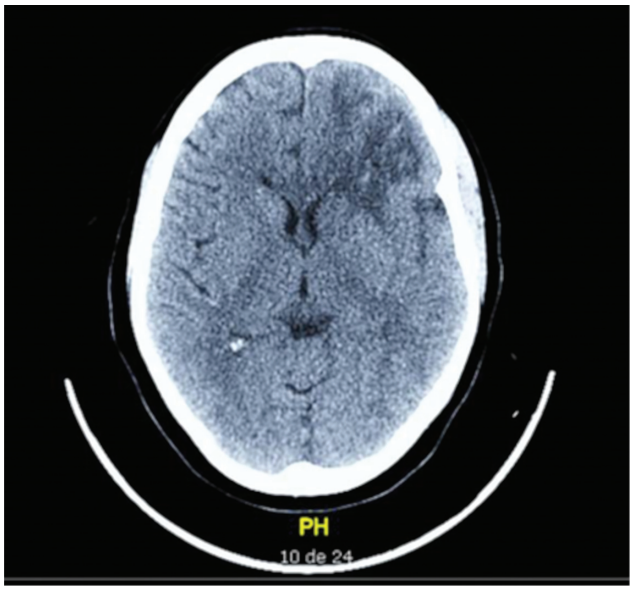

Fig. 1 Computed tomography scan of the brain showing subcortical ischemic lesion in the left frontal region.

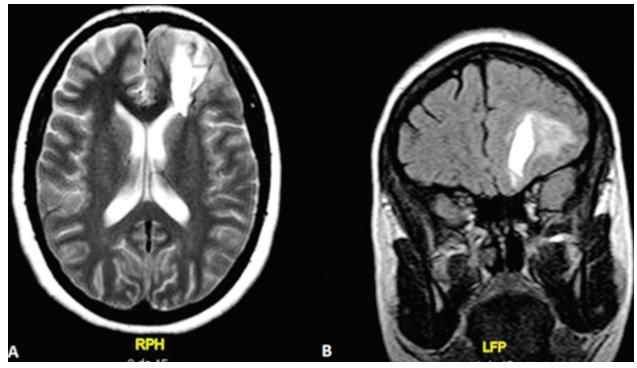

Fig. 2 Magnetic resonance image. (**A**) Axial and (**B**) sagittal T2-weighted magnetic resonance imaging showing ischemic injury with hemorrhagic transformation in the left frontal region and perilesional edema.

fortnightly doses of eculizumab (1,200 mg) and exhibits normal hematological parameters, stable renal function, and a latest estimated glomerular filtration rate (eGFR) of 61 mL/min/1.73 m^2, indicating sustained remission of the disease.

To predict her risk of relapse and identify a disease mechanism, the patient has undergone flow cytometric immunophenotyping and whole-exome sequencing. Anti-FH antibodies were not detected in the patient plasma. Sequencing of *CFH*, *CFI*, *CFB*, factor H-related protein 5 (*FHR5*), and components of the coagulation cascade: *ADAMTS13*, thrombomodulin (*THBD*), and diacylglycerol kinase E (*DGKE*) genes were normal. However, the patient had a heterozygous likely pathogenic variant c.1A > G (p.Met1?) in the *MCP* gene, a substitution that affects the translation initiation codon. This finding confirmed that the patient had P-aHUS caused by a *MCP* gene mutation.

Discussion

The primigravida described above presented with a complex medical condition involving preeclampsia, HELLP syndrome, and P-aHUS, with a rare mutation in the *MCP* gene as the

