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Case Report

CASE REPORT

Early eculizumab use in atypical haemolytic uraemic syndrome in a Jehovah's Witness refusing blood products

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ABSTRACT

Thrombotic microangiopathy (TMA) is characterized by microscopic angiopathic haemolytic anaemia, thrombocytopenia and organ injury. Supportive therapies include the use of blood products. Recently the terminal complement inhibitor eculizumab has been approved in atypical haemolytic uraemic syndrome (aHUS) in some countries. We report the case of a 23-year-old female Jehovah's Witness presenting with vaginal haemorrhage from thrombocytopaenia, severe anaemia (nadir Hb 28 g/L) and anuric acute kidney injury with TMA secondary to aHUS. Despite a life threatening illness, the patient declined the use of blood components and plasma exchange. Eculizumab was administered early with subsequent improvement and resolution of haemolysis, return to baseline renal function whilst avoiding use of blood products. This case demonstrates the effective use of eculizumab for life saving therapy in a patient refusing blood products. It highlights the importance of accessibility for high cost therapies, but the disparity in access between healthcare systems.

INTRODUCTION

Atypical haemolytic uraemic syndrome, a cause of thrombotic microangiopathy (TMA), is associated with significant morbidity [1] and mortality [2]. Therapeutic options for atypical haemolytic uraemic syndrome (aHUS) have increased in recent years to include the terminal complement inhibitor eculizumab. Early treatment has reduced sequelae and improved outcome by limiting a secondary endothelial cascade thereby hopefully reducing the burden of co-morbidities associated with aHUS [3, 4]. Eculizumab is approved for therapy in a number of countries (including the UK) as standard care for diagnosed cases of aHUS [5]. Diagnostic uncertainty in the initial presentation of TMA can delay the delivery of this therapy. Diagnostic criteria for aHUS rely on exclusion of other causes of TMA based on investigations and extra-renal manifestations. UK guidelines recommend the availability of normal level results for the ADAMTS13 assay before commencing treatment [6]. Avoidance of blood products is required by specific patients and thus access to alternative therapies can be life saving.

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CASE REPORT

Presentation

A 23-year-old female Australian citizen, with permanent Canadian residency, visited the UK on holiday and presented to the Emergency Department (ED, Day 1) with a seven-day history of non-bloody diarrhoea and vomiting. The patient had no previous medical history or significant family history. She was clinically stable with an unremarkable clinical examination and was discharged with a diagnosis of viral gastroenteritis. Near patient testing indicated a haemoglobin of 127 g/L (normal female range: 115–165 g/L), but neither formal laboratory bloods nor stool culture were obtained.

On Day 3, she re-presented to the ED with heavy vaginal bleeding and lower abdominal pain. Her diarrhoea and vomiting had resolved and there were no other signs on examination. Near patient testing indicated a drop in haemoglobin to 79 g/L and she was transferred to the Gynaecology team for further investigation. Initial treatment included norethisterone, tranexamic acid and ferrous sulphate. Laboratory blood tests on Day 4 indicated a haemoglobin 54 g/L, haematocrit 0.16 L/L (female range: 0.37–0.47 L/L) and platelets 34 × 10^9/L (range: 150–450 × 10^9/L). The haematologist suspected haemolytic uraemic syndrome and requested an urgent blood film which showed multiple red cell fragments and polychromasia and biochemical profile, which revealed serum creatinine 856 μmol/L (normal female <60 years range: 50–101) and serum urea 47.4 mmol/L (normal female range: 2.6–7.1) and lactate dehydrogenase LDH 3077 U/L (normal adult female range: 135–214).

During this time, discussions with the patient regarding potential therapies took place. She informed medical staff she was a Jehovah's Witness and had made an advanced medical directive that clearly stated, 'I direct that no blood transfusions (whole blood, red cells, white cells, platelets or blood plasma) be given to me under any circumstances, even if deemed necessary to preserve my life or health'. The advanced directive was attached to her medical notes and all future discussions regarding the patient's refusal of all blood products were clearly documented. Therapies including high dose erythropoietin stimulating agents (ESAs) injections and intravenous iron were discussed and commenced.

