Cryptogenic colitis due to occult cytomegalovirus infection

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Colitis secondary to cytomegalovirus infection is well recognised and usually straightforward to diagnose. Here two cases are reported in whom all initial investigations failed to demonstrate the presence of virus, with potential adverse consequences for its treatment. A case is made for empirical antiviral therapy despite negative investigations if clinical suspicion is high.

Introduction

Cytomegalovirus (CMV) is a herpes virus known to infect the gastrointestinal tract. The majority of patients are immunocompromised but exacerbations of inflammatory bowel disease and colitis in immunocompetent individuals are well recognised phenomena.^{1,2} It typically responds well to antiviral treatment with agents such as ganciclovir. The diagnosis is usually obvious from biopsies obtained at the time of endoscopy that characteristically contain numerous inclusion bodies and from which virus can be demonstrated immunohistochemically, by PCR or in culture.³ Here we report two unusual cases of CMV colitis in whom biopsies were not diagnostic. The first patient was treated with immunosuppressants and ultimately underwent colectomy before infection was proven. The second was treated empirically with antivirals and made a full recovery.

Case reports

Case No 1

Presenting features and medical history

A 59-year-old man with a 30 year history of pan-ulcerative colitis was admitted to hospital with bloody diarrhoea, opening his bowel up to 10 times/day. He had been seen in the gastroenterology outpatient clinic a month previously complaining of a flare of his colitis. He had until this time been maintained in remission on balsalazide. This was changed to oral and rectal mesalazine, with a reducing dose course of oral prednisolone. Unfortunately, his

symptoms continued to deteriorate. His other past medical history included β thalassaemia and an elevated prostate specific antigen, under surveillance in the urology clinic. He smoked 1–2 cigarettes/day.

On admission, he was afebrile and haemodynamically stable. Examination was unremarkable apart from mild left-sided abdominal tenderness. Bowel sounds were normal.

Investigations and treatment

Blood tests showed haemoglobin of 12.9 g/dl, white cell count of $9.0 \times 10^9/l$, neutrophil count of $8.21 \times 10^9/l$, platelets of $230 \times 10^9/l$, C reactive protein (CRP) of 4.2 mg/l, erythrocyte sedimentation rate of 4 mm/h and albumin 40 g/l. A plain abdominal x-ray showed proximal constipation but no toxic dilatation. Intravenous hydrocortisone 100 mg four times daily was started. Stool cultures sent for routine microbiology and *Clostridium difficile* toxin assay were all negative. CMV superinfection or reactivation was considered: serology was negative for immunoglobulin M (IgM) and positive for IgG antibodies, consistent with past infection.

A flexible sigmoidoscopy was performed on day 2 of admission which revealed moderately severe colitis with ulceration, with some restoration of normal mucosa seen in the distal transverse colon (figure 1A). Histology from the biopsies was consistent with severe active ulcerative colitis with no inclusion bodies and negative immunostaining for CMV (figure 1B, C). On day 9, CRP increased to 50.2 mg/l with continuing bloody diarrhoea and abdominal pain. Repeat flexible sigmoidoscopy showed confluent severe colitis up to 60 cm with repeat histology again showing severe active colitis with negative immunostaining for CMV. Intravenous steroids were continued and oral ciclosporin 200 mg

twice daily added, with no clinical or biochemical evidence of improvement. On day 17 of admission, he was referred to the colorectal surgeons in view of his refractory disease who performed a subtotal colectomy with end ileostomy. Histology of the colectomy specimen showed florid active distal colitis with extensive mucosal ulceration. Immunohistochemistry was positive for CMV but with a patchy distribution (figure 1D) and numerous inclusion bodies were seen within the submucosa (figure 1E, F).

Outcome and follow-up

Postoperatively, his discharge was delayed by transient urinary retention and a hospital acquired chest infection. He was quickly weaned off steroids and discharged home on day 32. He was reviewed 2 weeks post discharge in the outpatient clinic when he was well with no symptoms from the remaining

rectal stump; he was therefore not started on antiviral medication.

Case No 2

Presenting features and medical history

A 54-year-old woman with previously diagnosed stage IV serous papillary ovarian carcinoma was admitted to hospital with a 10 day history of diarrhoea and a 2 day history of vomiting.

The oncological diagnosis had been made 12 months previously at which time a total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy were performed. Chemotherapy with carboplatin and paclitaxel was given. Peritoneal disease persisted following treatment but she remained otherwise well. Liposomal doxorubicin was commenced for radiological and symptomatic disease progression 11 months after the original presentation and 1 month before the current admission.

