SUSPECTED ATYPICAL HAEMOLYTIC URAEMIC SYNDROME IN TWO POST-PARTUM PATIENTS WITH FOETAL-DEATH IN UTERO RESPONDING TO ECULIZUMAB

Justin Chua[a], Kathy Paizis[a], Simon Z. He[b], Peter Mount[a]

[a] Department of Nephrology, Austin Hospital, Victoria, Australia
[b] Department of Clinical Haematology, Austin Hospital, Victoria, Australia

INTRODUCTION

Atypical haemolytic uraemic syndrome (aHUS) is a rare and life-threatening condition with the triad of microangiopathic haemolytic anaemia, thrombocytopenia and acute kidney injury.[1] It is due to the pathological over-activation of the alternative complement pathway causing thrombotic microangiopathy and endothelial damage. Pregnancy is known to be a precipitating factor for aHUS, with a previous study finding 21% of aHUS cases associated with pregnancy[2]. However, there are other conditions which present in a similar manner in the peri-partum period.[2, 3] Due to the systemic nature of complement activation of aHUS, multiple organ systems can be involved and it can be difficult to reach a diagnosis.

We describe two cases of suspected aHUS, who presented post-partum with foetal death-in-utero at 33 and 37 weeks respectively. Both presented with the triad features of aHUS but had considerably different clinical courses. Both received eculizumab, the fully humanised monoclonal antibody that blocks the cleavage of C5, which prevents the further amplification of the complement system.[4] This resulted in a reduction in haemolysis with rapid and sustained reduction in LDH and normalised platelet counts, and complete recovery of renal function in both cases. Currently, there is uncertainty regarding the optimal duration of eculizumab therapy in patients who are in remission from aHUS.

CASE REPORT #1

A 34-year-old female who was 33 weeks pregnant presented with per-vaginal bleeding, decreased foetal movements, intermittent right upper quadrant abdominal pain and was hypertensive with a blood pressure of 180/100. An ultrasound revealed a foetal-death-in-utero of 33 weeks gestation. There was no pre-eclampsia prior to presentation. She did not have significant co-morbidities and her medications consisted only of pregnancy multivitamin supplementation. Her prenatal follow-up had been unremarkable.

Prior to planned medical delivery, the patient developed thrombotic microangiopathic disease with multi-organ involvement necessitating emergency caesarean section and admission to the intensive care unit. Within 72 hours, her haemoglobin dropped from 169g/L to 62g/L and her platelet count dropped from 174×10^9/L to 88×10^9/L. She had undetectable haptoglobin, raised LDH of 749 (normal range 135-214), increased reticulocyte count of 135×10^9/L and her blood film demonstrated spherocytes and red cell fragments. She was coagulopathic with an INR of 2.1 and APTT of 52sec. The patient had acute renal failure with a creatinine of 328micromol/L and proteinuria with a spot urine protein-creatinine ratio of

