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(CASE REPORT)

No HELLP at all: Post-partum atypical hemolytic uremic syndrome treated with Eculizumab: A case report

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Abstract

Atypical hemolytic uremic syndrome (aHUS) is a rare condition among thrombotic microangiopathies (TMA). Pregnancy is a known precipitating factor of complement mediated TMA. The occurrence of microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury presents diagnostic and therapeutic challenges. Diverse causes include hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome) in pregnant women. In pregnancy or postpartum, the occurrence of aHUS is a critical complication requiring urgent diagnosis and treatment. aHUS is considered to be the result of the underlying condition, with the understanding that therapy is focused on the underlying condition. Five documented cases of pregnancy-associated aHUS treated with Eculizumab have been reported, making the condition extremely rare. We present the case of a pregnant woman with HELLP syndrome induced aHUS. The patient presented with evidence of dysregulation of the complement system and renal insufficiency. Since the initiation of Eculizumab, a C5 complement inhibitor, the development of renal insufficiency diminished and the patient became dialysis independent.

Keywords: HELLP syndrome; Eculizumab; Hemolytic uremic syndrome; Microangiopathic hemolytic anemia

1. Introduction

Hemolytic uremic syndrome (HUS) is a condition characterized by thrombocytopenia, acute kidney injury (AKI) and microangiopathic hemolytic anemia. Typical HUS is caused by Shiga toxin-producing Escherichia coli infection. Atypical HUS (aHUS) is due to an overactivation of the alternative pathway of the complement cascade. aHUS is a rare microangiopathic hemolytic anemia affecting 0.23 in every 1 million people [1]. Thrombotic microangiopathy can have numerous etiologies, all of which show morphologic overlap. These include accelerated hypertension, disorders of complement regulation (atypical HUS), infections, and ADAMTS13 abnormalities among others. Thrombotic microangiopathies can complicate pregnancy and threaten the lives of both mother and fetus. A majority of cases occur in the post-partum period [2].

Pregnancy related aHUS is associated with high rates of end stage renal failure disease of approximately 78% at 24 months' post-partum without Eculizumab therapy [3]. Diagnosis of aHUS requires consideration of the patient presentation and exclusion of similar conditions including HELLP syndrome and pre-eclampsia. Compared to other conditions presenting with similar symptoms, such as microangiopathy and AKI, pregnancy related aHUS has been affiliated with a greater degree of renal dysfunction (Figure 1).

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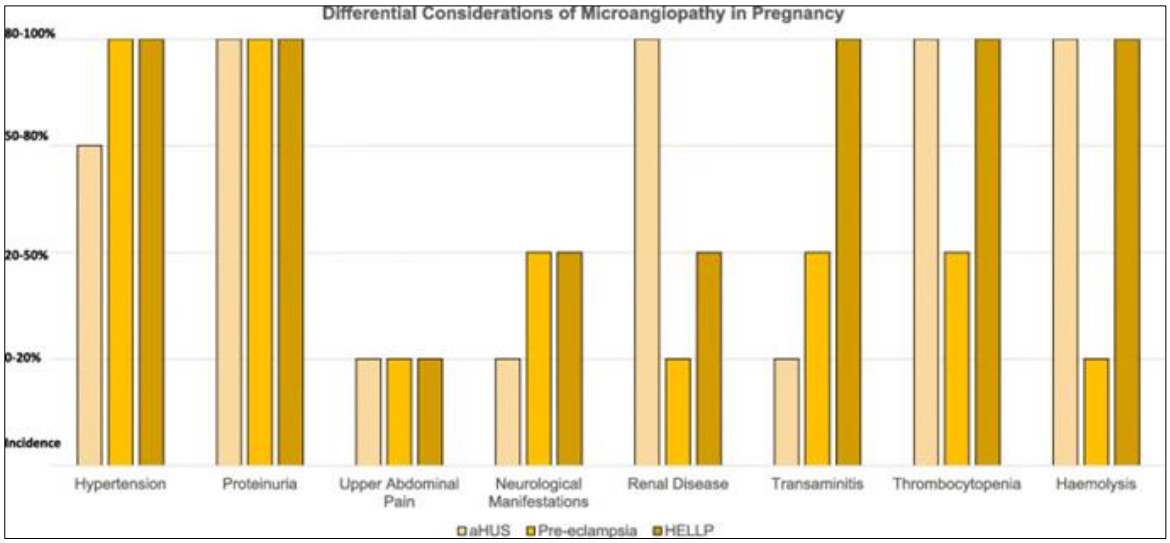

Figure 1 Differential Diagnosis Considerations of Microangiopathy in Pregnancy. Adapted from Bergmann & Rath (2015) [3].

