


CASE REPORT

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Haemolytic uraemic syndrome - a rare case report of bloody diarrhoea in adults



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Abstract

Background: Haemolytic uraemic syndrome is a rarely seen in adults often leading to critical illness. This case highlights how difficult it can be to establish a diagnosis and treat when a patient presents with bloody diarrhoea.

Case presentation: A 17-year-old Iraqi man presented to the emergency department with abdominal pain and bloody diarrhoea. He was initially treated as acute appendicitis, undergoing an appendectomy but following a recurrence in his symptoms a colonoscopy was performed. A diagnosis of shiga toxin-producing *Escherichia coli* leading to HUS was suspected following histology obtained at colonoscopy and this was confirmed on antibody testing. Despite intravenous fluids and supportive therapy the patient's symptoms and condition deteriorated. He developed seizures and acute renal failure requiring intubation and plasma exchange in the intensive care setting. He eventually required treatment with ecluzimab therapy; a monoclonal antibody and subsequently made a full recovery.

Conclusions: Haemolytic uraemic syndrome is a triad of progressive renal failure, thrombocytopenia and haemolytic anaemia which is a condition rarely seen in adults. It is usually associated with an *E. coli* infection and supportive therapy remains the mainstay of treatment.

Keywords: Bloody diarrhoea, Haemolytic uraemic syndrome, *E.coli* 0157, Plasma exchange, Shiga-toxin

Background

Infection with *E.coli* 0157 can present with a variety of symptoms including bloody diarrhoea and abdominal cramps. The bacterium is commonly transferred by a feco-oral route and undercooked meat is a known culprit [1]. This infection is linked to Haemolytic uraemic syndrome (HUS) which presents with the triad of progressive renal failure, thrombocytopenia and haemolytic anaemia. HUS can be classified as either typical (diarrhoea associated) or atypical (non-diarrhoea associated such as following a urinary tract infection), [2]. We present a case of a 17-year-old male with bloody diarrhoea who proceeded to be affected by severe HUS including neurological sequelae. Our case highlights the difficulties in establishing a diagnosis and treatment when a patient presents with bloody diarrhoea.

Case presentation

A 17-year-old Iraqi male presented to the emergency department with a 2 day history of right iliac fossa pain, vomiting and a few episodes of diarrhoea. A clinical diagnosis of appendicitis was made and he was treated with intravenous antibiotics and underwent an appendectomy, the histology of which was normal. At the time of the operation, the surgeon noted the right colon appeared to be inflamed. The patient had no prior medical history and his family history was nil of note.

A computed tomography (CT) scan was performed postoperatively which showed thickening of the ascending colon with some submucosal oedema in the caecum with associated local regional lymph nodes. However the patient's condition improved enough to be sent home the day after his operation.

Two days later he returned to hospital with bloody diarrhoea up to ten times a day, with associated fever and a tender abdomen. Baseline admission investigations are shown in Table 1. Initial stool cultures were negative including for *Escherichia coli* 0157 (*E. coli*), and the patient was started on intravenous cefuroxime and

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Table 1 Baseline admission investigations

	Measurement	Normal Range
Haemoglobin	182 g/L	130–168 g/L
Mean cell volume	88.2 fL	83.5–99.5 fL
Platelets	$332 \times 10^9/L$	$130\text{--}370 \times 10^9/L$
White cell count	$12.4 \times 10^9/L$	$4.2\text{--}10.6 \times 10^9/L$
Neutrophils	$7.7 \times 10^9/L$	$2.0\text{--}7.1 \times 10^9/L$
Lymphocytes	$3.4 \times 10^9/L$	$1.1\text{--}3.6 \times 10^9/L$
Sodium	141 mmol/L	133–146 mmol/L
Potassium	4.1 mmol/L	3.5–5.3 mmol/L
Urea	3.6 mmol/L	2.5–7.8 mmol/L
Creatinine	68 $\mu\text{mol/L}$	60–125 $\mu\text{mol/L}$
Bilirubin	9 $\mu\text{mol/L}$	0–21 $\mu\text{mol/L}$
Alkaline phosphatase	106 IU/L	60–370 IU/L
Alanine aminotransferase	15 IU/L	0–40 IU/L
Abdominal radiograph	No toxic megacolon	

metronidazole. An abdominal radiograph did not reveal colonic dilatation. A colonoscopy was performed which showed patchy pan-colitis, maximal in the ascending and descending colon.

