Eculizumab in the Successful Treatment of Postpartum Hemolytic Uremic Syndrome - A Case Report

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Eculizumab in the Successful Treatment of Postpartum Hemolytic Uremic Syndrome - A Case Report

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INTRODUCTION:

- Preeclampsia, HELLP syndrome, and Pregnancy associated atypical hemolytic uremic syndrome (P-aHUS) represent a continuum of complex pathophysiologic processes which remain the subject of ongoing investigation.[1-4]
- Preeclampsia occurs in approximately 3-8% of pregnancies[1,5,6] and is characterized by new onset or worsening hypertension and proteinuria after 20 weeks gestation. HELLP syndrome, a severe variant of preclampsia, affects 0.1-0.2% of pregnancies[7] and is defined by the presence of hemolysis, elevated liver enzymes and low platelets.[7]
- Pregnancy-associated thrombotic microangiopathies (p-TMA) are rare, affecting 1 per 25,000 pregnancies[8] accounting for 8%–18% of all cases of TMA. TMA is defined by the occurrence of thrombi of fibrin and/or platelets in the microvasculature (arterioles and capillaries) of various organs, mainly the kidney and brain.[2]
- Pregnancy-associated atypical HUS occurs mainly in the first 6 months after delivery.[9]
- Complement mediated injury has been implicated in severe preeclampsia.[2-5]
- Eculizumab is a monoclonal antibody that inhibits the terminal complement pathway.
- Eculizumab is FDA-approved for the treatment of Paroxysmal Nocturnal Hemoglobinuria (PNH)[10], and more recently atypical hemolytic uremic syndrome (aHUS).[11]
- A case report has suggested Eculizumab may safely prolong pregnancy in patients with preeclampsia[12] and it's use has been suggested in the setting of post-partum TMA.[2]

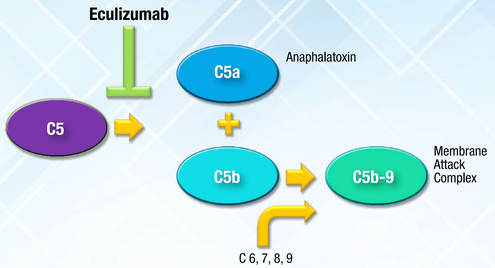

Figure 1. Schematic representation of Eculizumab inhibiting the cleavage of C5, preventing the formation of C5a and the membrane attack complex.

CASE PRESENTATION:

The patient is a 39 year old G2P1 woman admitted to the hospital at 37 weeks and 4 days after presenting with new-onset headaches at a routine prenatal visit.

Her obstetric history was significant for preeclampsia with her first pregnancy with c-section delivery. She had developed gestational diabetes during this current pregnancy as well has hypertension.

Her family history consists of a mother with a history of pulmonary embolus and father with a history of DVT.

The patient had undergone a thrombophilia workup earlier in her pregnancy which revealed heterozygosity for MHTFR (G677T), and homozygousity for PAI-1 (4G/4G).

On evaluation, She was found to be proteinuric with worsening hypertension. She was diagnosed with preeclampsia and subsequently underwent a successful emergent cesarean section delivery with no immediate complication. In her subsequent post-partum course, the patient demonstrated some vaginal bleeding which prompted laboratory studies which revealed a profound drop in her hemoglobin from 11.0 to 5.7gm/dL, accompanied by a decrease in her platelet count from 200k to a nadir of 57k. The peripheral blood smear demonstrated the presence of schistocytes. AST rose from 17 to 210 U/L and ALT from 22 to 118 U/L. Laboratory studies also demonstrated an elevated LDH of 2011 U/L and normal PT/INR. The patient was diagnosed with HELLP syndrome. She became progressively oligoanuric with an elevation in serum creatinine from a baseline of 0.64 to a peak of 5.15 mg/dL. In view of her acute kidney injury and out of proportion elevation of LDH, Atypical Hemolytic Uremic Syndrome (aHUS) was suspected.

Renal Ultrasound: The left kidney measures 12.1 cm and the right measures 11.1 cm. Low normal parenchymal thickness with modestly increased echogenicity - Suggestive of medical renal disease.

She was treated with daily therapeutic plasma exchange (TPE) with fresh frozen plasma with improvement in hematologic parameters. Her renal failure progressively worsened, and she was placed on intermittent hemodialysis (HD) and continued on daily TPE.

Due to lack of renal recovery three weeks after delivery, the patient underwent a native renal biopsy which demonstrated active thrombotic microangiopathy involving the glomeruli and arterioles,. She was treated with Eculizumab, and demonstrated rapid response to therapy, and was able to discontinue TPE and HD within 48 hours. She remains on Eculizumab with a serum creatinine of 1.4mg/d.