Eculizumab therapy has lowered the risk of complications in pregnancy associated aHUS. The observational studies remain limited in regards to Eculizumab's safety profile [4]. The safety data of Eculizumab during pregnancy stems mostly from patients with paroxysmal nocturnal hemoglobinuria (PNH), with a reduction in maternal complications and a high rate of fetal survival [5].

In this case report, we present a woman with HELLP syndrome, triggering a pregnancy related aHUS. She has been successfully treated with Eculizumab and no longer dialysis-dependent. The patient's risk of reoccurrence in future pregnancies remains unknown as she has yet to assess her risk through genetic sequencing.

2. Case study

A 22-year-old G2P1, 26-week pregnant woman with a history of preeclampsia presented with a 2-day history of headaches, blurred vision as well as nausea and non-bloody, nonbilious vomiting. On admission, initial vital signs were notable for a blood pressure of 201/123 mmHg. Physical examination showed bilateral lower extremity edema and was accompanied by significant proteinuria on urinalysis. Laboratory workup revealed hemoglobin 6.9 gm/dL, platelet count 78,000/uL, haptoglobin <8 mg/dL, reticulocytes 3.3%, LDH 5568 U/L, albumin 1.9 g/dL, AST 776 U/L, and ALT 239 U/L, creatinine 0.77 mg/dL and schistocytes on peripheral smear, concerning for thrombotic microangiopathy. Additional workup including antinuclear antibody (ANA), beta-2 glycoprotein antibody, anticardiolipin, Lupus anticoagulant, PTT, PT/INR, total complement activity (CH50), complement C3 and C4 levels as well as direct and indirect Coombs' tests were all within normal limits or negative. Shiga toxin tests were negative, so HUS associated with *E. coli* was ruled out.

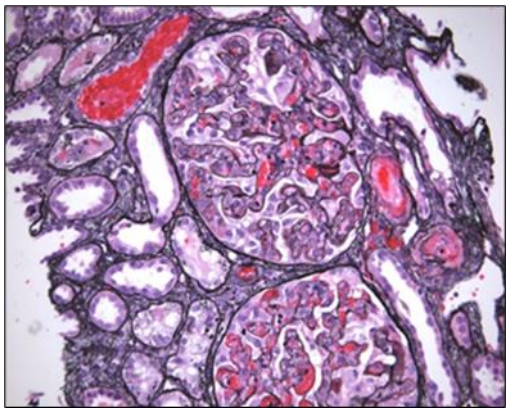

Figure 2 The glomeruli show mesangiolysis and fibrin thrombi.

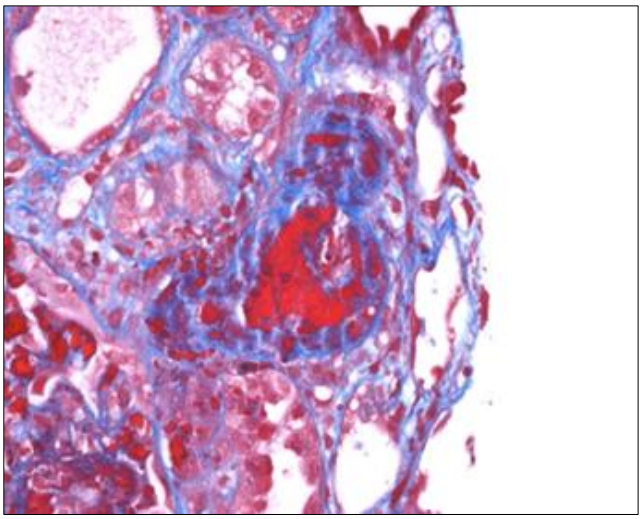

Figure 3 Focal artery containing intraluminal fibrin thrombus.

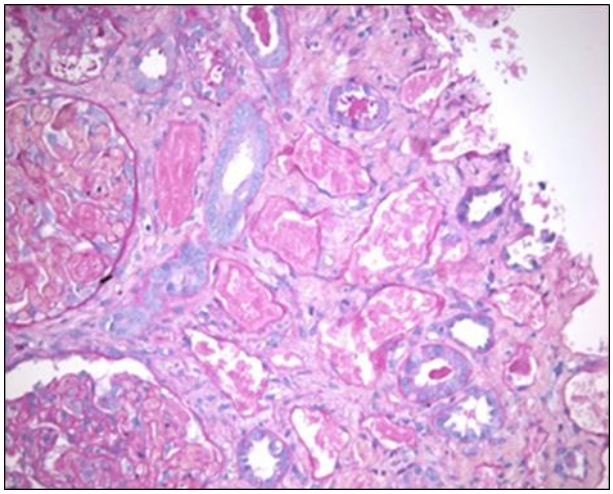

Figure 4 Focal coagulative necrosis within the tubular epithelium.

