Rare disease

Concomitant *Clostridium difficile* colitis and cytomegalovirus colitis in an immunocompetent elderly female

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Summary

A 78-year-old Japanese woman with diarrhoea and abdominal pain was admitted for PCR test (PCR)-proven *Clostridium difficile* colitis. The patient's symptoms persisted despite multiple courses of antibiotics including intravenous metronidazole, oral vancomycin and oral fidaxomicin. She underwent a stool transplant without improvement. Biopsies from a colonoscopy revealed concomitant cytomegalovirus (CMV) infection. The patient was immediately started on intravenous ganciclovir. Unfortunately, she developed sepsis secondary to colitis, and underwent definitive treatment with a total colectomy. Although CMV is a rare colonic pathogen in the immunocompetent patient, it should be considered in patients with severe or refractory *C difficile* colitis.

BACKGROUND

Cytomegalovirus colitis is most commonly diagnosed in immunocompromised patients, though it has been recognised in immunocompetent hosts as a cause for acute diarrhoeal illness.¹ We report a case of *Clostridium difficile* and cytomegalovirus (CMV) co-infection in an immunocompetent patient causing an inflammatory, refractory colitis and sepsis ultimately requiring a colectomy. Due to rarity in healthy patients, CMV colitis is often initially overlooked, but should be considered especially in elderly patients with refractory diarrhoea or intractable *C difficile* colitis infections.

CASE PRESENTATION

This case involved a 78-year-old Japanese woman with a medical history significant only for dementia, gastroesophageal reflux (GERD) and one episode of *C difficile* colitis 6 months prior to presentation while hospitalised for a left hip fracture. She was evaluated in the emergency department for abdominal pain and frequent loose, black stools for 1 week. Additional review of systems was negative, and the patient denied antibiotic use within the last 6 months. The patient lived at home with her spouse and was functionally independent. She had no remarkable social or family history.

INVESTIGATIONS

Initial laboratory evaluation was notable for a leucocytosis of 18 000/l and a positive *C difficile* PCR. CT of the abdomen/pelvis showed a thickened bowel wall of the transverse and sigmoid colon in the distribution of the inferior mesenteric artery.

DIFFERENTIAL DIAGNOSIS

The initial differential for this patient with abdominal pain and bloody diarrhoea included ischaemic colitis versus an infectious or inflammatory colitis. Also, mesenteric ischaemia within an inferior arterial distribution was considered, but was thought to be less likely with a

normal lactate. Given the significant leucocytosis, positive *C difficile* PCR and history, *C difficile* colitis was considered the most likely diagnosis.

TREATMENT

Initially, the patient was treated with metronidazole 500 mg intravenous every 8 h and vancomycin 500 mg oral every 6 h for moderate-to-severe *C difficile* colitis. Her leucocytosis resolved within several days, but she continued to have frequent loose and haemorrhagic stools. After 10 days of this antibiotic regimen, the patient was transitioned to fidaxomicin 200 mg oral twice a day. Probiotic supplements, cholestyramine and stool-bulking agents were added to her regimen without change in symptoms. A nasogastric tube (NGT) was placed for enteral nutrition. In addition, the patient was started on empiric mesalamine 800 mg oral three times a day for several days as per the gastroenterologist's recommendations to improve existing colonic inflammation. With the persistence of symptoms despite maximum antibiotic therapy, a flexible sigmoidoscopy was performed which demonstrated severe colitis and fine pseudomembranes (figure 1). Biopsy was consistent with acute inflammation of the mucosa.

Due to lack of significant improvement approximately 3 weeks into the hospital course, a colonoscopy was performed which demonstrated worsening colitis (figure 2). The patient simultaneously underwent a stool transplant that was collected from her husband. Colonic biopsies were taken at the time of stool transplant, and initial biopsy results were consistent with chronic inflammation.

The patient failed to respond to the stool transplant. The refractory symptoms raised the question of an underlying, albeit atypical, inflammatory bowel disease (IBD). Given the possibility of IBD and the patient's failure to respond to therapy, she was treated with two doses of methylprednisolone 40 mg intravenously. However, at this time, the colonic biopsy results returned with positive immunohistochemistry (IHC) for CMV, and characteristic

Figure 1 Flexible sigmoidoscopy demonstrated severe colitis and fine pseudomembranes.

eosinophilic inclusions. The patient was diagnosed with CMV colitis; thus, methylprednisolone was subsequently discontinued and therapy with ganciclovir was initiated.

