Pregnancy-induced atypical haemolytic uremic syndrome: A new era with eculizumab

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Abstract

Pregnancy is a well-recognised trigger of atypical haemolytic syndrome (P-aHUS) and often occurs in the post-partum period. Similar to atypical haemolytic uremic syndrome, it carries a poor prognosis with high morbidity particularly in the form of renal failure. Early recognition and intervention is crucial in its management particularly with the recent availability of eculizumab, a humanized monoclonal antibody to complement component C5, which has demonstrated drastic improvement in prognosis. The issue, however, is arriving at a timely diagnosis given the considerable amount of overlap in the clinical and biochemical manifestation of P-aHUS, HELLP syndrome (haemolysis, elevated liver enzyme and low platelet count) and other hypertensive disorders of pregnancy. We present a case report and literature review that highlights the clinical conundrum of arriving at the diagnosis. We also highlight the importance of early management of P-aHUS with eculizumab and its impact on improving morbidity.

Keywords

Atypical haemolytic uremic syndrome, haemolysis, elevated liver enzymes, low platelet syndrome, eculizumab, preeclampsia, renal failure

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Background

Atypical haemolytic uremic syndrome (aHUS) is both an acute and chronic disease of complement-mediated thrombotic microangiopathy (TMA) with high mortality and morbidity.^{1,2} Pregnancy is a well-recognised trigger (P-aHUS) with 75% reported to occur in the post-partum setting.³ The clinical and biochemical features of P-aHUS overlap with preeclampsia and HELLP syndrome, hence, often resulting in a clinical conundrum.^{4–6} The introduction of eculizumab has revolutionized the way clinicians manage aHUS with demonstrable improvement in morbidity.^{7,8} Our case highlights the importance of early recognition and management of P-aHUS.

Case report

A 27-year-old primigravid Caucasian was diagnosed with preeclampsia at her routine antenatal follow-up in a peripheral hospital at 32 + 2 weeks gestation. Diagnosis was made based on new onset hypertension (blood pressure (BP) of 160/108 mmHg), proteinuria (urinary protein to creatinine ratio (PCR) of 450 mg/mmol) and renal impairment (serum creatinine of 103 µmol/L). In the preceding nine years, her serum creatinine fluctuated between 75 and 100 µmol/L in the absence of haematoproteinuria or significant personal or family medical history.

She was transferred to our institute, a metropolitan tertiary centre, within 24 h and was noted to have mild thrombocytopenia (platelet count $133 \times 10^9/L$), normal haemoglobin level (125 g/L) and mildly elevated alkaline phosphatase (179 U/L) with the rest of the liver function within normal limits. Her blood pressure was well controlled with oral labetalol 100 mg BD and delivery was induced the following day due to the worsening of renal function (serum creatinine 110 µmol/L). At 32 + 5/40 gestation, a live female infant (1.63 kg, <5th centile) was delivered via normal vaginal delivery with a grossly normal placenta and subsequent normal histopathology. Within 2 h of delivery, a sudden rise in BP up to 190/100 mmHg (from 130/85 mmHg) associated with blurred vision, headache and severe right upper quadrant and epigastric pain was noted. Her blood pressure was managed and maintained at a target of 130/80 mmHg with both oral and