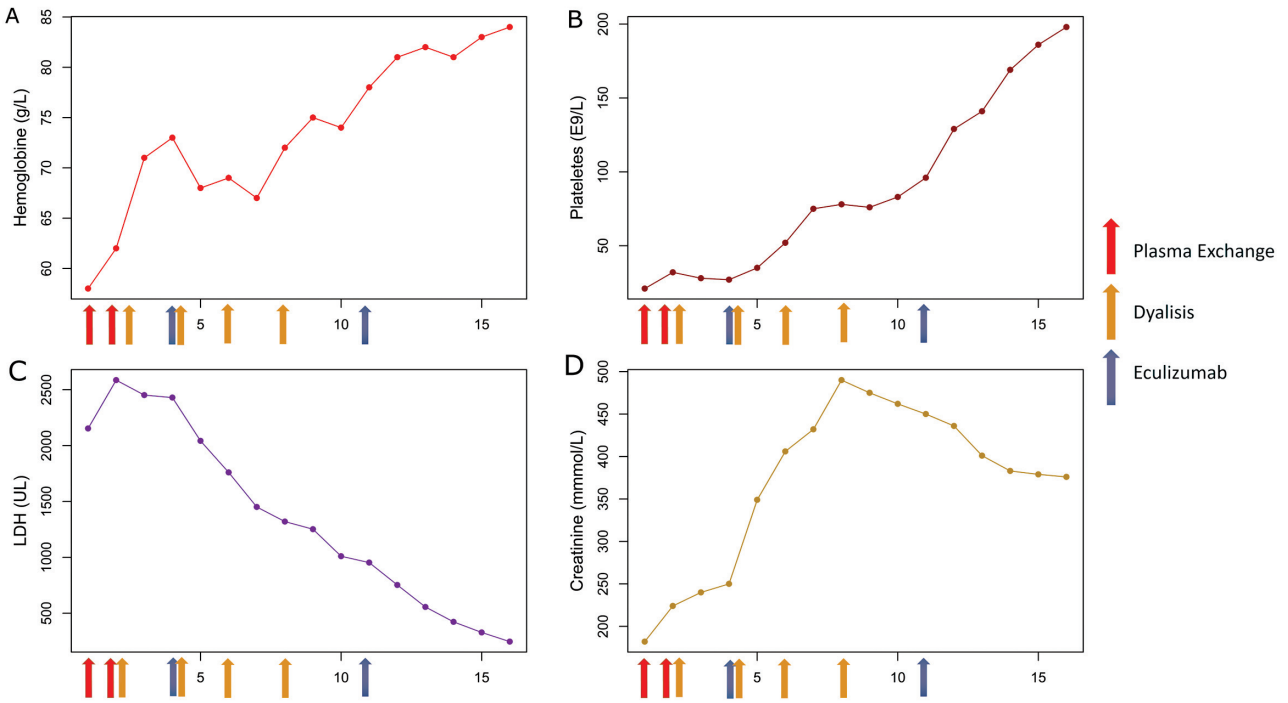

Fig. 3 Laboratory values during the early stages of the pregnancy-associated atypical hemolytic uremic syndrome and the timing of plasma exchange, hemodialysis, and administration of eculizumab. (**A**) Blood hemoglobin measurements, (**B**) number of platelets, (**C**) serum lactate dehydrogenase (LDH) level, and (**D**) serum creatinine level across 16-day follow-up period. Day of sample (0 = admission).

underlying cause. This case underscores the diagnostic challenges in identifying P-aHUS. Notably, the clinical features shared among TMA syndromes, including typical HUS, aHUS, and TTP, such as MAHA, thrombocytopenia, and pathological endothelial cell injury, contribute to the development of ischemic complications in various end organs.[3,11] In this case, cerebral involvement in the presence of hypertension was observed, adding to the complexity of the clinical presentation.

Central nervous system (CNS) involvement is the most common extrarenal manifestation in aHUS, with symptoms reported in up to 48% of cases. Seizures, vision loss, hemiparesis, headache, altered consciousness, hallucinations, and encephalopathy are the most common symptoms.[12] In the global aHUS registry P-aHUS analysis, up to 33% cases had central nervous system involment.[6] The findings related to cerebral imaging associated with TMA can display significant variation and encompass changes in the posterior white matter, posterior cortex, deep white matter, thalami, brainstem, and basal ganglia.[12,13] In our case, the patient presented a lesion in the left frontal lobe consistent with ischemic injury and hemorrhagic transformation. This manifestation may be explained by direct involvement of the CNS vasculature and secondary to P-aHUS complications.[3]