Figure 1 Case No 1. Endoscopic and histological appearances of the colon. (A) Views at flexible sigmoidoscopy demonstrating confluent inflammation and ulceration; low power (B) and high power (C) views from biopsies acquired at the time of endoscopy showing an inflammatory infiltrate but no inclusion bodies. (D) Histology from resected colon immunostained positive for cytomegalovirus (CMV) in a patchy distribution. (E) Inclusion bodies were present. (F) These were also shown to contain CMV.

Three days prior to admission she received her second cycle of liposomal doxorubicin. At that time, her stool had been looser than normal but diarrhoea was not prominent. Apart from a longstanding right-sided malignant pleural effusion, she had no other comorbidities. In particular, she had no previous bowel disorders or recent antibiotic use. On admission, she was afebrile and the abdomen was soft and non-tender.

Investigations and treatment

Initial investigations revealed an elevated white cell count of $12.5 \times 10^9/l$, neutrophil count of $9.86 \times 10^9/l$ and CRP of 441.8 mg/l. She was in acute renal failure with a urea of 18.0 mmol/l and creatinine of 201 $\mu\text{mol/l}$ (baseline 6.4 mmol/l and 74 $\mu\text{mol/l}$, respectively). CA125 prior to admission was 2902 kIU/l. Urine analysis was positive for nitrites and leucocytes, and so empirical co-amoxiclav and clarithromycin were started to cover both lower respiratory and urinary tract infection. Culture of blood, stool and urine was negative, as was stool *C difficile* toxin assay.

On admission, she was opening her bowels 5–10 times/day. Over the following 5 days the frequency of diarrhoea increased to 16 times/day but no passage of blood or mucus and she began to spike temperatures $>38^\circ\text{C}$. On day 7 of admission, antibiotics were changed to oral ciprofloxacin and metronidazole. An abdominal CT scan demonstrated left-sided colitis but no intra-abdominal collections. CRP at this stage had fallen to 172.1 mg/l and the fevers settled but diarrhoea persisted. On day 16 she spiked further fevers associated with re-elevation of CRP to 362.2 mg/l. Repeat stool cultures and *C difficile* toxin were negative throughout. On day 17, flexible sigmoidoscopy demonstrated confluent inflammation to the limit of examination with multiple discrete ulcers (figure 2A). These were thought to be infective in origin, potentially herpes simplex virus (HSV) or CMV; there was no evidence of pseudomembranous colitis. She was not neutropenic, HIV-1 and HIV-2 were not detected, and both CD4 and CD8 counts were normal. She had received a 2 unit blood transfusion prior to her second cycle of liposomal doxorubicin but both were CMV negative.

On day 20 she deteriorated, developing abdominal distension, guarding and high pitched bowel sounds. A plain abdominal radiograph showed toxic megacolon, confirmed on repeat CT (figure 2B, C), which also excluded perforation. In view of the clinical, endoscopic and radiographic findings, a working diagnosis of HSV or CMV colitis was made and intravenous aciclovir and ganciclovir were commenced. CRP fell rapidly (figure 3), with marked clinical improvement.

On day 34 of admission, antivirals were discontinued. Within 2 days, CRP rose to 110.2 mg/l and ganciclovir was restarted. CRP subsequently normalised again. Nonetheless, on reviewing her histopathology there were no positive findings to support a viral

aetiology. Active colitis was seen but with no inclusion bodies. HSV, CMV and Epstein–Barr virus (EBV) were not detected by immunostaining and/or PCR; nor were adenovirus, rotavirus or norovirus.

Outcome and follow-up

The patient was discharged on a 6 week course of oral valganciclovir. She remained clinically stable for the next 3 months, with no diarrhoea and a normal CRP. Unfortunately, her ovarian cancer then progressed and she subsequently passed away from complications of her oncological disease.

Discussion

We have reported here two patients with severe colitis but multiple non-diagnostic biopsies. In the first case, inflammation was attributed to a flare of his underlying ulcerative colitis, leading to treatment with potent immunosuppressants and ultimately colectomy, before the responsible CMV infection was identified. The second was an apparently immunocompetent patient who developed toxic megacolon clearly ameliorated by ganciclovir but in whom CMV infection was never proven.

