CASE REPORT

Cytomegalovirus pouchitis in a patient with Crohn's disease

Nigel Tapiwa Mabvuure,¹ Laura Maclean,² Karin Oien,² Daniel Gaya²

¹Lister Department of Surgery, NHS Greater Glasgow and Clyde, Glasgow, UK
²NHS Greater Glasgow and Clyde, Glasgow, UK

Correspondence to

Dr Nigel Tapiwa Mabvuure,
 bsms1491@uni.bsms.ac.uk

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SUMMARY

Colectomy with ileoanal pouch formation is usually contraindicated in patients with Crohn's disease (CD) due to the risk of recurrent disease and pouch failure. We report the case of a patient, initially thought to have ulcerative colitis (UC), who underwent such surgery but subsequently developed perianal CD. She presented with diarrhoea and weight loss. Inflammatory markers were raised. Pouchoscopy revealed deep ulcers within the pouch. The main differential diagnoses were idiopathic pouchitis and recurrent CD. However, immunohistochemical staining demonstrated positivity for cytomegalovirus (CMV). Stool frequency, C reactive protein and albumin normalised within 48 h of starting oral valgancyclovir. At 15 weeks, pouch appearances were improved, no histological evidence of CMV was found and baseline pouch function had returned. This case highlights that CD can present many years after surgery for apparent UC. Also, CMV pouchitis should be considered as a differential cause of pouchitis especially as it is treatable with antiviral therapy.

BACKGROUND

Colectomy with ileoanal pouch formation is usually contraindicated in patients with Crohn's disease (CD) due to the risk of recurrent disease and subsequent pouch failure. However, some patients initially thought to have ulcerative colitis (UC) undergo such surgery and subsequently turn out to have CD. We report such a case where the patient developed perianal CD postoperatively and then presented with diarrhoeal symptoms with deep ulcers within the pouch on pouchoscopy. The aetiology of the ulcers was cytomegalovirus (CMV) infection. This report highlights CMV pouchitis as an important, treatable and easily forgotten differential diagnosis in this setting.

CASE PRESENTATION

A 29-year-old woman presented to our hospital with a stool frequency of more than 20 motions per day. Inflammatory bowel disease (IBD) was diagnosed at the age of 7 in 1991. At the time, a diagnosis of UC had been made on the basis of features on barium enema (pancolitic mucosal abnormality), sigmoidoscopy (mucosal inflammation and contact bleeding) and colonic biopsy (crypt architectural distortion, crypt abscesses and absence of granulomas). She suffered from Cushing's syndrome secondary to prolonged usage of steroids as well as autoimmune thrombocytopenia as a child. Although the thrombocytopenia was confirmed to be immune mediated by the presence of

megakaryocytes on bone marrow aspirate, sulfasalazine use had been restricted nonetheless. Steroid use failed to control the disease adequately. As a result, and due to the high number of disease flares, she underwent colectomy with sparing of the rectum and fashioning of an end ileostomy in 1998. She underwent restorative proctectomy in 2000 when an ileoanal pouch was formed.

The possibility of CD was raised in 2001 after she developed an anal fissure and erythema nodosum. Re-examination of the colectomy and proctectomy pathology specimens revealed that while the inflammatory process was confined to the mucosa and submucosa and was diffused with no ileal involvement, several well-formed granulomas were present in the superficial submucosa. A revised diagnosis of CD was made and discussed with the patient and her mother. The patient subsequently developed several episodes of perianal CD including abscesses and fistulae. The patient has also had several episodes of non-specific pouchitis. Medical management since the diagnosis of CD had largely consisted of long-term azathioprine and periodic use of prednisolone when needed. Surgical management included perianal abscess drainage, fistulotomy and seton insertion.

