CASE REPORT

Recurrent case of pregnancy-induced atypical haemolytic uremic syndrome (P-aHUS)

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SUMMARY

Pregnancy-induced atypical haemolytic uremic syndrome (P-aHUS) is a rare condition characterised by microangiopathic haemolytic anaemia, thrombocytopenia and renal failure. It accounts for approximately 7% of total HUS cases. Here, we present a case of recurrent P-aHUS in a 25-year-old Hispanic woman. Pregnancy was the clear trigger in both instances, and the disease manifested in first week of the postpartum period. Because of her significant obstetric history, a multidisciplinary approach was adopted to monitor her second pregnancy antepartum and post partum. As the patient developed recurrence of P-aHUS 4 days after her delivery, she was immediately administered eculizumab within few hours of disease manifestation. The patient normalised her haematological parameters within 1 week but sustained dialysis-requiring renal failure for a total of 6 weeks. This case highlights the advances as well as the ongoing uncertainties, especially with respect to the use of eculizumab, in this rare but morbid disease.

BACKGROUND

Pregnancy-induced atypical haemolytic uremic syndrome (P-aHUS) is a rare disease, together with thrombotic thrombocytopenia, it occurs with an incidence of 1 in 25 000 pregnancies.¹ Pregnancy is a known trigger for an aHUS episode. Traditional treatments, such as plasmapheresis and plasma exchange, have not shown good efficacy in both

pregnancy and non-pregnancy-related aHUS.² The advent of eculizumab, a monoclonal antibody to C5 in the complement cascade, has transformed the outcome of these patients. However, it is unclear how often this disease recurs in a subsequent pregnancy, and whether empiric treatment with eculizumab should be given in a subsequent pregnancy before disease manifestation. In this case, we will highlight our current knowledge and controversies on this very interesting subject.

CASE PRESENTATION

We present a 25-year-old G4P1 Hispanic woman with a history of P-aHUS who is now being admitted for an elective caesarean section (C-section) at 39 weeks gestational age (GA). The patient's obstetric history includes a first pregnancy which resulted in a miscarriage at 16 weeks GA due to preterm premature rupture of membranes requiring dilatation and curettage, a second pregnancy which resulted in an emergent C-section at 39.5 weeks due to fetal bradycardia but no further complications. The patient's third pregnancy was delivered by elective C-section at 39 weeks and was complicated by postpartum haemorrhage which responded to transfusions of three units of packed red blood cell and three units of fresh frozen plasma. After the stabilisation and subsequent discharge from the hospital the patient returned to the emergency department 1 day after (4 days post partum) with nausea, vomiting and abdominal pain. On laboratory examination, she was found

Figure 1 Patient response to plasmapheresis and eculizumab.

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Table 1 Laboratory values during hospitalisation

Laboratories	Day 1 of admission	Day 2	Day 4	Day 5	Day 6	Day 7	Day 9	6 weeks
Haemoglobin (13.5–17.5 g/dL)	11.2	9.3	8.3	7.5	7.2	6.8	9.7	11.2
White cell count (3.9–10.6×10 ⁹ /L)	13.1	9.4	8.3	7.0	6.7	7.2	7.5	5.1
Platelet count (150–440×10 ⁹ /L)	353	320	210	174	141	103	70	415
Blood urea nitrogen (5–26 mg/dL)	5	6	10	16	21	29	41	17
Creatinine (0.1–1.5 mg/dL)	0.6	0.6	1.3	1.9	2.6	3.6	4.2	1.1
Total bilirubin (0.1–1.2 mg/dL)	0.3	0.2		0.6	0.7	0.9	1.6	0.1
Alkaline phosphatase (30–115 units/L)	194	139		124	113	117	122	94
Aspartate aminotransferase (5–40 units/L)	24	18		30	33	43	66	18
Alanine aminotransferase (1–40 units/L)	8	7		12	14	17	22	17
Lactate dehydrogenase, blood (100–210 units/L)		374	385	594	896	1130	1323	206
Haptoglobin (34–200) mg/dL		142						183
Retic count (0.5%–2.0%)			3.3	3.4	4.4			
ADAMTS-13 (ref. interval: >67%)							100%	
on Willebrand factor, ristocetin cofactor (50%–150%)							144%	
Complement C3 (90–180 mg/dL)				95.3	94.1			84.1
Complement C4 (10–40 mg/dL)				46.2				40.6
Complement total CH50 (42–60 units/mL)						<12	<12	
Urinalysis						Large blood, protein ≥300 mg/dL		Large blood, 7–20 RBC/hpf, protein 100 mg/dL
Urine protein to creatinine ratio (≤84 mg/g)		182 mg/g				7173 mg/g		232 mg/g

hpf, high-power field; RBC, red blood cell.