intravenous antihypertensive agents. Rapid deterioration of liver and renal function with thrombocytopenia and anaemia (microscopic haemolysis noted on blood film) was noted (Table 1) and based on which, the diagnosis of HELLP syndrome was made. Within 12 h of delivery, she became progressively oliguric (20 mls/4 h) with worsening liver function and haematological parameters and was transferred to the intensive care unit where her parameters continued to worsen (Table 1). While the presence of microangiopathic haemolysis on blood film with elevated lactate dehydrogenase supported the diagnosis of HELLP syndrome, the disproportionately impaired renal function (serum creatinine of 554 µmol/L and urea of 23.4 mmol/L) with microscopic haematuria and oliguria raised strong suspicion of P-aHUS. Based on this, plasma exchange was commenced and haemodialysis was indicated due to fluid overload and acidosis. Intravenous eculizumab 900 mg was administered on day-3 postpartum, after which improvement in haematological parameters (within 24 h) followed by renal function (within 4 days) was observed with no further dialysis or plasma exchange (Table 1 and Figure 1). A renal biopsy was performed at day-9 post-partum (six-days post-eculizumab) in which features of acute tubular necrosis were noted. A second dose of eculizumab 900 mg was administered a week later (day-13 post-partum) and continued improvement in biochemical and clinical parameters was observed (Table 1). She was discharged at day-15 post-partum, after which she received a final induction dose of 900 mg eculizumab on day-21 post-partum. This was followed by ongoing maintenance therapy of eculizumab at 1200 mg fortnightly. Meningococcal vaccine and prophylactic oral amoxicillin were administered and the patient breastfed through the duration of therapy.

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Table 1. Biochemistry results.

	9 years prior	6 years prior	5 years prior	(-) Day 2 [#]	(-) Day 1 [#]	DAY 0 (PRE) [^]	DAY 0 (POST) ^{^^}	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 8	Day 13	Day 15	Day 22
Urea (mmol/L)	3.4	3.7	2.8	7	10.8	10.1	12.9	16.5	23.4	14.9	19.7	22.4	24.9	23	13.4	12.9	11.3
Creatinine (μmol/L)	100	75	90	103	110	102	192	316	544	396	541	606	721	664	310	247	105
ALT* (units/L)	20	10	10	16	13	11	310	660	609	271	207	164	92	79	21	18	13
AST** (units/L)	18	16	19	30	21	19	113	1037	712	236	94	52	24	22	11	13	10
Haemoglobin (g/L)	144	127	136	125	106	112	113	100	79	73	85	86	78	106	110	116	116
Platelet (× 10 ⁹ /L)	206	179	265	128	134	128	66	44	48	48	68	94	158	204	453	528	436
LDH*** (units/L)	162	153	169					3789	1990	796	828		576		216		194
Haptoglobin (g/L)								<0.08		0.09		0.34	0.81			1.54	

*Alanine aminotransferase (ALT).

**Aspartate aminotransferase (AST).

***Lactate dehydrogenase (LDH)

#Inpatient antenatal blood results.

^Blood results from day of delivery: pre delivery.

^^Blood results from day of delivery: post delivery (at time of hypertensive emergency episode).

ALT: Alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase.

Vasculitic, thrombophilic screen and ADAMTS 13 activity level were normal. Complement Factor I and H level were both normal at 17.30 mg/L and 413 mg/L, respectively. Granulocyte expression of membrane cofactor protein (MCP/CD45) was reduced; however, common aHUS MCP genetic abnormalities were not detected. Follow-up biochemistry done at two months post-partum showed a serum creatinine of 110 μmol/L with normal haematology and liver function parameters.

Discussion

Atypical HUS is a result of dysregulation of the alternative complement pathway (ACP) and is characterised by the triad of thrombocytopenia, microangiopathic haemolytic anaemia and acute renal failure.^{1,2,9} Physiologically, the ACP is spontaneously activated and regulated by plasma and membrane bound factors, mainly Factor H (FH), Factor I (FI), membrane cofactor protein (MCP/CD46) and decay accelerating factor (DAF/CD55).^{3,10-12} The presence of acquired (anti FH antibodies), constitutional inactivating mutations in FH, FI or MCP coding genes or activating mutations in factor B and C3 coding genes leads to dysregulation of the ACP.¹²⁻¹⁴ The loss of adequate ACP regulation results in over-activation of C3 convertase which leads to complement-induced insult of the host cells, mainly endothelial cells.^{2,3,15}