At this stage, it was difficult to distinguish between diarrhoea associated HUS and aHUS (which can present with diarrhoea in 30% of cases) [7]. Plasma exchange was discussed, and declined by the patient and she was transferred to the critical care unit (CCU) on Day 4 with rapid deterioration on blood parameters and the imminent need for renal replacement therapy (RRT).

A TMA screen was sent, including complement 3 and 4, total complement activity (CH50), complement genetics, anti-factor H

Table 1: Clinical variables, laboratory values and interventions during treatment of illness*

	Day														
	1	3	4	5	7	8	13	14	15	16	18	19	20	23	31
		A+E and Gynaecology ward		Critical care unit								Ward based care			
Clinical variables															
Temperature (°C)	37.6	36	36.5	36.2	37.6	36.5	36.9	37.4	37.5	37.3	37	37.0	36.8	37.1	36.5
Heart rate (beats/min)	106	76	94	111	117	110	117	124	117	119	90	96	110	90	85
Systolic blood pressure (mmHg)	117	112	126	125	110	101	100	150	138	116	120	136	129	133	117
Diastolic blood pressure (mmHg)	75	74	65	68	56	38	65	63	78	77	80	74	59	80	68
Respiratory rate (breaths/min)	17	19	15	15	15	15	14	17	16	14	11	16	18	17	16
Oxygen saturation (%)¬	98	99	98	100	94	100	100	96	97	94	99	98	100	99	98
Supplemental oxygen (Fi02)	21	21	21	21	40	40	40	36	21	21	21	21	21	21	21
Glasgow coma scale (/15)	15	15	15	15	9	9	14	15	15	15	15	15	15	15	15
Laboratory values															
Haemoglobin (g/L)	127^	79^	55	49	31	28	37	35	–	41	59	61	69	71	111
Platelets (×10^9/L)	–	–	34	32	75	106	126	125	–	167	202	207	209	264	302
Mean cell volume (fL)				83	100	108	114	114	–	118	122	121	117	111	102
Lactate deydrogenase (U/L)	–	–	3077	–	2275	–	545	–	–	–	–	–	409	356	312
Urea (mmol/L)	–	–	47	20.1	6.8	3.9	3.3	3.8	–	9.2	10.3	7.2	4.6	2.7	4.7
Creatinine (μmol/L)	–	–	856	370	214	164	103	93	–	166	145	121	95	75	78
Interventions															
RRT				Renal replacement therapy											
¬Intubation					Intubation										
∞Eculizumab 900 mg IV				E				E						E	E

Haemoglobin normal female range: 115–165 g/L. Platelets normal range: 150–450 × 10^9/L. MCV normal range: 80–99 fL. LDH normal range adult females: 135–214 U/L. Urea female <30 years normal range: 2.6–7.1 mmol/L. Creatinine female <60 years normal range: 50–101 μmol/L.

*Data are for the period starting with the patient's first presentation to the Queen Elizabeth Hospital Birmingham, and ending the day the patient was discharged.

∞The patient received Eculizumab 900 mg IV on Days 5, 14, 23 and 31.

^Near patient testing results provided the haemoglobin values in A + E.

¬A period of intubation from Days 7 to 13.