to have haemolytic anaemia, thrombocytopenia and acute kidney injury. The patient was presumed to harbour either the diagnosis of thrombotic thrombocytopenic purpura (TTP) or P-aHUS and she was empirically started on plasmapheresis while an ADAMTS-13 activity level was sent. She was also started on intermittent haemodialysis (IHD) due to uremic symptoms. The patient subsequently received a total of four sessions of plasmapheresis and three doses of dexamethasone (40 mg intravenous once and 15 mg intravenous two times) followed by one dose of 100 mg prednisone orally. After 48 hours, the ADAMTS-13 activity returned to be normal at 75% which excluded TTP as a diagnosis and justified the discontinuation of plasmapheresis and steroids. The patient was now given the diagnosis of P-aHUS. As eculizumab is the drug of choice for P-aHUS, the patient was prophylaxed with the meningococcal vaccine followed by administration of eculizumab. Seventy-two hours later, the patient's platelet count improved and her haemoglobin stabilised (see figure 1). However, because her renal function did not improve, a renal biopsy was performed, which revealed subacute and chronic changes with thrombotic microangiopathy, predominantly involving glomeruli, with patchy acute tubular injury and mild interstitial fibrosis and interstitial inflammation. The patient continued to require IHD for 5 more weeks as an outpatient before complete renal recovery. In the end, her treatment with eculizumab was discontinued 4 months after initiation. The patient had remained well until her fourth pregnancy 2 years later (present case). Given her complicated previous delivery, the patient was scheduled for

an elective C-section with careful postpartum monitoring. Though the C-section was uneventful, 3 days post partum (day 4) the patient developed clinical signs of P-aHUS once again (see table 1) (see figure 2). Table 2 shows thrombotic microangiopathy complement panel result at 35 weeks and 5 days GA of current pregnancy

INVESTIGATIONS

Renal biopsy during the first episode of P-aHUS:

1. Thrombotic microangiopathy, subacute and chronic, predominantly involving glomeruli, with focal arteriolar involvement (postpartum HUS/clinical).
2. Acute tubular injury, patchy.
3. Tubular atrophy, interstitial fibrosis and interstitial inflammation, mild.

TREATMENT

In the present case, as soon as the patient developed recurrence of P-aHUS, she was administered eculizumab 900 mg intravenously. The patient's ongoing haemolytic anaemia was supported by six units of red blood cell transfusions. The patient's renal failure, once again, did not immediately improve and required the initiation of IHD for uremic symptoms 3 days after the first eculizumab dose. Eculizumab response was monitored by measuring the inhibition of complement total CH50 activity which remained below 12 units/mL (normal range 42–60 units/mL).

Table 2 Thrombotic microangiopathy complement panel at 35 weeks and 5 days GA.

Factor H (47–68 mg/dL)	Factor I (2.4–4.9 mg/dL)	Factor H autoantibody (≤22 unit/mL)	Factor B (13.3–31.5 mg/dL)	C3 (71–150 mg/dL)	C4 (15.7–47 mg/dL)
43.7 mg/dL	4.7 mg/dL	<22 unit/mL	26.3 mg/dL	143 mg/dL	48.1 mg/dL

Figure 2 Patient response to eculizumab.

OUTCOME AND FOLLOW-UP

One-week post-administration of eculizumab, the patient's haematological parameters improved but she required continued IHD support for a total of 6 weeks before her renal function normalised. During that time, the patient continued to receive

eculizumab as an outpatient as per protocol (900mg weekly for 4 weeks followed by 1200mg every 2 weeks). She has since received a total of 12 doses before the treatment was discontinued based on persistent clinical and laboratory remission. The aHUS genetic susceptibility panel (see [table 4](#)) revealed that the

Figure 3 Complement system pathways. FB, factor B; FD, factor D; FH, factor H; FI, factor I; MBL, mannose-binding lectin; MASP12, mannan-binding lectin serine protease 1, 2.