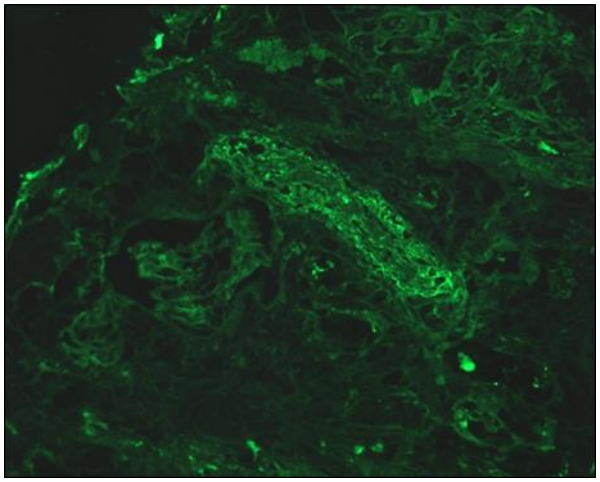

Figure 5 Glomerular capillary lumens and arteries show intraluminal staining by fibrinogen. There is no other significant staining (IgG, IgM, IgA, C3, C1q, albumin, kappa and lambda light chains) present.

Our patient underwent a Cesarean section for intrauterine fetal demise on a background of previously normal antenatal visits. Of note, she had an unremarkable personal history of systemic illnesses. Post-operatively, her transaminases normalized but she had persistent anemia, thrombocytopenia, and AKI with anuria and creatinine of 6.7 mg/dL. Prior to the initiation of hemodialysis, a renal biopsy was obtained for evaluation of her unexplained AKI. The renal biopsy results showed acute thrombotic microangiopathic changes in glomeruli and arteries/arterioles (Figures 2-5). TMA-associated pathologic changes can cause multiple organ lesions leading to a variety of clinical manifestations, in which kidney is the most commonly affected organ, and renal involvement is associated with poor outcome [6].

Days following her admission, her ADAMTS13 level returned at 60.8%, not significantly low to suggest idiopathic thrombotic thrombocytopenic purpura (TTP) [7]. 72 hours after her presentation in the setting of worsening MAHA, severe renal impairment and resolved coagulopathy, HELLP syndrome triggering aHUS remained the most probable diagnosis; HELLP syndrome would have shown signs of improvement by this point. She received daily plasmapheresis, for the suspected secondary TTP, followed by empiric treatment with eculizumab. Within three weeks of treatment, her hematological parameters improved and her renal function began to recover. She was also given the quadrivalent and serogroup B Meningococcal vaccinations.

The patient was discharged with close follow-up with Nephrology and Hematology for continued care. It was ten months following eculizumab therapy that renal function improved and she became dialysis independent. To predict her relapse risk in future pregnancies, the patient will be able to identify a disease mechanism via a genetics service which can stratify any risk-conferring mutations [8, 9]

3. Discussion

A HUS is important to distinguish from typical HUS, HELLP syndrome and TTP because the treatment of aHUS requires Eculizumab in addition to plasmapheresis [8]. Our case highlights the difficulties in diagnosis and treatment of aHUS in the peripartum period. We believe our patient's fetal death in-utero with HELLP syndrome was the inciting event, given the normal renal and hematological studies during pregnancy. She received treatment within a week of hospitalization, while data suggests at least two weeks to diagnosis of the condition [9]. The optimal timeframe duration of treatment, long term impact on renal indices and consideration of future pregnancies remains unclear [9].

Our patient demonstrated improvement in renal and hematological outcomes following use of Eculizumab therapy and dialysis. A European retrospective analysis of the aHUS registry demonstrated that out of the four patients that received Eculizumab, three had complete recovery, with the fourth developing ESRF [3]. The results were similar to a Spanish retrospective analysis which showed 90% of the patients who received Eculizumab therapy had renal recover [9]. However, both analyses failed to mention the recommended duration of therapy.