OUTCOME AND FOLLOW-UP

Unfortunately, several days after initiating antiviral therapy, the patient became acutely febrile and hypotensive, refractory to intravenous fluid boluses. She was transferred to the intensive care unit and started on vasopressor support and empiric antibiotic therapy. Blood and urine cultures, as well as chest radiographs were unremarkable. Aside from the colitis, no other source for infection was found. The patient underwent an emergency total colectomy, and empiric antibiotics were discontinued. Despite her haemodynamic compromise, she tolerated the procedure well. The colectomy specimen was submitted for further pathological examination and the diagnosis of CMV was confirmed with repeat IHC stains (figure 3). She was discharged home 3 weeks later; however, given concerns for persistent CMV enteritis, the patient was transitioned to a 6-week course of oral valganciclovir under the guidance of the infectious disease consultant. The patient has since recovered from her serious illness and is back to her baseline health status.

DISCUSSION

CMV colonisation is common in the general population. It is prevalent in 40–100% of adults by the age of 30 years and in approximately 70% of the population over the age of 60 years.^{2–3} Active infection is well described in the immunosuppressed hosts, but is much less common in immunocompetent individuals.^{3–6} Our review of the English language literature revealed 54 reported cases of CMV colitis in immunocompetent patients, although most of these patients were elderly or had associated comorbidities such as sepsis, end-stage renal disease requiring haemodialysis and IBD.^{6–14}

CMV colitis typically presents with abdominal pain, fever and bloody diarrhoea. Imaging often reveals a thickened bowel wall similar to other colonic entities such as *C difficile* colitis, ischaemic colitis, IBD and cancer.^{12–15} With a non-specific presentation, the clinician must have a high index of suspicion to diagnose CMV colitis,

A

B

C

Figure 2 Colonoscopy reveals friable, spontaneously bleeding, inflamed, and ulcerated mucosa of the caecum (A), descending colon (B) and sigmoid colon (C).

particularly in the immunocompetent host. The estimated rate for colectomy in patients with CMV colitis is 20–30% and is higher for patients with a delayed diagnosis and treatment.¹⁶ Thus, it should be considered as an early alternate diagnosis, even in immunocompetent hosts with comorbidities or intractable symptoms.

Figure 3 High-power photomicrograph of inflamed colonic mucosa with a cell infected with cytomegalovirus. The characteristic eosinophilic nuclear inclusions can be appreciated at this power.

C difficile and CMV co-infection also may confound the clinical picture, resulting in delayed diagnosis and subsequent treatment. As of 2011, there have been nine reported cases of *C difficile* and CMV colitis co-infection, although eight of the nine patients possessed significant underlying immunosuppression (ie transplant recipients, AIDS, lymphoma and ulcerative colitis).¹⁵ A sequential CMV infection may arise secondary to disruption of the colonic mucosa and a relative immunosuppressed state from the initial *C difficile* colitis.¹⁷ With the emergence of increasingly virulent strains of *C difficile* that more frequently require invasive therapies including faecal transplant or colectomy, it can be more challenging to appreciate a coexistent or sequential CMV infection.^{18 19}

In addition, we considered the possibility of pre-existing IBD; however, prior endoscopy reports did not indicate a diagnosis of Crohn's or ulcerative colitis. This patient did not have symptoms of IBD before her acute gastrointestinal illness. We feel that it is of low probability that she suffered from IBD prior to the onset of her *C difficile* and CMV infections.

Learning points

- ▶ Although more commonly associated with immunocompromised patients, consider cytomegalovirus (CMV) colitis in elderly immunocompetent hosts with refractory or severe inflammatory diarrhoea.
- ▶ *Clostridium difficile* and CMV colitis co-infection is a rare entity, but should be considered even in immunocompetent patients who fail to respond to initial therapy.
- ▶ Clinicians must have a high index of suspicion to diagnose CMV colitis in otherwise healthy patients, but a delay in diagnosis is associated with significant morbidity.

Competing interests None.

Patient consent Obtained.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Kurtz M, Morgan M. Concomitant *Clostridium difficile* colitis and cytomegalovirus colitis in an immunocompetent elderly female. *BMJ Case Reports* 2012;10.1136/bcr-2012-007273, Published XXX

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