Table 3 Summary of case reports

Different cohorts	Cohort characteristics	Complement gene mutations percentage	Treatment and outcome
Fakhouri <i>et al</i> ¹⁸	<ul style="list-style-type: none"> ▶ A small French cohort of 21 female patients with P-aHUS. ▶ Risk of P-aHUS was highest during second pregnancy. ▶ 79% of women experienced P-aHUS episode during postpartum period. 	<ul style="list-style-type: none"> ▶ 86% of patients with complement gene mutations. ▶ 48% were due to the CFH mutation. 	<ul style="list-style-type: none"> ▶ Treatment consisted mainly of PE in 15 of 18 patients (83%). ▶ No treatment record available for four patients and two patients did not receive any treatment (one patient MRI showed cortical necrosis). ▶ Long-term outcome was poor with 76% of females reached ESRD by 1 month or underwent renal transplantation by last follow-up.
Bruehl <i>et al</i> ⁶	<ul style="list-style-type: none"> ▶ A European study of 87 women. ▶ P-aHUS during first pregnancy in 58% of cases. ▶ 76% in postpartum period. 	<ul style="list-style-type: none"> ▶ 56% of patients with complement gene mutations. ▶ 30% were due to CFH. 	<ul style="list-style-type: none"> ▶ Follow-up period of 7.2 years. ▶ 53% of patients reached ESRD. ▶ 19% had CKD. ▶ 28% experienced a-HUS relapse. ▶ 42% had a-HUS recurrence in a subsequent. ▶ 54% had recurrence after transplantation. ▶ Of four patients (5%) who received eculizumab, three had complete renal recovery.
Huerta <i>et al</i> ³	<ul style="list-style-type: none"> ▶ A Spanish study of 22 women. ▶ 16 patients (72%) presented during the first pregnancy. 	<ul style="list-style-type: none"> ▶ 66% of patients with complement gene mutations. 	<ul style="list-style-type: none"> ▶ 18% reached ESRD within first month. ▶ 27% required renal replacement therapy. ▶ Seven patients (32%) had a-HUS recurrence and among them, four had recurrence after renal transplant.
Noris <i>et al</i> ²	<ul style="list-style-type: none"> ▶ 273 patients (82 familial and 191 sporadic). 	<ul style="list-style-type: none"> ▶ CFH, C3, THBD, CFI, MCP mutations and autoantibodies to CFH noted. ▶ Among 273, 139 (51%) had mutations. 	<ul style="list-style-type: none"> ▶ Plasma therapy induced complete or partial remission in 55%–80% of patients with CFH, C3, THBD mutations or autoantibodies. ▶ MCP mutations responded most favourably at 97%. ▶ CFI mutations responded poorly to 25%.

CFH, complement factor H; CFI, complement factor I; CKD, chronic kidney disease; ESRD, end-stage renal disease; MCP, membrane cofactor protein; P-aHUS, pregnancy-induced atypical haemolytic uremic syndrome; PE, plasma exchange; THBD, thrombomodulin.

patient was a compound heterozygote for a variant in complement factor H (CFH), and for a likely pathogenic variant in C3. The CFH variant C.3408C>G is a nonsense variant which results in a premature stop codon. The C3 variant C.193A>C leads to substitution of glutamine for lysine at amino acid 65.

DISCUSSION

The P-aHUS is a rare condition and constitutes approximately 7% of total aHUS cases and up to 20% of all aHUS cases in women.^{3,4} The complement system is activated via three pathways: the classical, lectin and alternative pathways. Phagocytosis and direct lysis are two main mechanisms through which these pathways eliminate the target. C3b and C5a components of the complement system promote phagocytosis by opsonisation and chemotaxis, respectively. All three pathways ultimately lead to the formation of the membrane attack complex (MAC) which causes cell lysis⁵ (see figure 3). The alternative pathway is unique as compared to the two other pathways because it is continuously active at a low level. Plasma proteins such as CFH and complement factor I (CFI) as well as membrane proteins like CD35, CD46, CD55 and CD59 are considered 'complement regulatory proteins' that regulate the alternative pathway; a loss of regulation at any of these control points may be responsible for unchecked complement activity.⁵ The complement system is more active in pregnancy as compared with the non-pregnant state. Mutations in complement regulatory proteins that are mostly implicated include CFH, CFI, factor B, membrane cofactor protein, thrombomodulin have now been described in a majority of women who developed P-aHUS⁶ (see table 3). Our patient was also found to be heterozygous for a variant in CFH and likely a pathogenic variant in C3 (see table 4). The C3 variant C.193A>C leads to the substitution of glutamine for lysine at amino acid 65, which results in a missense mutation and decreased binding of C3b to CFH in vitro; three adult patients who acquired aHUS after renal transplantation have found to