Given the age of the patient and location of his symptoms, plus the initial findings on the CT scan, a diagnosis of inflammatory bowel disease was considered. The other main differential was an infective colitis caused by *Campylobacter*, *Shigella*, *E. coli* or *Clostridium difficile*. Tuberculosis (TB) was another possibility and although the patient was originally from Iraq there was no recent history of foreign travel or relevant contact history of TB exposure. The appearances at colonoscopy were most suggestive of Crohn's disease so the patient was commenced on intravenous hydrocortisone. Colonic biopsies were taken with the histology results shown in Fig. 1.

Despite 24 h of steroid therapy, the patient still had on-going bloody diarrhoea although his pain had now settled. His renal function had declined from a normal baseline to a serum urea of 11.3 mmol/L and a serum creatinine of 170 $\mu\text{mol/L}$, and despite being adequately hydrated with intravenous fluids he became anuric. He was also noted to be thrombocytopenic with a platelet count of 81. Additionally, the patient became anaemic and his blood film showed Red cell fragments: 10 fragments per $\times 40$ objective field, indicating haemolysis. Clinically the patient became disorientated and agitated and he rapidly deteriorated developing partial-complex seizures. This rapid deterioration required intubation and he was promptly admitted to the intensive care unit (ITU). A diagnosis of typical Haemolytic Uraemic Syndrome (HUS) was made following the history of gastrointestinal illness coupled with an acute kidney injury and thrombocytopenia. His levels of ADAMTS13 were

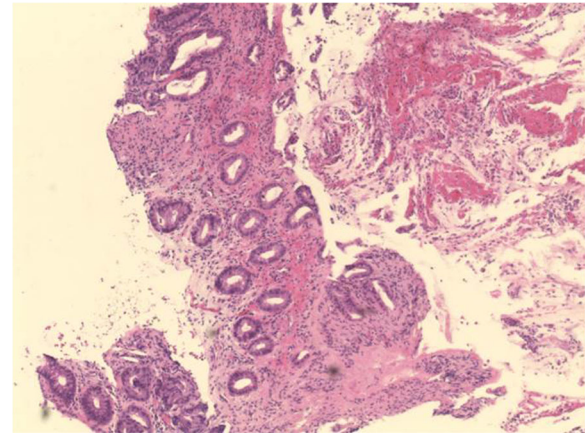


Fig. 1 "Large bowel mucosa showing withered atrophic crypts near the surface and lamina propria hyalinisation along with haemorrhage. Free lying pseudomembranous exudate composed of mucus, inflammatory exudate and blood is noted near the luminal surface. These findings are highly suggestive of enterohaemorrhagic *E.coli*"

normal, making a diagnosis of Thrombotic Thrombocytopenic Purpura (TTP) less likely. The patient received haemofiltration and plasma exchange with fresh frozen plasma but showed little signs of improvement so after 10 days he was commenced on Eculizumab a monoclonal antibody. He remained on the ITU for a further 35 days and spent a further 28 days on renal high-dependency unit during which time he gradually improved. He remained seizure free with normalisation of his platelets and biochemical profile and was discharged well from hospital.

Discussion and conclusions

HUS is a rare condition characterized by progressive renal failure, thrombocytopenia and haemolytic anaemia. It can be classified as either typical (diarrhoea associated) or atypical (non-diarrhoea associated such as following a urinary tract infection), [2]. A well-recognised cause of HUS is due to infection with shiga toxin-producing bacteria, the most common of which is *E.coli* O157: H7, [3]. This mainly occurs in childhood, and is characterised by a prodromal acute gastroenteritis followed by haemolytic anaemia, thrombocytopenia and acute kidney injury.

Shiga toxin releasing *E.coli* (STEC) gastroenteritis can be difficult to diagnose as patients may not present with all the hallmark features. Bloody diarrhoea can occur a median of 3 days after ingestion of contaminated food and some patients may also report to suffer from severe abdominal pain and painful defecation, [4]. The latter may help to distinguish STEC from other causes of bacterial gastroenteritis where these symptoms would be unusual, [5].

The primary pathophysiological mechanism in typical HUS is vascular endothelial cell injury by both inflammatory and non-inflammatory mechanisms, such as cytokine release, [2]. Renal dysfunction in HUS is thought to be caused by microthrombi of platelets and fibrin in arterioles and capillaries, [6]. Approximately 40% of patients with STEC require renal replacement therapy, and of these, 20% will have permanent renal dysfunction, [7]. Coagulopathy and thrombocytopenia occur due to increased platelet consumption. Fragmented red cells, a key feature of HUS, is due to mechanical damage from shear stress in fibrin lined vessels as well as peroxidative damage.

