CASE REPORT

Ulcerative colitis: a case of steroid refractory disease

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A 21-year-old lady was admitted to a hospital with an 8-week history of bloody diarrhoea. She had been diagnosed with ulcerative colitis 2 years previously and had remained in remission until the gradual onset of bloody diarrhoea. Her bowel frequency was 20 times per day and associated with significant abdominal pain and weight loss. She was started on intravenous steroids, topical therapy and anti-tumour necrosis factor therapy; however, this failed to achieve symptom control. Histology of tissue obtained from flexible sigmoidoscopy eventually demonstrated cytomegalovirus (CMV)-associated colitis. Intravenous anti-viral valganciclovir was initiated and the patient made a rapid recovery. This case discusses the differentials for steroid-refractory ulcerative colitis, including the common pitfall of inflammatory bowel disease management and CMV infection. This case also discusses CMV pathophysiology including histological features, appropriate investigations and current management guidelines.

BACKGROUND

This case is important for a number of reasons.

With the advent of guidelines and objective scoring systems such as the 'Oxford Criteria', the management of ulcerative colitis is being increasingly standardised. However, there are a number of different reasons why a patient may be having worsening of their symptoms and this may not necessarily be due to an established underlying disease process. In this case, the patient nearly had a colectomy for refractory severe ulcerative colitis when the actual diagnosis was of cytomegalovirus (CMV)-related colitis.

Second, this study revisits one of the common pitfalls of inflammatory bowel disease (IBD) management and the issue of CMV infection. CMV infection is a relatively rare, but important, cause of a chronic worsening of gastrointestinal symptoms in IBD patients. Early recognition can lead to rapid symptom control. This case not only is a revision on the characteristic histological findings but also gives recommendation on the latest treatment guidelines.

CASE PRESENTATION

A 21-year-old woman was electively admitted to hospital with an 8-week history of bloody diarrhoea. She had been diagnosed with ulcerative colitis 2 years previously and had remained in remission until the gradual onset of bloody diarrhoea. Her bowel frequency was 20 times per day, associated with significant abdominal pain and weight loss of 4 kg. Over the previous 8 weeks, she had remained on mesalazine 4.8 g daily, steroid

enemas, azathioprine 120 mg and high-dose prednisolone (40 mg), but noticed no improvement in her symptoms.

INVESTIGATIONS

She had a pulse of 92/min and a blood pressure of 142/65 mm Hg, and clinical examination revealed cushingoid appearances. Laboratory investigations revealed haemoglobin 6.2 g/dl, C-reactive protein (CRP) 175 mg/l, white cell count (WCC) $6.1 \times 10^9/l$ and albumin 21 g/l. All other bloods were unremarkable, including her thiopurine methyltransferase (TPMT) levels. A flexible sigmoidoscopy was performed and this demonstrated severe ulceration from the rectosigmoid junction extending beyond the limit of endoscopy.

DIFFERENTIAL DIAGNOSIS

A majority of patients with ulcerative have steroid-responsive disease; however, a small proportion have steroid-dependent or steroid-refractory disease.

Steroid dependence is defined as an inability to taper the steroid dose to less than 10 mg/day. Steroid refractory disease is defined as a lack of clinical response to high-dose prednisolone.

The differential diagnosis for steroid-refractory disease includes:

- ▶ Severe phenotype ulcerative colitis
- ▶ Poor compliance with medications
- ▶ Non-response to medications, in particular hypermethylators of azathioprine.
- ▶ Secondary concurrent pathology. This may include extra-gastrointestinal pathology (endocrine disorders, diet or drugs) or gastrointestinal causes (infections, ischaemic, neoplastic or infiltrative).

TREATMENT

After admission, she was started on IV hydrocortisone 100 mg four times a day and nutrition was optimised. There was no clinical response by day 3 of admission, and based on the 'Oxford Criteria', infliximab was initiated and a surgical opinion was sought. At day 5, her bowels were still opening 8 times per day and the surgical consort strongly advocated a surgery.

However, at day 5, the histology from the flexible sigmoidoscopy also returned showing not only severe colitis but also 'inclusion bodies'. Furthermore, the CMV PCR returned confirming a high viral load.

To cite: Lee L, Akhtar MM, Gardezisanjiajk A, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-009784

OUTCOME AND FOLLOW-UP

Intravenous Valganciclovir was initiated, and within 48 h her bowel frequency returned to twice a day and patient felt symptomatically better.

DISCUSSION

CMV is a member of the Herpes virus family, and patients with both ulcerative colitis and Crohn's disease are at increased risk of CMV reactivation and colitis. The virus is transmitted through close personal contact; in the general adult population, 40–70% has evidence of prior infection. In normal individuals, CMV infection is rarely symptomatic and usually self-limited. However, in the context of IBD, the pro-inflammatory cytokines and iatrogenic immunosuppression increase the risk of CMV-harboured monocytes reactivating and differentiating into active macrophages. A number of cohort studies have been performed; while the incidence of CMV disease has not been clearly demonstrated to be associated with anti-tumour necrosis factor or thiopurine therapy, patients who are on long-term steroids have at least a 10-fold increased risk of developing the condition.¹ The majority of the patients with CMV colitis treated promptly with intravenous antiviral therapy are able to go into disease remission, although it remains controversial whether an episode of CMV colitis changes the course of ulcerative colitis in terms of colectomy rates or disease prognosis.² The gold standard for diagnosing the condition is the histological examination of diseased colon as CMV PCR levels correlate poorly with disease activity. On histological examination, CMV-infected cells are typically 2–4-fold larger than the surrounding cells and demonstrate a thickened nuclear membrane and granular intracytoplasmic inclusions. The characteristic 'owl's eyes' appearances indicate active CMV-replicating nucleoprotein cores. Front line therapy for CMV remains ganciclovir or valganciclovir, but viral resistance has been documented, and second line therapies include foscarnet, cidofovir and

leflunomide. The decision whether immunosuppressants such as infliximab/thiopurines/steroids be withdrawn during a course of antiviral therapy remains extremely contentious and remains an evidence-free area.

Learning points

- ▶ Patients with uncontrolled gastrointestinal symptoms should have their treatment escalated at day 3 based on the 'Oxford Criteria'.
- ▶ Cytomegalovirus is a very important differential to exclude in patients with a flare of their IBD. This may be done by either serology or histology.
- ▶ Compared to patients with Crohn's disease, ulcerative colitis patients have a modest to absent CRP response.³ During a flare of ulcerative colitis, the average CRP from the clinical trials was only 15 and rarely above 54.^{3 4}

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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