harbour this mutation.⁷ The CFH variant, on the other hand, is unique in our patient as it is never reported in the aHUS literature before, but is considered pathogenic because it leads to a premature stop codon and has been described in one individual with Marfan syndrome.⁸

The advent of eculizumab has the potential to dramatically improve the outcome of this highly morbid disease.⁹ Eculizumab is a humanised monoclonal antibody that blocks the cleavage of the terminal complement protein C5 preventing formation of MAC¹⁰ and has been used to treat P-aHUS with improvement in haematological and renal parameters in a patient who carried heterozygous mutations in the CFH and CFI genes.¹¹ The duration of eculizumab treatment for P-aHUS remains unclear at this time. A 2-year analysis of phase 2 studies in aHUS demonstrated that longer term eculizumab therapy improved haematological and renal parameters.¹² Some patients remain on lifelong eculizumab while others discontinue after recovery and only restart if disease recurred. A more recent analysis of the aHUS cases from the 2014 Johns Hopkins' Thrombotic Microangiopathies Registry reveals a discontinuation rate of 26%.¹³ Merrill *et al* suggested that eculizumab can be safely discontinued once clinical remission is achieved.¹⁴ The approach of early eculizumab initiation with continued therapy until clinical remission followed by a cessation trial with regular laboratory monitoring will result in good long-term renal outcome while resulting in minimising side effects and significant cost savings.¹⁴ Side effects

Table 4 Genetic Panel (Sequence analysis)

CFH	Allele 1: c.3408C>G (p.Tyr1136)
	Allele 2: no mutation identified
C3	Allele 1: c.193A>C (p.Lys65G1n)

Allele 2: No mutation identified.
CFH, complement factor H.

are generally minimal as the drug is well tolerated, though it is recommended to vaccinate against the meningococcus bacteria due to risk of bacteraemias. The costs, however, remain quite high, quoted to be from US\$5000 to US\$7696.80 per 300 mg vial, which may remain a significant barrier to many, especially to those in resource-poor countries.^{14 15} The use of eculizumab appears to be safe in pregnancy and breast feeding, as eculizumab has not been detected in umbilical cord or neonates' blood samples¹⁶ and breast milk.¹⁷ It is also very well tolerated with minimal side effects, with few cases of anaemia, diarrhoea and bacteriuria.¹² It is important to vaccinate with the meningococcal vaccine prior to drug administration due to the risk of bacteraemia, though this occurrence has not been reported in clinical trials.¹² We believe that if aHUS occurs in the presence of a known trigger, such as pregnancy, it is reasonable to discontinue eculizumab when that trigger has been removed, and when the patient has normalised all haematological and renal derangements. Whether we should empirically treat a patient who has a history of P-aHUS in a subsequent pregnancy is unclear: the true recurrence rate in pregnancy is not known and there has been no clear observed differences in recurrence between carriers and non-carriers of mutations (irrespective of pregnancy status).¹² We do, however, recommend a multidisciplinary approach and prolonged monitoring, up to 3 months post partum, for signs of recurrence and immediate treatment on recurrence.

Patient's perspective

The patient said at recent follow up: "Medicine made me very sick, but I remained optimistic."

Learning points

- Pregnancy-induced atypical haemolytic uremic syndrome (P-aHUS) is a rare and life-threatening disease and pregnancy is a potent trigger.
- Eculizumab is the drug of choice for P-aHUS.
- Despite lack of clear data on recurrence rates of P-aHUS, closely monitoring such high-risk patients in a multidisciplinary fashion is able to achieve a favourable outcome.

Contributors The author contributions are as follows: DK participated in the renal care for the patient and prepared the manuscript. MK participated in the obstetric care for the patient and contributed to writing of the manuscript. BJ contributed to the care of the patient and the writing of the manuscript. AA supervised the writing and clinical care of the patient.

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