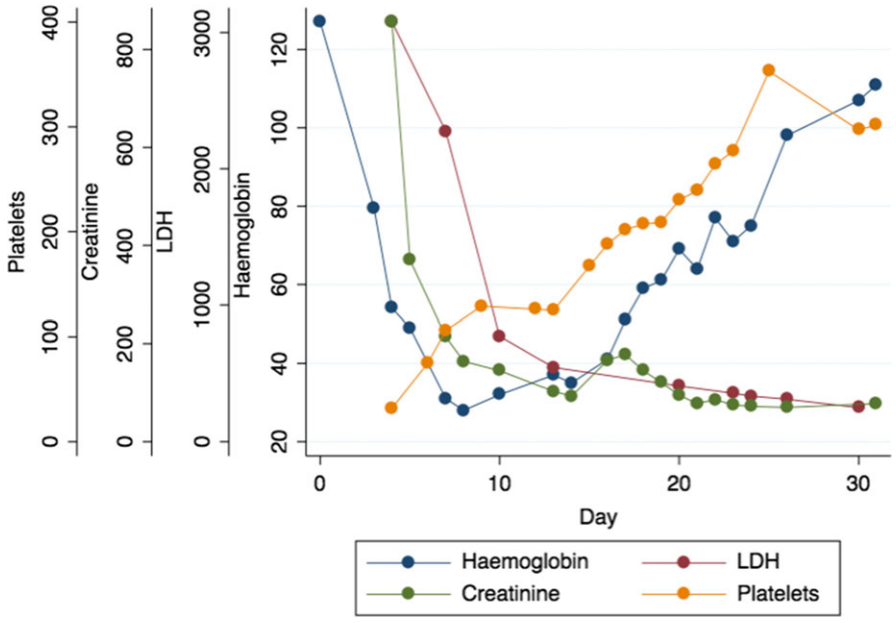

Figure 1: Platelet, haemoglobin, creatinine* and lactate dehydrogenase trends during treatment of illness.
*Between Days 4 and 15 the patient had renal replacement therapy.
Haemoglobin normal female range: 115–165 gL. Platelets normal range: 150–450 × 10^9/L. Creatinine female <60 years normal range 50–101 μmol/L. Lactate dehydrogenase (LDH) normal range: 135–214 U/L.

autoantibody, and ADAMTS13, as well as antibodies for renal specific immune mediated disease (which were subsequently within normal range, Table 1 footnote). Stool cultures were negative for *Escherichia coli* O157 endotoxin antibodies and polymerase chain reaction for verotoxin Escherichia coli. Meanwhile urgent discussions took place with the UK national aHUS on-call service (which controls UK national funding for eculizumab) [8]. Given the clinical situation and refusal of blood products, the decision was made to proceed with administration of eculizumab (dose 900 mg, given Day 5) without waiting for ADAMTS13 activity. This was accompanied by vaccination for meningococcal disease and a prophylactic course of ciprofloxacin.

Further decrement in haemoglobin (Fig. 1) precipitated more discussions regarding blood products, including an assessment of mental capacity. The patient stated that 'if I lost consciousness I would not wish to receive any blood products even if it was life threatening', which her family members supported. The patient deteriorated neurologically and a decision was made to intubate and ventilate the patient (Day 7) due to confusion. The nadir haemoglobin was on Day 8 (28 g/L). The patient remained intubated and on RRT.

The patient continued to receive darbepoetin (total cumulative dose 600 micrograms) and iron sucrose (total cumulative dose 1200 mg) treatment. The patient was extubated on Day 13 with no neurological deficit. RRT was discontinued on Day 14 and the second dose of eculizumab (900 mg) was administered. On discharge from critical care (Day 18), her haemoglobin was 59 g/L, platelets 202 × 10^9/L and creatinine 145 μmol/L, with reduction in markers of haemolysis. A third dose of eculizumab (900 mg) was given on Day 23. The fourth dose of eculizumab (900 mg) was given on Day 31 when discharged with normal range creatinine 78 μmol/L and a haemoglobin of 111 g/L and platelet count of 302 × 10^9/L (Fig. 1). Follow up was organized with a haematologist in Canada, her country of residence, to explore options to secure funding for further eculizumab treatment.