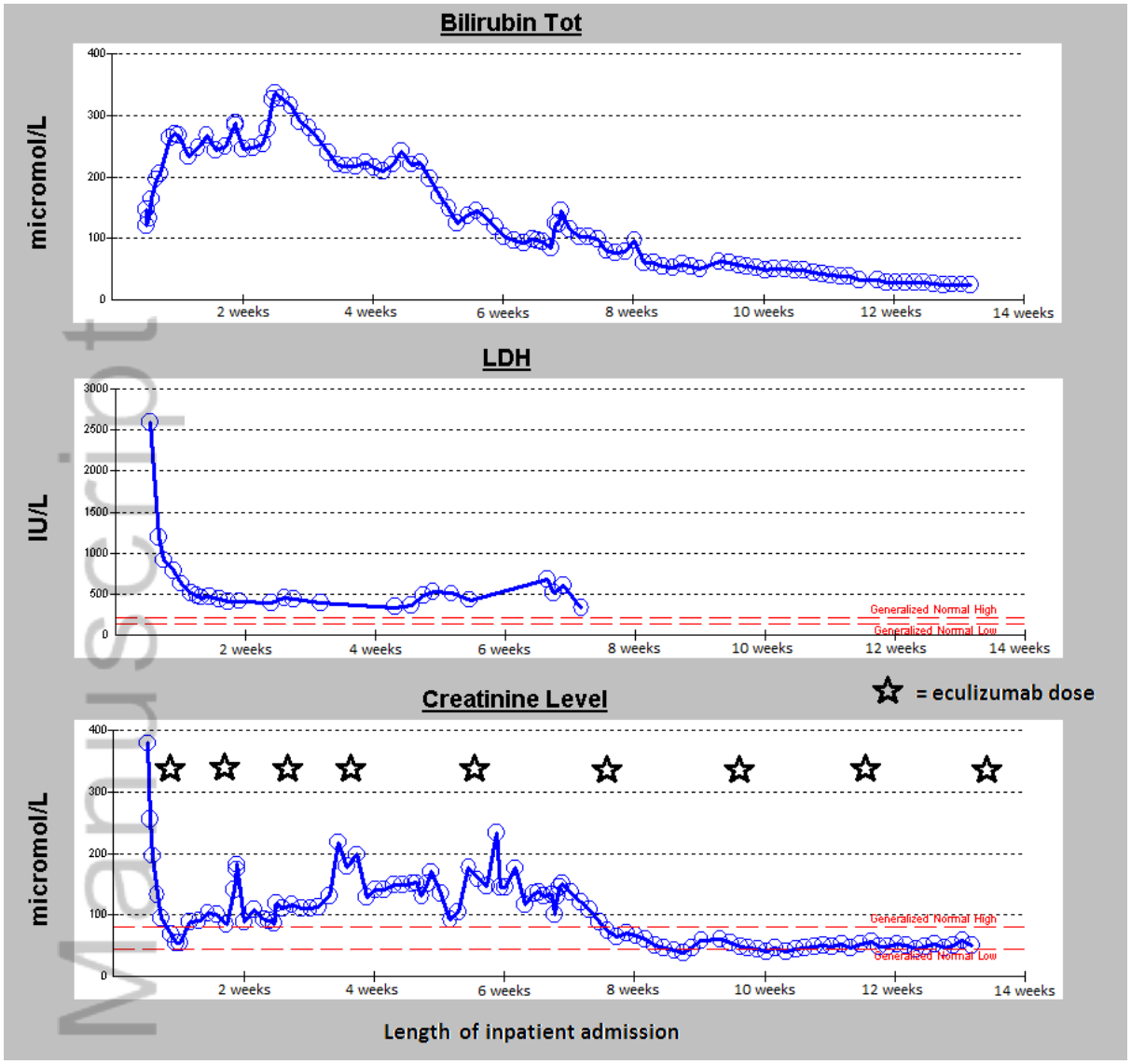
This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/nep.12935

0.14g/mmol. She also developed liver pathology with a bilirubin of 112micromol/L and deranged liver-transaminases with ALT 333, ALP 219 and GGT 137.

The patient had five sessions of plasma exchange but continued to deteriorate. She had ongoing haemolysis with fragmentation on blood-film and rising LDH of 2592, which precipitated a haemoglobin drop down to 55g/L requiring multiple blood transfusions. The patient developed neurological complications with reduced conscious state requiring intubation. A magnetic resonance imaging of the brain did not demonstrate pathology and an electroencephalogram confirmed severe encephalopathy. The patient continued to have ongoing coagulopathy and conjugated hyperbilirubinemia. A liver ultrasound demonstrated fatty infiltration and a hepatitis screen was negative. Despite the creatinine stabilising to around 300micromol/L, the urea increased to 32.1mmol/L and the patient became anuric, requiring commencement of haemofiltration 7 days post-caesarean section.

Further complications included culture negative febrile episodes, pulmonary embolism, pleural effusions, pancreatitis, recurrent abdominal collections, splenic artery branch perforation requiring radiological embolisation, ischaemic bowel requiring partial bowel resection and end colostomy, critical illness myopathy and malnutrition.

