CASE REPORT

An unusual case of *Escherichia coli* O157:H7 infection with pseudomembranous colitis-like lesions associated with haemolytic-uraemic syndrome and neurological sequelae

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SUMMARY

A 75-year-old man was admitted with abdominal pain and fresh rectal bleeding. Significantly, he had no risk factors for *Clostridium difficile* infection. An abdominal CT demonstrated colonic thickening, and flexible sigmoidoscopy identified pseudomembranous colitis-like lesions. After initial treatment as *C. difficile* colitis, a stool sample revealed *Escherichia coli* O157:H7 infection. Antibiotic therapy was stopped due to the risk of lysis-mediated toxin release, but unfortunately, the patient continued to deteriorate. He developed several of the severe sequelae of *E. coli* O157:H7 infection, including haemolytic-uraemic syndrome with an acute kidney injury necessitating haemofiltration, plus progressively severe seizures requiring escalating antiepileptic treatment and intubation for airway protection. After a prolonged intensive care admission and subsequent recovery on the ward, our patient was discharged alive.

BACKGROUND

July 2016 saw an outbreak of the phage type (PT) 34 *Escherichia coli* O157:H7 across the UK, with 161 cases eventually reported.¹ This represents a particularly severe form of *E. coli* infection, with several known sequelae. Up to 9% of enterohaemorrhagic *E. coli* (EHEC) O157:H7 infections are complicated by haemolytic-uraemic syndrome (HUS), a primary thrombotic microangiopathy (TMA) syndrome which is characterised by microangiopathic haemolytic anaemia, acute kidney injury and thrombocytopenia.^{2–3} Neurological involvement is recognised in 30% of cases, the most common manifestation of which is generalised or partial seizure activity.⁴

A severe colitis carrying many similarities to pseudomembranous colitis—which is classically associated with *Clostridium difficile* infection—as the presenting feature such as in this case, has been reported after *Salmonella*, *Staphylococcus aureus* and *E. coli* O157:H7 infections.^{5–7} Our case uniquely presented with *E. coli*-associated pseudomembranous colitis-like lesions and acute kidney injury secondary to HUS which progressed with neurological sequelae requiring airway protection.

CASE PRESENTATION

A fully independent 75-year-old man with a medical history of metastatic prostate cancer was admitted to hospital with a 3-day history of lower abdominal pain, diarrhoea and three episodes of fresh blood per rectum. The patient had no recent travel history of note, could not recall consuming any extraordinary food items and had no unwell contacts. He was an ex-smoker with a 10 pack-year history, no evidence of alcohol excess, and prior to this admission was a carer for his wife, was independent with his activities of daily living and had an unlimited exercise tolerance. Other than advanced age, he had no risk factors for *C. difficile* infection (eg, recent antibiotic exposure, proton pump inhibitor exposure or prolonged hospital stay).⁸ On examination, abdomen was soft with mild suprapubic tenderness but no guarding or rigidity. Rectum examination was unremarkable. Respiratory, cardiovascular and neurological examinations on admission were normal. White cell count was raised on admission at $11.1 \times 10^9/L$ with a neutrophilia of $9.78 \times 10^9/L$, and C reactive protein was 107 mg/L.

The patient was oliguric on admission with a normal serum creatinine of 86 $\mu\text{mol/L}$ (estimated glomerular filtration rate (eGFR) 76 mL/min) which increased on day 7 to 418 $\mu\text{mol/L}$ (eGFR 11 mL/min). He was also found to have an elevated total bilirubin of 31 $\mu\text{mol/L}$ (upper limit of normal 20 $\mu\text{mol/L}$). Also of note, on day 7, he had a serum urea of 39.3 mmol/L (normal range 2.5–7.8 mmol/L), a serum sodium of 136 mmol/L (normal range 133–146 mmol/L), a serum potassium of 4.4 mmol/L (normal range 3.5–5.3 mmol/L), an adjusted calcium of 2.23 mmol/L (upper limit of normal 2.60 mmol/L), a serum phosphate of 2.28 mmol/L (upper limit of normal 1.50 mmol/L), an albumin of 20 g/L (normal range 25–50 g/L), an alkaline phosphatase level of 136 U/L (upper limit of normal 130 U/L) and an alanine aminotransferase of 23 U/L (upper limit of normal 41 U/L). At this stage, his venous blood gas showed a pH of 7.42, a $p\text{CO}_2$ of 4.8 (normal range 4.5–6.0 kPa), a $p\text{O}_2$ of 4.8 kPa, a lactate of 1.0 (normal range 0.5–2.2 mmol/L) and a base excess of -0.7 (normal range -2 to 2). His full blood count on day 7 showed a haemoglobin