DISCUSSION

Whilst the treatment of aHUS with eculizumab has been established as best practice, typical treatment of early, potentially life threatening haematological complications uses supportive therapies with blood products whilst awaiting confirmatory tests [5, 9–11]. The acute management of this patient was challenging due to religious beliefs preventing the use of blood products and, due to the high clinical suspicion of aHUS resulted in early administration of eculizumab prior to diagnostic test results (centrally authorized by UK national aHUS group). Management of on-going acute haemolysis poses a significant and unique challenge to the maintenance of significant circulating red cell population in individuals who decline blood products. Various therapies have been used as alternatives for blood related products [12] including albumin and vincristine for thrombotic thrombocytopenic purpura [13, 14]; however, this is the first reported case of eculizumab administration in such a scenario.

The successful outcome was attained due to prompt recognition of TMA and early discussion regarding eculizumab use. Whilst the clinical decision to use eculizumab was taken based on risk to the patient's life, without confirmation of ADAMTS13 levels, the use of eculizumab had significant costing (four treatments cost GBP 37 800 [15], approximately US $55 500). Its use as an alternative to supportive therapies, which may otherwise have been adequate for treatment, is entirely appropriate based on an individual's personal beliefs. However on a population basis, this poses key financial and thus ethical considerations. Whilst the principles of utilitarianism and beneficence could be argued as reasons for avoiding high cost therapies, the role of non-maleficence both for the individual patient's personal rights and the damage to the wider trust in the medical profession is an important consideration in not overruling individual patient's viewpoints. As Macklin describes 'Moreover, because physicians owe stronger obligations to their patients than to

other parties who may be affected (the patient's family or the community), it is ethically preferable to give priority to the patient's own assessment of the good and bad consequences of refusing of blood.' [16] While this supports individualized medicine, other valid ethical models are available.

The optimal duration of eculizumab treatment in the setting of aHUS is unclear [17] and the current license is for lifetime use once treatment is commenced however there is no consensus on withdrawal of eculizumab. Whilst no inherited and acquired complement abnormalities were identified, possibly putting the patient in a lower risk group of disease recurrence, only 70% of patients have a genetic abnormalities identified, leaving 30% with an unknown abnormality [18].

Following the inpatient episode, her insurance company was keen to repatriate her to Canada, but liaison with a haematologist in Canada for on-going care revealed that eculizumab was not currently approved for therapy in aHUS. Conversely, if she was to return to Australia (country of birth), the use of eculizumab had only been approved for aHUS on 1st Dec 2014, approximately one month after her initial presentation to hospital. Disparities between countries for licensing of eculizumab and other expensive medications for rare diseases are typically not known by clinicians, let alone patients and had this illness presented whilst in Canada, the outcome would have been unclear.

In summary, this case highlights the successful treatment of aHUS with the early administration of eculizumab in a patient who declined blood products due to religious beliefs. It highlights disparities for high cost medications within industrialized nations and potential health economic issues for patients declining 'standard' care regardless of reason.

TMA SCREEN RESULTS

No known pathogenic DNA mutations were identified in 'C3', 'CFB', 'CFH', 'CFI' or 'CD46'.

ADAMTS13 activity (Fret substrate) was normal—104%.

Alternate and Classical pathway complement function was both normal.

Anti-H antibodies not detected. Complement Factor H level was 441 mg/L (normal range: 345–590). Complement C3 levels 0.96 g/L (normal range: 0.75–1.75) and C4 0.17 g/L (normal range: 0.14–0.54).

Anti-Cardiolipin antibodies IgG and IgM negative (<15 GPL U/ml and <13 MPL U/ml respectively). Antinuclear antibodies positive 1:40 but double stranded DNA antibodies negative (<20 kU/L, normal range: 0–75). Anti-B2GP1 abs 6 EU/ml (normal range: 0–20).

ENA ab's negative (ENA screen assay includes: Sm, RNP, SSA, SSB, Jo-1 and Scl-70 antigens).