Our patient did have microangiopathic haemolysis, acute renal failure, thrombocytopenia and was eventually found to be STEC antibody positive, which confirmed a diagnosis of typical HUS, [8]. The cause of his seizures was unclear but neurological involvement in HUS is a recognized complication and is the most frequent cause for fatalities, [7]. The pathophysiology is thought to be multifactorial and still poorly understood but may be due to a combination of microinfarctions in key anatomical regions such as the brainstem or the effect of increased inflammatory cytokines seen to be present in higher concentrations in patients with neurological complications such as seizures and encephalopathy, [9].

Neurological complications are also a clinical feature of thrombotic TTP and both TTP and HUS are considered to be on a spectrum of thrombotic microangiopathies, [10]. Though TTP shares a similar clinical picture, in this syndrome there is a deficiency or formation of antibodies to ADAMTS13, a von Willebrand cleaving protease which helps to differentiate the two conditions, [11].

Supportive therapy remains the mainstay of treatment in HUS with adequate fluid rehydration where required, [12]. The role of antibiotics is controversial in STEC gastroenteritis with some evidence that antibiotic therapy may be detrimental triggering further release of shiga toxin by bacterial lysis [13–15], which may explain the delayed deterioration in our patient.

A likely contribution to the pathogenesis of STEC-HUS is activation of the alternative complement pathway and so patients with life threatening complications may receive benefit with short term therapy with eculizumab, a monoclonal antibody against C5, which inhibits terminal complement complex formation. This has already been reported as an effective treatment in atypical HUS where the role of the complement pathway is well established, [5, 15, 16]. In a case series following an outbreak of STEC (*E.coli* O104:H4) in Germany, rapid clinical improvement following eculizumab was reported, [17, 18]. All patients had renal failure and neurological involvement which had not responded to plasma exchange. Due to the cost of the drug, its use is limited

to only the most severe cases and therefore treatment is often delayed, [19]. Within a paediatric population, early treatment of HUS with eculizumab in patients with neurological complications led to better outcomes, compared to delayed therapy initiation in patients with rapidly progressive HUS, [20].

Plasma exchange therapy in typical HUS is controversial in adults as there is a lack of evidence for its efficacy but it is used in some cases where severe neurological abnormalities exist, [21, 22]. In addition, immunoadsorption with intravenous immunoglobulins (IVIG) can also be used in this setting and has been shown to lead to improvement [23]. The rationale is based on a suspected immune-mediated mechanism to neurological sequelae, which explains the delayed onset of these symptoms in disease course.

Learning points

- HUS secondary to STEC is well described condition in the paediatric population but its incidence and epidemiology in adults is relatively unknown.
- The classic triad in HUS is haemolytic anaemia, acute renal failure and thrombocytopenia. Early checking of ADAMTS13 and for STEC is advised if indicated.
- Antibiotics are relatively contraindicated in *E.coli* associated HUS.
- The role of the histopathologist is crucial in the recognition of *E.Coli* as this can speed up diagnosis and onward management decisions.
- Treatment is largely supportive with fluid resuscitation and dialysis if required, although more recently eculizumab and immunoadsorption provide additional treatment options for patients who are not clinically improving.

Abbreviations

CT: Computed tomography; *E.coli*: *Escherichia coli*; HUS: Haemolytic uraemic syndrome; ITU: intensive care unit; IVIG: intravenous immunoglobulins; STEC: Shiga toxin releasing *E.coli*; TB: Tuberculosis; TTP: Thrombotic Thrombocytopenic Purpura

Authors' contributions

STR admitted and reviewed the patient when they were first admitted, was also responsible for the initial case report write up. AR edited and reviewed the manuscript. AKU reviewed and edited the manuscript and helped with the literature review. PC performed histological analysis of the patient's colonic biopsies. JL reviewed the patient from a renal perspective and reviewed the patient as an outpatient. JT was the lead consultant who was responsible for the patient's care when he was first admitted, prior to his ITU admission. All authors have read and approved the manuscript.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Patient consent for the case report was obtained from the patient by STR. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Consent from the patient was obtained in 2018, at which point the patient was aged 19, hence no parental/guardian consent was obtained. A copy of the written consent is available for review by the editor of this journal.

Competing interests

The authors declare that they have no competing interests.

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