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of 127 g/L (normal range 130–180 g/L), a white cell count of 22.0 (normal range 3.6–11.0) and a platelet count of $74 \times 10^9/L$ (normal range $140\text{--}400 \times 10^9/L$).

On day 11 of his admission, he had a short self-terminating generalised seizure, with upward rolling of the eyes, clenched fists and flexed posture.

INVESTIGATIONS

- ▶ CT abdomen and pelvis on admission showed 'thickening of the ascending, transverse and part of the descending colon, suggestive of a colitis' (see figure 1).
- ▶ *E. coli* O157:H7 PT34 (verotoxin gene positive, sequence type 11, stx subtype stx2a/stx2c and SNP address 5.156.1329.2502.2965.3081.3414) isolated from admission stool sample—result available on day 4 of admission, and Public Health England (PHE) was notified.
- ▶ Flexible sigmoidoscopy on day 4 of admission showed 'appearances of severe pseudomembranous colitis throughout the examined colon extending from the rectum to the mid transverse' (see figure 2).
- ▶ Biopsy from the flexible sigmoidoscopy showed 'much of the surface epithelium is denuded and replaced by an exudate of fibrin, karyorrhectic debris and neutrophil polymorphs. Where intact, the mucosa shows significant crypt withering associated with active inflammation in the form of cryptitis and crypt abscess formation. The appearances are those of pseudomembranous colitis'.
- ▶ Five days into the admission, a repeat CT showed that 'the colon remains thickened and oedematous ... the distal sigmoid and rectum are now also abnormal. The most dilated segment is the relatively normal looking caecum (7 cm). The thickened segments of the more proximal colon measure up to 4 cm'.
- ▶ Blood film on day 5 of admission showed 'neutrophilia with left shift; platelets mildly reduced; moderate number of red cell fragments present, moderate red cell crenation; there are red cell fragments present which would be consistent with a microangiopathic process'. Reticulocyte count at this point was 1.78% (normal range 0.2%–2.0%).
- ▶ *C. difficile* toxin was not isolated on days 1, 7, 20 and 30 of admission, making *C. difficile* infection extremely unlikely.⁹ Testing was compliant with the PHE National Standards Methods for investigation and used the *C. difficile* Tox A/B II and *C. diff* Chek-60 enzyme immunoassays both from TechLab.
- ▶ Initial doubt as to whether the apparent seizure episode was truly a seizure led to a concurrent serum prolactin to be taken; this was returned as 1022 mIU/L (upper limit of normal 450 mIU/L), evidence consistent with this episode having been a seizure.
- ▶ Microscopy, culture and sensitivity testing from blood, urine and central line tip samples were persistently negative throughout admission.
- ▶ CT brain performed on the day of seizure onset showed 'a 10 mm well-defined area of rounded area of low attenuation in the right parietal lobe suggestive of an established area of damage, such as infarction', but no new focal cause for the seizures.

Figure 1 A transverse CT slice showing thickening of the transverse colon, suggestive of a colitis.

DIFFERENTIAL DIAGNOSIS

- ▶ Ischaemic colitis—no specific risk factors present;
- ▶ Inflammatory bowel disease—no personal or family history; endoscopic features not typical;
- ▶ Infective colitis—other possible aetiological agents included EHEC, *Salmonella* spp, *Shigella* spp and *C. difficile*; the sigmoidoscopy finding of pseudomembranous colitis greatly escalated suspicion of *C. difficile*, with the identification of *E. coli* O157:H7 in the stool considerably changing the course of management;

Thrombotic thrombocytopenic purpura (TTP), another primary TMA, was considered when the patient began to have seizures, but in the presence of a positive *E. coli* O157:H7 result and when coupled with his acute kidney injury, this pointed toward a diagnosis of HUS. Of note, our patient did not also have purpura on examination of the skin. Confidence in the

Figure 2 Photograph taken at flexible sigmoidoscopy demonstrating appearances of severe pseudomembranous colitis.

diagnosis was increased as there had been other cases locally, although less severe.