At presentation, the patient had suffered 1 month of increased loose, watery stool frequency (>20 pouch openings/day). This was severe enough to prevent her working. Her oral intake of fluids and food was reduced contributing to a 5 kg weight loss. A 2-week course of ciprofloxacin had been beneficial initially but, at presentation, had been discontinued for 2 weeks due to recurrence and worsening of her symptoms. Her sole medication was azathioprine 150 mg once daily. The patient had also experienced several episodes of night sweats with no rigours. A temperature of 38.5°C was recorded. Abdominal examination was unremarkable apart from her laparotomy scars. Perianal examination failed to reveal any source of sepsis. Blood was cultured after temperature spikes.

INVESTIGATIONS

Urea and electrolytes were normal throughout admission. Liver function tests were also unremarkable apart from an albumin level of 25 g/L. C reactive protein (CRP) on admission was raised at 62, erythrocyte sedimentation rate was raised at 129 mm/h but leucocytes were within the normal range at $4.5 \times 10^9/L$. Haemoglobin was 102 g/L. No specific microbes were cultured from blood or faeces. Specifically, *Clostridium difficile* was not grown from stool cultures.

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The main differential diagnoses were idiopathic pouchitis and recurrent CD. Endoscopic examination of the pouch revealed inflammation and 'punched out' ulceration within the pouch (figure 1). Biopsies were obtained for analysis and viral immunostaining was specifically requested. Pathological specimens showed severe distortion of glandular architecture with severe acute and moderate chronic inflammation.

There were also occasional nuclear eosinophilic inclusions on H&E staining (figure 2A), as well as distinct and relatively well-spread positivity for CMV on immunohistochemistry (figure 2B). Following this result, virological tests were performed. PCR did not show Epstein-Barr virus or adenovirus but a CMV viraemia of <2500 copies/mL was present.

TREATMENT

A 21-day course of oral valgancyclovir 900 mg twice daily was started. Within 48 h, stool frequency, CRP and albumin had normalised. The patient was discharged on a 17-day supply of valgancyclovir.

OUTCOME AND FOLLOW-UP

Follow-up pouchoscopy was performed after 15 weeks. Macroscopic appearances were much improved following anti-CMV therapy. Microscopic examination did not reveal any histological evidence of CMV. Clinically, the patient reported being back to her baseline pouch function (6–8 pouch bowel motions/day).

DISCUSSION

In March 2014, a search of AMED, EMBASE, MEDLINE, BNI and CINAHL with no language or date restrictions and combining the terms "pouch*, Crohn's disease and cytomegalovirus OR CMV" returned no results. This suggests that this may be the first published report of CMV pouchitis in a patient with CD who had undergone colectomy and pouch fashioning. However, an expansion of the search to "cytomegalovirus AND pouchitis" returned 13 unique results. This consisted of case reports^{1–3} and case series^{4,5} all reporting CMV pouchitis in UC. This is in keeping with the findings of Garrido *et al*⁶ that CMV

Figure 1 Appearance of pouch on endoscopic examination (pouchoscopy). 'Punched out' ulcers within the pouch are clearly visible.

Figure 2 (A) Nuclear eosinophilic inclusions (pink) on H&E staining and (B) positivity (brown staining) for cytomegalovirus on immunohistochemistry.

is more likely to complicate UC than CD. However, lessons from the management of CMV pouchitis are transferrable to the management of CMV pouchitis in CD, as demonstrated by this case.

The diagnosis of CMV pouchitis is based on history, examination and several investigations including pouchoscopy, histopathology, immunohistochemistry, serology and molecular studies such as the DNA PCR. Risk factors should be sought in the history. McCurdy *et al*⁴ analysed their experience of managing seven patients with CMV pouchitis (five UC and two indeterminate colitis). The median age was 35 years old (range 10–53), five (71%) were women and five (71%) were receiving immunosuppressive medications,⁴ a profile fitting the patient presented in the report. These findings are also concordant with previous reports associating female sex and prolonged corticosteroid use to CMV infection in IBD.⁷ The most commonly reported presenting symptoms were diarrhoea, crampy abdominal pain and fever.^{1–5} However, these symptoms alone do not differentiate CMV pouchitis from disease relapse or idiopathic pouchitis, although fever may have a higher predictive value since it is uncommon in idiopathic pouchitis.⁵ Also, although pouchoscopy may reveal mucosal inflammation and ulceration (figure 1), this again does not differentiate between the possible diagnoses. For a specific diagnosis, microbiological, serological, pathological and molecular tests may be performed to identify the virus. The identification of CMV IgM can be used to