Patients with these mutations often manifest the disease when exposed to a trigger; one of which is pregnancy, which is an inciting event in 20% of female with adult onset aHUS.^{3,15} Pregnancy-associated aHUS (P-aHUS) occurs in every 1 of 25,000 pregnancies with more than 75% occurring in the postpartum period.^{1,3} Pregnancy is a physiological state of complement activation due to the maternal-fetal immunological cross interaction and is regulated by the maternal and trophoblast ACP regulatory factors.^{3,16,17} In pregnancy, uncontrolled maternal ACP activation is further regulated by trophoblast surface expression of DAF/CD55, MCP/CD46 and CD59.¹⁸⁻²⁰ Thus, the integrity of these regulatory factors from the trophoblast provides an effective control of the maternal complement activation, even in women with ACP regulatory factor mutations.^{3,21} At delivery, the inflammatory stress of delivery and the release of fetal cells into maternal circulation leads to amplified activation of the maternal ACP.^{3,16,21} In women with defective ACP regulation, the absence of effective regulatory mechanism from the trophoblast after delivery leads to the clinical and biochemical manifestation of P-aHUS.³

The diagnosis of P-aHUS is made based on biochemical features of haemolysis, acute renal failure and systemic thrombotic microangiopathy.^{1,15,22} The issue, however, is differentiating P-aHUS from HELLP syndrome as demonstrated in our case and in the literature.^{4-6,15,23} The initial diagnosis in our case was HELLP syndrome; however, the rapid deterioration in renal function with new microscopic haematuria raised the strong clinical suspicion of aHUS. The difference between aHUS and HELLP syndrome is often subtle, if present, with P-aHUS demonstrating a more severe form of acute kidney injury (AKI) with TMA and HELLP syndrome demonstrating more hepatic ischemia.^{15,24} This difference, however, is lost when the peri-partum period is complicated by haemodynamic instability, particularly hypotension.^{25,26} In our case, the clinical suspicion for aHUS was strengthened by the presence of oliguric AKI in the absence of significant hypotensive or hypovolaemic events. A renal biopsy often strengthens the diagnosis of aHUS when evidence of TMA is observed. In our case, however, the renal biopsy was performed six days after eculizumab therapy and when renal recovery was evident. It is now understood that both P-aHUS and HELLP syndrome share a common pathophysiology in the dysregulation of the ACP, thus accounting for the biochemical similarity which often leads to a clinical conundrum.^{12,15,23} This has therefore raised the question if both P-aHUS and HELLP make up a spectrum of TMA with ACP dysregulation and is a subject of ongoing research.

The poor prognosis of aHUS is well documented with a 25% mortality rate and 70% reaching dialysis dependent end stage renal disease

Figure 1. Graph illustrating biochemical changes with therapy.

(ESRD) within three years despite plasma exchange.^{1,9} Eculizumab, a monoclonal antibody, inhibits complement-mediated TMA and demonstrates substantial improvement in the prognosis of aHUS.^{7,27} Current data suggest rapid and sustained improvement in renal function and haematological parameters with reduced need for plasma exchange/infusion, particularly when eculizumab is initiated within two months and with chronic maintenance therapy.^{7,27,28} The efficacy of eculizumab in improving morbidity of P-aHUS is evident in our case report which is in keeping with the literature.^{29,30} There remains paucity in data and guidelines on the appropriate duration of eculizumab therapy and the prophylactic management for subsequent pregnancies in these patients. In the absence of concrete guidelines, we plan to continue chronic eculizumab therapy in our patient including the possibility of continuing therapy during her subsequent pregnancy.^{3,31}

Our report highlights the importance of considering aHUS as a differential diagnosis in patients with a clinical and biochemical scenario suggesting preeclampsia or HELLP syndrome. Early recognition and treatment of P-aHUS with eculizumab improves morbidity particularly with minimizing the progression to ESRD. The clinical use of eculizumab for HELLP syndrome is subject to ongoing investigation and we anticipate a potential therapeutic role in the near future.³²

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