Figure #1: Bilirubin, LDH and creatinine levels in relation to eculizumab doses for the first case during her admission



Initial ADAMSTS13 activity was borderline-low (10.3%) and normal on repeat testing (42.6%) after 8 weeks. Faecal testing was negative for Shiga-toxin. An autoimmune screen, including antiphospholipid antibodies, was unremarkable. aHUS was considered the most unifying diagnosis and the patient was urgently commenced on eculizumab, with the dosing of 900mg weekly for four treatments, followed by maintenance 1200mg fortnightly. She was given meningococcal vaccinations and had prophylactic antibiotics.

The patient had a slow recovery with eculizumab therapy. Her renal function improved and she was able to come off haemofiltration on day 48 of her admission in ICU, without further requirement of renal replacement therapy. The haemolytic markers improved with rapid reduction in LDH 4 days after the first dose of eculizumab, and her liver transaminases slowly trended back to the normal range, with the bilirubin peaking at 336micromol/L and

returning to normal 4.5 months later. The patient was able to be transferred to the ward 73 days after her initial admission and was discharged to rehabilitation 20 days later.

The patient continues to receive eculizumab 1200mg on a fortnightly basis and is closely monitored as an outpatient. She remains well, with remission of aHUS 8.5 months after initial presentation. Her renal function has normalised and there are no findings of haemolysis. Genetic testing for aHUS is pending.

CASE REPORT #2

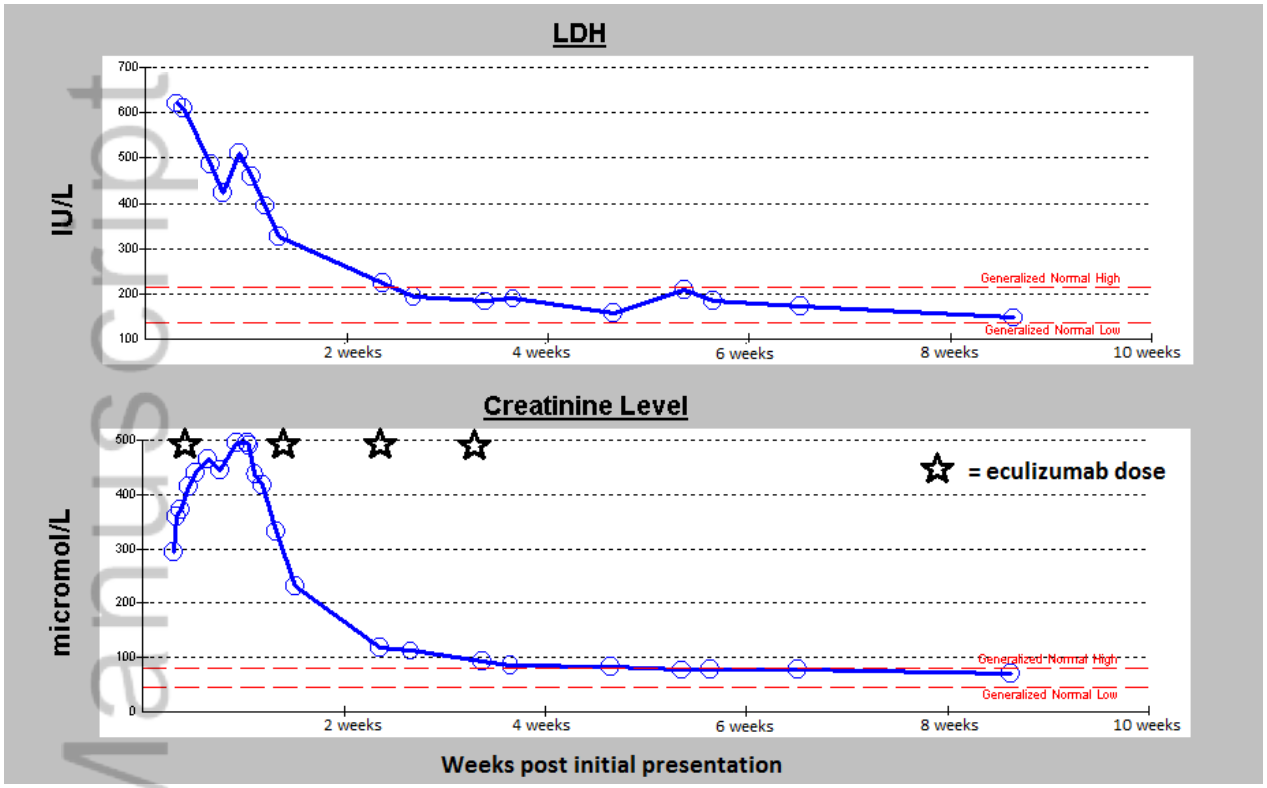
A 29-year-old female who was 37 weeks pregnant, presented with abdominal pain and had foetal-death-in-utero in the setting of peri-partum pre-eclampsia. She had normal blood pressure and urinary protein six days prior to presentation. She did not have significant co-morbidities and was not on medications. The patient spontaneously went into labour and delivered the foetus, complicated by post-partum haemorrhage of one litre.