Placental inflammation plays a crucial role in the development of endothelial dysfunction in hypertensive disorders of pregnancy. Both preeclampsia and aHUS exhibit disrupted endothelial integrity, leading to the activation of complement and coagulation pathways.[11] The activation of the complement system has been observed in severe cases of preeclampsia and HELLP syndrome. Elevated levels of the terminal complex (C5b-9) have been identified in the urine of patients with severe preeclampsia.[1,3,14] Furthermore, it has been postulated that compromised maternal endothelium contributes to the subsequent maternal morbidity observed in severe preeclampsia and other hypertensive pregnancy disorders later in life.[5,15]

Complement regulation abnormalities are highly prevalent in P-aHUS, with reported rates up to 86%. This prevalence is higher compared with P-HUS cases, where complement abnormalities are reported in up to 60% of cases.[13] In P-aHUS patients, the most commonly observed causative mutations are related to complement regulatory proteins: *CFH*, *CFI*, *CFB*, *MCP*, and *THBD*.[7,8,16] CFH mutations are the most prevalent, accounting for up to 20% of all adult cases, followed by mutations in MCP and CFI at 12 and 15%, respectively.[17] In the case of our patient, a rare heterozygous likely pathogenic variant in *MCP,* gene, c.1A > G (p.Met1?), was found. The *MCP* variant identified in our patient represents a novel finding in the P-aHUS literature, demonstrating its potential pathogenicity by a substitution that affects the translation initiation codon. In contrast, a distinct nucleotide change at the same amino acid position, c.2T > A (p.Met1?), has been previously documented as disease-causing in aHUS.[18]

Observational evidence suggests that the relapse rate of aHUS remains substantial in patients who have undergone transplantation.[9] Genetic testing can help predict the likelihood of disease relapse, which is an important consideration in the long-term management of aHUS.[3] Patients harboring underlying mutations in the complement factors CFH, MCP, and CFI exhibit relapse rates of up to 90%, 20%, and 80%, respectively. Although the frequency of mutations in CFB is low at 2%, they are associated with the highest relapse rate of 100%.[13,19]

Clinical trials have provided compelling evidence for the efficacy of eculizumab in reducing complement-mediated hemolysis, thrombocytopenia, and kidney injury in nonpregnant adults with aHUS.[20] Thus, the successful use of eculizumab in treating P-aHUS aligns with our current understanding of this disorder as a complement-mediated TMA. Importantly, international registry data have revealed that P-aHUS shares numerous similarities with adult aHUS in various aspects and should be approached similarly in terms of treatment.[6,9] Furthermore, a decreased risk of end-stage renal disease was observed in P-aHUS cases treated with eculizumab compared with non-P-aHUS cases who did not receive this treatment. Notably, an increase in mean eGFR from baseline also indicated improved renal outcomes for women in both aHUS groups treated with eculizumab. The similarity in response to complement C5 inhibition suggests a shared disease pathophysiology between P-aHUS and aHUS is not associated with identifiable triggers.[6]

Conclusion

This case study highlights the diagnosis and therapeutics challenges that exist with P-aHUS. The patient's severe symptoms, including hypertensive emergency, cerebral ischemic injury, anuric renal failure, and CNS involvement, underscore the potentially devastating nature of this condition. We were able to make a prompt diagnosis from the time of presentation. The administration of eculizumab, along with supportive care, led to prompt recovery, resolution of hemolysis, and improvement in renal function. Presently, the patient's renal function has returned to baseline. The identification of a rare *MCP* gene mutation in this case contributes to our understanding of the genetic basis of P-aHUS. Further investigations should focus on elucidating the specific pathogenic mechanisms related to this mutation and exploring potential risk factors for relapse in patients with similar genetic profiles.

Ethical Approval

This study was approved by the Ethics Committee of the Clinica de la Costa, Barranquilla, Colombia. All procedures were performed under the relevant guidelines and regulations.

Informed Consent

Written informed consent was obtained from the patient for publication. There are no identifying images or other personal or clinical details of the patient that compromise her anonymity in this manuscript.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author's Contributions

A.D.V. contributed to the conceptualization and writing of the original draft. H.J.G.T. and F.A. contributed to data curation. D.S. contributed to visualization; E.E., G.A.M., and C.G.M. contributed to writing, review, and editing. All authors read and approved the final manuscript.

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Conflict of Interest

None declared.

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