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DISCLOSURES

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CONTRIBUTIONS

Participated in research design: M.A., A.B., M.J., G.L. Participated in the writing of the article: M.A., A.B., M.J., W.L., G.L. Participated in the performance of the research: M.A., A.B., M.J., W.L., G.L. Participated in data analysis: M.A., A.B., M.J.

REFERENCES

1. Clark WF. Thrombotic microangiopathy: current knowledge and outcomes with plasma exchange. *Semin Dial* 2012;**25**:214–9.
2. Campistol JM, Arias M, Ariceta G, Blasco M, Espinosa M, Grinyo JM, *et al*. An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document. *Nefrologia* 2013;**33**:27–45.
3. Schmidtko J, Peine S, El-Housseini Y, Pascual M, Meier P. Treatment of atypical hemolytic uremic syndrome and thrombotic microangiopathies: a focus on eculizumab. *Am J Kidney Dis* 2013;**61**:289–99.
4. Fremeaux-Bacchi V, Fakhouri F, Garnier A, Bienaime F, Dragon-Durey MA, Ngo S, *et al*. Genetics and outcome of atypical hemolytic uremic syndrome: a nationwide French series comparing children and adults. *Clin J Am Soc Nephrol* 2013;**8**:554–62.
5. Legendre CM, Licht C, Muus P, Greenbaum LA, Babu S, Bedrosian C, *et al*. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Eng J Med* 2013;**368**:2169–81.
6. Sheerin NS, Kavanagh D, Goodship TH, Johnson S. A national specialized service in England for atypical haemolytic uraemic syndrome-the first year's experience. *QJM* 2016;**109**:27–33.
7. Noris M, Caprioli J, Bresin E, Mossali C, Pianetti G, Gamba S, *et al*. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. *Clin J Am Soc Nephrol* 2010;**5**:1844–59.
8. NICE. Eculizumab for Treating Atypical Haemolytic Uraemic Syndrome. 2015.
9. Ardissino G, Wally Ossola M, Baffero GM, Rigotti A, Cugno M. Eculizumab for atypical hemolytic uremic syndrome in pregnancy. *Obstet Gynecol* 2013;**122**:487–9.
10. Mache CJ, Acham-Roschitz B, Fremeaux-Bacchi V, Kirschfink M, Zipfel PF, Roedl S, *et al*. Complement inhibitor eculizumab in atypical hemolytic uremic syndrome. *Clin J Am Soc Nephrol* 2009;**4**:1312–6.
11. Cataland SR, Wu HM. How I treat: the clinical differentiation and initial treatment of adult patients with atypical hemolytic uremic syndrome. *Blood* 2014;**123**:2478–84.
12. Drummond MW, Green R, Callaghan T, Watson D, Simpson K. Management of a Jehovah's witness with thrombotic thrombocytopaenic purpura/haemolytic uraemic syndrome. *J Clin Apher* 2000;**15**:266–7.

13. Chai W, Chaudhry A, Rabinowitz AP. Successful management of thrombotic thrombocytopenic purpura in a Jehovah's Witness without plasma exchange. *J Clin Apher* 2015;**30**:46–9.
14. Dabak V, Kuriakose P, Raman S. Successful management of a Jehovah's Witness with thrombotic thrombocytopenic purpura unwilling to be treated with therapeutic plasma exchange. *J Clin Apher* 2007;**22**:330–2.
15. Joint Formulary Committee. *British National Formulary (online) London*: BMJ Group and Pharmaceutical Press. http://www.medicinescomplete.com (4 January 2016, date last accessed).
16. Macklin R. Applying the four principles. *J Med Ethics* 2003;**29**: 275–80.
17. 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. *Am J Kidney Dis* 2014;**64**:633–7.
18. Bienaime F, Dragon-Durey MA, Regnier CH, Nilsson SC, Kwan WH, Blouin J, *et al.* Mutations in components of complement influence the outcome of Factor I-associated atypical hemolytic uremic syndrome. *Kidney Int* 2010;**77**:339–49.