Post-partum, the patient subsequently had rapidly declining renal function with polyuria. Her creatinine which was normal prior to presentation, increased to a peak of 495micromol/L six days post-partum. She also developed proteinuria, with a spot urine protein-creatinine ratio of 0.32g/mmol. The patient had microangiopathic haemolytic anaemia, evidenced by an elevated LDH which peaked at 620 and moderate red cell fragments seen on blood-film. The patient's haemoglobin dropped acutely to 68g/L and platelets fell to $70x10^9$/L, which was monitored but did not require blood product support. Liver tests were unremarkable apart from an ALP of 201.

The patient's ADAMSTS13 activity was normal at 62% and an autoimmune screen was unremarkable. The patient was given a presumptive diagnosis of aHUS and underwent two sessions of plasma exchange prior to commencement of eculizumab 900mg weekly. The patient received meningococcal vaccinations and was commenced on prophylactic antibiotics.

The patient remained clinically stable throughout her admission and did not require dialysis. She was discharged one week after initial presentation, with improving creatinine and haemolysis markers. LDH and creatinine normalised 2.5 weeks and 1 month from first presentation respectively. The patient was given a total of four doses of eculizumab, and as she was stable, was trialled off eculizumab, with close monitoring to assess for relapse of disease. At present, 7 months post-stopping eculizumab, the patient remains well with normal renal function and no evidence of haemolysis. Genetic testing for aHUS is pending. Post mortem of the foetus revealed acute asphyxia thought secondary to a knot in the umbilical cord. The placenta had histological evidence of mild pre-eclampsia.

Figure #2: LDH and creatinine levels for the second case over time in relation to eculizumab doses



DISCUSSION

The two cases demonstrate the wide variation in the clinical manifestations of aHUS. In particular, the first case resulted in significant multi-organ failure and highlighted the life threatening nature of aHUS. In both cases, the diagnosis of aHUS was not immediately clear, emphasising the importance of having early clinical suspicion for the disease. There are several causes of microangiopathic haemolysis which occur in the peri-partum period to consider in the differential diagnosis, and there is overlap between these conditions. These include HELLP syndrome (haemolysis, elevated-liver-enzymes and low-platelets), severe pre-eclampsia, thrombotic thrombocytopaenic purpura (TTP), acute fatty liver of pregnancy and Shiga toxin-producing Escherichia coli haemolytic uraemic syndrome (STEC-HUS).[2, 3]

HELLP syndrome is considered a form of severe pre-eclampsia, though this is controversial.[5] It most often presents with hypertension and proteinuria and usually occurs in the third trimester, but resolves within one week of delivery.[5] Haemolytic anaemia and thrombocytopenia are sometimes present, and there is normally only mild-to-moderate acute

kidney injury. Liver transaminases are usually elevated. Both patients were not hypertensive until the time of delivery, at which time they both had proteinuria.