differentiate chronic and acute infection.⁴ Serology was not performed in this case. Histopathological examination of H&E stained biopsies may reveal pink CMV inclusions (figure 2A) and brown staining on immunohistochemistry (figure 2A). However, the most sensitive test is PCR to amplify CMV DNA.

Despite the low viral load (<2500 copies/mL) in our patient, antiviral therapy was started without delay. The resolution of the patient's symptoms within 48 h of starting oral valganciclovir suggests that this level of viraemia was clinically important in this patient. Oral valganciclovir 900 mg twice daily for 21 days has been shown to be beneficial in this and other cases.² Similarly rapid improvements within 48 h have also been reported in other cases.² Others have opted for an initial 21-day courses of intravenous ganciclovir or longer if symptomatic resolution was not achieved.^{4 5} Munoz-Juarez *et al*⁵ used a dose of 10 mg/kg/day of valganciclovir. No randomised controlled trials have been performed to assess the relative efficacies of oral or intravenous regimens. Therefore, the choice between intravenous and oral therapy is usually based on the patient's performance status.² Both regimens are effective, have a low incidence of adverse effects although in one case intravenous ganciclovir was stopped after 10 days due to a drug eruption.⁵ The possibility of spontaneous resolution in the present and previously reported cases^{1–5} is unclear since all patients were promptly treated with antivirals at presentation. This possibility may be better examined in a placebo-controlled study. However, due to the low incidence of CMV pouchitis, it may be difficult to conduct such studies with sufficient statistical power.

This case serves as a reminder to clinicians to consider CMV as an aetiological factor in pouchitis in patients with, not just UC, but also CD. Although CMV complicating IBD is well described in the literature, CMV is not routinely tested for in many units. Our differential diagnosis of idiopathic pouchitis was based on the fact that most cases are considered idiopathic.⁴ However, up to 30% of cases of pouchitis are thought to have a secondary aetiological factor.⁸ This is especially true for cases refractory to antibiotics⁸ as was the case with this patient. Although immunosuppressed patients are at increased risk of opportunistic infections such as CMV, immunocompetent patients can also be affected. A quarter (25.6%) of patients in published cases were immunocompetent.¹ A high degree of suspicion is therefore required. This is regarded by some as the most important factor in diagnosis of this treatable condition.^{1 5}

This case also reminds clinicians of the difficulty of differentiating some cases of IBDs, even with histopathological evidence. As in this case, although a diagnosis of UC had been made on the basis of histopathological evidence at the time, leading to pouch surgery, the possibility of CD presenting at a later date must be considered.

Competing interests None.

Patient's perspective

As an inflammatory bowel disease sufferer for 23 years, the pain experienced with cytomegalovirus colitis was identical to the pain I experienced with Crohn's disease previously. However, the differences between a 'normal' relapse and this occasion were significant to me. The fact that there was no blood at any time made me think that there could be another explanation. Furthermore, the night sweats, which were extreme (and often) were something that I had never experienced previously. The fact that once diagnosed and treated with the appropriate antibiotics I felt well within a week was such a relief given the serious nature of the symptoms when I was admitted to the ward.

Learning points

- ▶ Histopathological examination is not 100% sensitive at differentiating Crohn's disease and ulcerative colitis.
- ▶ Patients who have had colectomy and pouch formation for ulcerative colitis may present with Crohn's disease at a later date.
- ▶ The diagnosis of cytomegalovirus (CMV) pouchitis requires a high index of suspicion.
- ▶ Tests to identify CMV include culture, pathological staining, immunohistochemistry and PCR.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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