TREATMENT

Our patient was discussed early with general surgery and was deemed for conservative management but was transferred to the intensive care unit (ICU) on day 5 of admission in anticipation of requiring renal replacement therapy. He started continuous veno-venous haemofiltration to manage his acute kidney injury—review by renal physicians recommended ongoing supportive care at this point.

With regard to antibiotic therapy, he was initially started on intravenous metronidazole 500 mg every 8 hours for presumed *C. difficile* infective colitis. Early on day 5, additional antibiotics (intravenous tigecycline, intravenous teicoplanin, intravenous metronidazole and oral vancomycin) were added. Later on day 5 of admission, in light of the positive *E. coli* O157:H7 result, the patient received a dose of intravenous immunoglobulin 0.4 g/kg, and all antibiotics were stopped due to the risk of bacterial lysis and toxin release.

A deterioration in the patient's condition and seizure onset on day 11 of admission prompted a shift to broad-spectrum antibiotics to cover for possible translocation and bacterial sepsis—initially, 1 day of intravenous piperacillin/tazobactam was given but then was escalated to intravenous meropenem to improve central nervous system (CNS) cover. There was low suspicion that seizures were due to CNS infection though, and no lumbar puncture was performed. Meropenem continued for 7 days, when all antibiotics were stopped and the patient was stepped down to the ward environment.

With regard to seizure management, the patient was initially loaded with intravenous levetiracetam, to which sodium valproate was added when it was thought seizure activity was persisting throughout the night. Despite treatment, seizure activity gradually increased, and lack of improvement in his Glasgow Coma Scale score led to intubation the following day to protect his airway. An electroencephalogram while intubated did not show ictal activity, and he was extubated successfully the following day. Levetiracetam dose was increased to cover continuing myoclonic jerks and then stopped altogether 7 days later.

OUTCOME AND FOLLOW-UP

The patient was discharged to a side room on the ward once stable and not requiring organ support. His renal function and stool habit gradually normalised on the ward after which he was successfully discharged home with a re-enablement care package. In total, our patient remained in the hospital for 43 days, 15 of which were spent in the ICU.

DISCUSSION

Our case is the only one to date to the authors' knowledge of pseudomembranous colitis resulting from *E. coli* O157:H7 infection (in the absence of *C. difficile* infection) associated with neurologically complicated HUS in an adult patient. Two other case reports of *E. coli* O157:H7 pseudomembranous colitis with *C. difficile* excluded exist in the literature, although one does not mention neurological involvement and the other is associated with TTP not HUS.^{10 11} One more recent case report of pseudomembranous colitis in *E. coli* O157:H7 infection describes a case in the absence of HUS in which progression to total colectomy was necessary.⁶

A feature of note in our case was the survival of the patient with supportive treatment despite poor prognostic features (elderly,

Learning points

- ▶ Although the most common cause of pseudomembranous colitis is *Clostridium difficile*, other causative organisms do exist including *Escherichia coli* O157:H7. Bear these organisms in mind if there is no clear recent history of antibiotic use.
- ▶ Evidence on use of antibiotics in haemolytic-uraemic syndrome (HUS) is mixed, but current advice is to avoid their use.
- ▶ Neurological involvement in HUS is relatively uncommon in adults.

requiring renal replacement therapy, comorbidities) in the face of a condition with considerable mortality.

Antibiotic therapy in *E. coli* O157:H7 infection is controversial, with studies suggesting they do not shorten duration of symptoms and that they may increase the risk of HUS through antibiotic-induced toxin release.^{12 13} However, results from the 2011 outbreak of *E. coli* O104:H4 in Germany showed no evidence of such toxin release with antibiotic therapy.¹⁴ In our case, empirical antibiotics were started when infective colitis was suspected, temporarily escalated due to concerns about sepsis and *C. difficile* and then stopped on microbiology advice following isolation of the *E. coli* O157:H7. The patient's renal function had already started to deteriorate at this point, so it would be impossible to disentangle whether initial antibiotic therapy truly had precipitated HUS.

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