Table 1. Laboratory Data Demonstrating Renal and Hematologic Parameters

Time	Date	SCr(mg/dL)	Hgb (g/dL)	Platelet (K)	LDH (IU/L)	AST	ALT	Urinalysis/Urine Protein	Uric Acid (mg/dL)	INR	Total Bilirubin	Fibrinogen	Fibrin Degredation Products	Haptoglobin	Reticulocytes
	09/16/2013	0.64	10.9	220		17	22	Neg Blood, Neg Protein	5.1						
14:14	09/20/2013		11.9	224				270mg (24hr)		0.9					
00:05	09/21/2013		6.8												
07:15	09/21/2013		5.2	124						1					
11:05	09/21/2013	2.47	5.7	118	898			Prot+1, blood +5 rbc 5:15			0.7	207	<40	18	
18:00	09/21/2013	2.88	7.1	53	1607									19	
22:05	09/21/2013	3.63			2011	210	118		8		1				
(TPE Provided)															
04:10	09/22/2013	4.09	6	81	984	89	48				1.2			74	3.60%
11:50	09/22/2013	5.15	6.2	77	1098						0.9	413			
18:30	09/22/2013		6.4	79	564	48						104			
(HD and TPE) Provided															
22:00	09/22/2013	2.02			575										

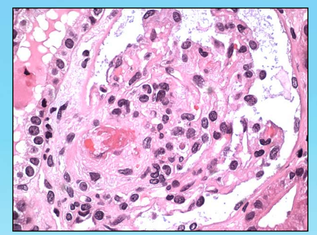

Figure 2a. Light Microscopy demonstrating acute fibrin thrombus.

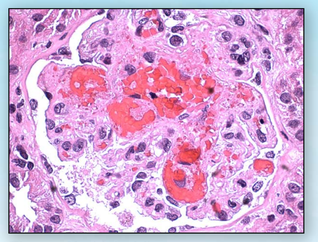

Figure 2b. Light Microscopy demonstrating organizing thrombus.

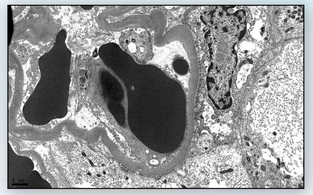

Figure 2c. Electron Microscopy.

PATHOLOGY:

1. Thrombotic Microangiopathy involving glomeruli and arterioles - (Acute and Subacute).
2. Tubular degenerative changes – diffuse.
3. Tubular atrophy and interstitial fibrosis – mild.

DISCUSSION:

The pathogenesis of preeclampsia, HELLP, and p-TMA continues to be a focus of research.

The terminal complement system appears to play an integral role in mediating preeclampsia/HELLP/P-aHUS.

Inhibition of the terminal complement pathwaywith eculizimab led to rapid and durable improvement in renal function and hemolytic anemia in this patient with P-aHUS.

This case demonstrates the effective use of Eculizumab in treating aHUS induced by pregnancy and highlights the utility of renal biopsy in diagnosis, prognosis, and management of post-partum renal failure following initiation of appropriate therapy with improvement in hematologic parameters but lack of recovery of renal function.

Patients receiving Eculizumab are at an increased risk for infection from encapsulated bacterium, and require a meningiococcal vaccine, and consideration for interim antimicrobial prophylaxis.

REFERENCES:

1. Levine RJ, Maynard SM, et al. Circulating angiogenic factors and the risk for preeclampsia. N Engl J Med 2004, 350: 672-683.
2. Fakhouri F, Vercel C, Fremeaux-Bacchi. Obstetric Nephrology: AKI and Thrombotic Microangiopathies in Pregnancy. Clin J Am Soc Nephrol: 7:2100-2106, 2012.
3. Burwick RM, Fichorova RN, et al. Urinary Excretion of C5b-9 in Severe Preeclampsia. Tipping the Balance of Complement Activation in Pregnancy. Hypertension 2013; 62:1040-1045.
4. Lynch AM, Salmon JE. Dysregulated Complement Activation as a Common Pathway of Injury in Preeclampsia and Other Pregnancy Complications. Placenta. 2010 July ; 31(7): 561–567.
5. Buurma A, Cohen D, et al. Preeclampsia is characterized by placental complement dysregulation. Hypertension. 2012 Nov;60(5):1332-7.
6. Carty DM, Delles C, Dominiczak AF. Preeclampsia and future maternal health. J Hypertens. 2010;28(7):1349-1355.
7. Pan C, Perumalswami PV. Pregnancy-related liver diseases. Clin Liver Dis. 2011;15(1):199-208.
8. Matthews JH, Benjamin S, Gill DS, Smith NA. Pregnancy-associated thrombocytopenia: definition, incidence and natural history. Acta Haematol. 1990;84(1):24-29.
9. Ruggenenti P, Cravedi P, Remuzzi G. Thrombotic microangipathies including hemolytic uremic syndrome. In: Floege J, Johnson R, Feehally J, eds. Comprehensive clinical nephrology. 4th ed. Mosby; Philadelphia, PA. 2010:344-355.
10. Charles J. Parker CJ, Kar S, Kirkpatrick P. Eculizumab. Nature Reviews Drug Discovery 6, 515-516 (July 2007).
11. Legendre CM, Licht C, et al. Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome. N Engl J Med 2013; 368:2169-2181.
12. Burwick RM, Feinberg BB, Eculizumab for the treatment of preeclampsia/HELLP syndrome. Placenta. 34 (2013). 201-203.

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FOR FURTHER INFORMATION:

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