Pregnancy-related TTP is due to a lack of ADAMTS13 enzyme which interferes with its ability to process von Willebrand Factor (VWF), causing extensive microthrombi formation with haemolysis and end-organ-effects.[5] It usually presents in the second or third trimester with no recovery after delivery, and has marked haemolytic anaemia but only mild-to-moderate acute kidney injury.[3] The basis of diagnosis is measurement of ADAMTS-13 activity <10%.[6] Both cases presented here had ADAMTS-13 activity above 10% and had renal failure which was severe and not in keeping with TTP.

Acute fatty liver of pregnancy usually occurs in the third trimester.[3] It regularly causes moderate acute kidney injury and derangement of liver transaminases. There is normally less haemolytic anaemia and the condition usually recovers 1-2 days post-delivery. In the first case there was marked liver dysfunction, however the prolonged nature of the illness post-partum and the degree of haemolysis was not in keeping with acute fatty liver of pregnancy. In the second case, there was only mild derangement of liver transaminases.

STEC-HUS is associated with symptoms of diarrhoea and occurs most commonly in children, though can occasionally occur in adults.[7] It is diagnosed by assessing for Shiga-toxin in a faecal specimen. Both patients did not report significant diarrhoea and the first case had a negative Shiga-toxin test.

Pregnancy-associated aHUS is due to the pathological over-activation of the alternative complement pathway causing thrombotic microangiopathy and endothelial damage.[5] It usually presents in the post-partum period and is often marked by severe acute kidney injury and usually some degree of haemolytic anaemia and thrombocytopenia. There can also be other system involvement including neurological and gastrointestinal pathology. These other organ manifestations were particularly severe for the first case.

The diagnosis of aHUS can be difficult to make and relies on meeting established and the exclusion of competing diagnoses. Specifically, it involves the demonstration of thrombocytopenia and microangiopathic haemolysis with renal impairment, with the exclusion of TTP with a ADAMTS13 activity >10% and STEC-HUS with a negative Shiga-toxin test.[8] Whilst genetic testing for an identifiable genetic mutation can be beneficial, 30-50% of aHUS patients do not have a mutation.[9] Furthermore, these genetic tests are only performed at specialised labs and the results are not immediately available. The relative rarity of aHUS, the non-specific investigation results and the turnaround time for investigations, coupled with the severity and rapid deterioration of patients, makes aHUS very challenging to promptly diagnose and manage, which was the common experience with the two cases.

The aim of early recognition of aHUS is to initiate prompt treatment with eculizumab, a humanized monoclonal IgG antibody that binds to complement protein C5, preventing cleavage into C5a and C5b, which are pro-inflammatory components of the complement system that are key to the pathogenesis of aHUS.[10] Eculizumab treatment has been demonstrated to achieve a complete thrombotic microangiopathic response in a high proportion of aHUS patients, with significant improvement in renal function allowing them to discontinue dialysis.[4] Furthermore, it has been shown that there is improved renal recovery in patients who had eculizumab initiated early.[11] The two cases in this report both achieved

complete renal recovery and cessation of thrombotic microangiopathic response following eculizumab treatment.

The optimal duration of eculizumab therapy is uncertain, particularly in those who have achieved remission of aHUS, as there is little evidence to provide guidance. A 2-year extended follow-up of phase-two studies of eculizumab use in aHUS demonstrated maintenance of earlier clinical benefits, however it is unclear whether these benefits would have been maintained even if eculizumab had been ceased.[12] A case series of ten patients who were monitored post-cessation of eculizumab found that three experienced a relapse of aHUS within six weeks of discontinuing, however they achieved complete response with recommencement of treatment.[13] With regards to the cases presented, in the first case, the decision has been made to continue the eculizumab due to the severity of clinical manifestations of aHUS, with ongoing review of a future cessation date. However with the second case, the decision was made to cease eculizumab with close monitoring due to the limited course of her aHUS disease.