Anti-complement therapy (Eculizumab) blocks formation of membrane attack complex (MAC) thought to mediate the microangiopathic changes and kidney injury in complement mediated TMA [5,9] (Figure 6). Pregnancy is a known trigger of aHUS, resulting in the development of TMA. Pregnancy associated aHUS is a rare but recognized phenomenon, often occurring in the postpartum period [10]. It is believed the intrauterine fetal demise triggered the HELLP syndrome, which in turn triggered and sustained the aHUS in our patient. There is only one other case of HELLP syndrome associated hemolytic uremic syndrome in the peripartum period that has been reported in literature [11].

In most cases, aHUS is related to complement gene mutations or acquired autoantibodies against certain complement regulatory proteins (complement factor H, I, B, and 3) [13]. Just having a gene mutation alone usually will not cause the disease. In adults with CM-TMA, gene variants appear to be more common than autoantibodies [14]. Complement testing for pathogenic variants in complement genes and for autoantibodies directed against CFH wasn't done as results of complement testing would've been done at outside facility and the results would've been delayed for weeks. An alternative explanation for the findings (MAHA, thrombocytopenia and AKI) include slight ADAMTS13 deficiency coupled with HELLP syndrome as the triggering event.

To our knowledge, there are only five previously documented cases of pregnancy-associated aHUS treated with Eculizumab [15]. Given there are so few reported cases detailing therapy regimens in pregnancy associated aHUS, there is still no protocol for Eculizumab therapy [16]. More case data are needed to determine optimal timing and dosing regimen.

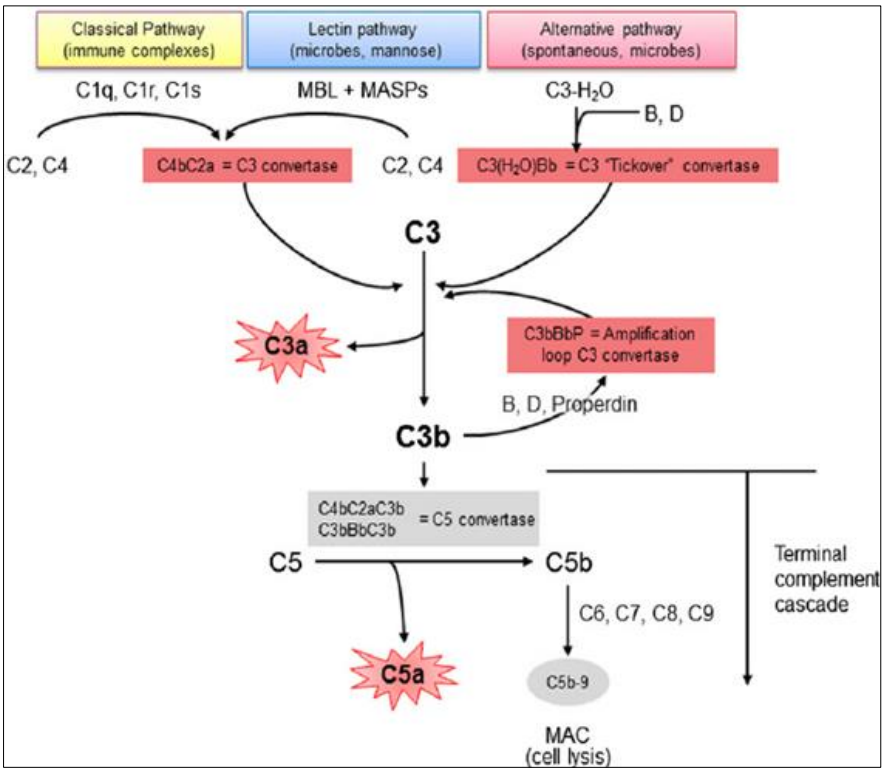

Figure 6 Normal complement cascade [15]

4. Conclusion

Our case demonstrates the importance of a timely diagnosis of pregnancy-associated aHUS. Although our patient is no longer on Eculizumab therapy and dialysis, her risk of relapse remains unknown.

Compliance with ethical standards

Disclosure of conflict of interest

The above listed authors, Drs. Asllanaj, Sheikhan, Benge, Valenta and Diaz have no conflicts of interest to declare.

Statement of informed consent

Informed consent was obtained from the individual participant included in the study.

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Author's contribution

Analysis and interpretation of results: Jordan Valenta, D.O. and Rosaly Diaz, M.D.; draft manuscript preparation: Blerina Asllanaj, M.D., Nazanin Sheikhan, M.D., and Elizabeth Benge, M.D. All authors reviewed the results and approved the final version of the manuscript.