CONCLUSIONS

A significant proportion of cases of aHUS are precipitated by pregnancy and it can be difficult to distinguish aHUS from other causes in peri-partum patients presenting with features of microangiopathic haemolytic anaemia, thrombocytopenia and acute kidney injury. Though aHUS is relatively rare, it is important to have clinical suspicion of this disease. Complicating the clinical urgency to treat aHUS early with eculizumab, is the challenge of making a diagnosis, as confirmatory tests for aHUS are not available. Furthermore, once eculizumab therapy is established, there is currently a paucity of evidence to guide the appropriate length of this treatment and further study is eagerly awaited.

REFERENCES

1. Noris M, Remuzzi G. Atypical hemolytic–uremic syndrome. New England Journal of Medicine. 2009;361(17):1676-87.
2. Fakhouri F, Roumenina L, Provot F, Sallée M, Caillard S, Couzi L, et al. Pregnancy-associated hemolytic uremic syndrome revisited in the era of complement gene mutations. Journal of the American Society of Nephrology. 2010;21(5):859-67.
3. Saad AF, Roman J, Wyble A, Pacheco LD. Pregnancy-Associated Atypical Hemolytic-Uremic Syndrome. American Journal of Perinatology Reports. 2016;6(01):e125-e8.
4. Fakhouri F, Hourmant M, Campistol JM, Cataland SR, Espinosa M, Gaber AO, et al. Terminal Complement Inhibitor Eculizumab in Adult Patients With Atypical Hemolytic Uremic Syndrome: A Single-Arm, Open-Label Trial. American Journal of Kidney Diseases. 2016.

5. Machado S, Figueiredo N, Borges A, Pais M, Freitas L, Moura P, et al. Acute kidney injury in pregnancy: a clinical challenge. 2012.
6. Cataland SR, Yang S, Wu HM. The use of ADAMTS13 activity, platelet count, and serum creatinine to differentiate acquired thrombotic thrombocytopenic purpura from other thrombotic microangiopathies. British journal of haematology. 2012;157(4):501-3.
7. Mayer CL, Leibowitz CS, Kurosawa S, Stearns-Kurosawa DJ. Shiga toxins and the pathophysiology of hemolytic uremic syndrome in humans and animals. Toxins. 2012;4(11):1261-87.
8. Caprioli J, Noris M, Brioschi S, Pianetti G, Castelletti F, Bettinaglio P, et al. International Registry of Recurrent and Familial HUS/TTP. Genetics of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome. Blood. 2006;108(4):1267-79.
9. Kavanagh D, Goodship TH, Richards A. Atypical haemolytic uraemic syndrome. British medical bulletin. 2006;77(1):5-22.
10. Loirat C, Frémeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet journal of rare diseases. 2011;6(1):1.
11. Walle JV, Delmas Y, Ardissino G, Wang J, Kincaid JF, Haller H. Improved renal recovery in patients with atypical hemolytic uremic syndrome following rapid initiation of eculizumab treatment. Journal of nephrology. 2016:1-8.
12. Licht C, Greenbaum LA, Muus P, Babu S, Bedrosian CL, Cohen DJ, et al. Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies. Kidney international. 2015;87(5):1061-73.
13. Ardissino G, Testa S, Possenti I, Tel F, Paglialonga F, Salardi S, et al. Discontinuation of eculizumab maintenance treatment for atypical hemolytic uremic syndrome: a report of 10 cases. American Journal of Kidney Diseases. 2014;64(4):633-7.

Author/s:
Chua, J;Paizis, K;He, SZ;Mount, P

Title:
Suspected atypical haemolytic uraemic syndrome in two post-partum patients with foetal-death in utero responding to eculizumab

Date:
2017-02-17

Citation:
Chua, J., Paizis, K., He, S. Z. & Mount, P. (2017). Suspected atypical haemolytic uraemic syndrome in two post-partum patients with foetal-death in utero responding to eculizumab. NEPHROLOGY, 22 (S1), pp.18-22. https://doi.org/10.1111/nep.12935.

Persistent Link:
http://hdl.handle.net/11343/292424