References

[1] Yan K, Desai K, Gullapalli L, Druyts E, Balijepalli C. Epidemiology of Atypical Hemolytic Uremic Syndrome: A Systematic Literature Review. Clin Epidemiol. 2020, 12:295-305. Published 2020 Mar 12.

[2] August P. Obstetric nephrology: pregnancy and the kidney--inextricably linked. Clin J Am Soc Nephrol CJASN. 2012, 7(12):2071–2072. doi: 10.2215/CJN.09450912.

[3] Bruel A, Kavanagh D, Noris M, Delmas Y, Wong EKS, Bresin E, et al. Hemolytic uremic syndrome in pregnancy and postpartum. Clin J Am Soc Nephrol CJASN. 2017, 12(8):1237–1247.

[4] Stefanovic V. The Extended Use of Eculizumab in Pregnancy and Complement Activation¯Associated Diseases Affecting Maternal, Fetal and Neonatal Kidneys-The Future Is Now?. *J Clin Med*. 2019;8(3):407.Cofiell R, Kukreja A, Bedard K, Yan Y, Mickle AP, Ogawa M, et al. Eculizumab reduces complement activation, inflammation, endothelial damage, thrombosis, and renal injury markers in aHUS. Blood. 2015, 125(21):3253–3262.

[5] Wu LH, Yu F, Tan Y, et al. Inclusion of renal vascular lesions in the 2003 ISN/RPS system for classifying lupus nephritis improves renal outcome predictions. Kidney International. 2013, 83(4):715–723.

[6] Gogia P, Gbujie E, Benge E, Bhasin S. Thrombotic Thrombocytopenic Purpura: Revisiting a Miss and an Inevitable Consequence. Cureus. 2020 Jul, 12(7).

[7] Bergmann F, Rath W. The differential diagnosis of thrombocytopenia in pregnancy. Dtsch Ärztebl Int. 2015, 112(47):795–802.

[8] Huerta A, Arjona E, Portoles J, Lopez-Sanchez P, Rabasco C, Espinosa M, et al. A retrospective study of pregnancy-associated atypical hemolytic uremic syndrome. Kidney Int. 2018, 93(2):450–459.

[9] Saad AF, Roman J, Wyble A, Pacheco LD. Pregnancy-associated atypical hemolytic-uremic syndrome. AJP reports. 2016 Mar, 6(1):e125.

[10] Mancini A, Ardissino G, Angelini P, Giancaspro V, La Raia E, Nisi M, Proscia A, Tarantino G, Vitale O, D'elia F. HELLP syndrome and hemolytic uremic syndrome during pregnancy: two disease entities, same causation. Case report and literature review. Giornale italiano di nefrologia: organo ufficiale della Societa italiana di nefrologia. 2019 Apr 1, 36(2).

[11] Fremeaux-Bacchi V, Fakhouri F, Garnier A, Bienaimé F, Dragon-Durey MA, Ngo S, Moulin B, Servais A, Provot F, Rostaing L, Burtey S. Genetics and outcome of atypical hemolytic uremic syndrome: a nationwide French series comparing children and adults. Clinical Journal of the American Society of Nephrology. 2013 Apr 5, 8(4):554-62.

[12] Zuber J, Le Quintrec M, Sberro-Soussan R, Loirat C, Frémeaux-Bacchi V, Legendre C. New insights into postrenal transplant hemolytic uremic syndrome. Nat Rev Nephrol. 2011, 7(1):23–35.

[13] Bruel A, Kavanagh D, Noris M, Delmas Y, Wong EK, Bresin E, Provôt F, Brocklebank V, Mele C, Remuzzi G, Loirat C. Hemolytic uremic syndrome in pregnancy and postpartum. Clinical Journal of the American Society of Nephrology. 2017 Aug 7, 12(8):1237-47.

[14] Puri, P., Hanxhiu, A., O'Hara, D.V. et al. A life-threatening case of pregnancy-related atypical Haemolytic uremic syndrome and successful treatment with Eculizumab. BMC Nephrol 21, 488 (2020).

[15] De Vriese AS, Sethi S, Van Praet J, Nath KA, Fervenza FC. Kidney Disease Caused by Dysregulation of the Complement Alternative Pathway: An Etiologic Approach. J Am Soc Nephrol. 2015 Dec, 26(12):2917-29.

[16] De Vriese AS, Sethi S, Van Praet J, Nath KA, Fervenza FC. Kidney Disease Caused by Dysregulation of the Complement Alternative Pathway: An Etiologic Approach. J Am Soc Nephrol. 2015 Dec;26(12):2917-29.