CMV is a herpes virus, acquisition of which is extremely common: seropositivity ranges from 60% to 100% in populations studied.⁴ Primary infection typically runs a mild course, often asymptomatic or presenting as an undifferentiated viral syndrome or mononucleosis-like illness that is usually benign and self-limiting. There remains, however, the potential for later reactivation which usually presents with organ specific involvement. CMV notably causes severe disease in immunocompromised patients, particularly affecting the gastrointestinal tract. It also has a potential role in exacerbating bowel inflammation in patients with ulcerative colitis or Crohn's disease in whom its reactivation and identification within the mucosa is not uncommon¹ although this does not routinely require antiviral medication.⁵

There is an emerging literature on severe CMV infection in immunocompetent individuals. The gastrointestinal tract is the primary site of involvement, and although any region may be involved, the predominant manifestation is colitis.^{2–6} Mortality can be as high as 6.2%,⁷ and younger age (particularly <55 years) predicts better outcome.² Although not overtly immunocompromised, the second patient reported here had recently received chemotherapy which may perturb lymphocyte function if not numbers.

All antivirals active against herpesviridae essentially target viral DNA polymerase. Those used for systemic CMV infection include ganciclovir, cidofovir and foscarnet. Their corresponding prodrugs, such as valganciclovir, have superior oral bioavailability.⁸ In practice, ganciclovir is used almost exclusively for treatment of CMV, due to its significant toxicity profile. The main risks are of bone marrow suppression (with prolonged treatment, 40% of patients develop granulocytopenia

Figure 2 Case No 2. Radiological and histological appearances of the colon. (A) Sigmoidoscopy revealed confluent inflammation with multiple discrete ulcers. (B) Cross sectional and (C) coronal CT images demonstrating colitis with thickening of the large bowel and marked dilatation of the caecum, ascending and transverse colon up to 8 cm in diameter.

Figure 3 Case No 2. Serum C reactive protein (CRP) concentrations. Timing of antibiotic and antiviral medications is shown. Although an initial reduction in CRP from presentation was seen, diarrhoea persisted and worsened until the introduction of antivirals.

and 15% thrombocytopenia or anaemia at 3 months) and nephrotoxicity (in approximately 20%); these are cumulative with dose and duration of treatment but usually reversible on its discontinuation.⁹ Ganciclovir is, however, active in vitro against many of the other herpesviridae, including HSV-1,¹⁰ HSV-2 and varicella zoster,¹¹ and human herpes virus (HHV)-8.¹² There is some clinical evidence that EBV is partially responsive but there is high variability possibly related to

subtherapeutic dosing.^{13–15} HHV-7 and HHV-8 appear poorly responsive.¹² There is, however, little evidence that herpesviridae other than CMV, HSV and EBV cause colitis, beyond their occasional detection in inflammatory bowel disease patients.¹⁶ There is no evidence that ganciclovir is active against other gastrointestinal viruses, including adenoviridae, enteroviridae, astroviridae or caliciviridae.

These cases are unusual in that multiple endoscopies and biopsies failed to detect CMV. In the first patient, this resulted in treatment which likely activated or exacerbated the underlying infection, and ultimately surgical resection. It is unclear whether a further endoscopy immediately prior to resection would have demonstrated virus, although its distribution was deep in the mucosa potentially overlooked by a standard pinch biopsy. In the second, empirical antiviral treatment was highly effective, resolving a toxic megacolon and averting surgery, even though the diagnosis was never formally proven. Coincidence is unlikely given disease recrudescence on withdrawal of ganciclovir and remission on its reintroduction. Diarrhoea may occur after liposomal doxorubicin but is rarely severe.

There are clearly two potential mechanisms of CMV colitis in our patients: primary infection and secondary reactivation. In the absence of a mononucleosis-like illness, positive IgM serology and no transfusion of CMV positive blood products, the latter is most probable. This agrees with data from organ transplant recipients, in whom strain analysis demonstrates that

the predominant source of infection derives from latent virus rather than transfer from a donor.¹⁷

CMV establishes lifelong persistence within hosts, predominantly within cells of the myeloid lineage, with sporadic reactivation events which are normally well controlled by cell mediated immune surveillance. Reactivation is determined by expression of viral immediate early (IE) genes, with subsequent activation of lytic genes responsible for pathogenicity. In the healthy host, peripheral blood does not carry infectious virus but contains a form that is capable of reactivation. Differentiation of monocytes from asymptomatic seropositive donors in vitro into macrophages is also known to result in expression of IE genes, and macrophages are permissive for viral replication and lytic infection.¹⁸

A speculative model of CMV latency in the seropositive healthy carrier would be that the virus is maintained in monocytes and their progenitors, in a dormant state with absence of lytic gene expression. This in itself may permit evasion of host immune responses. When terminal differentiation into macrophages occurs in the tissues, the block in viral IE expression is removed and the viral genome becomes fully reactivated such that these sites in the host may be regarded as 'infected'. In this situation, the host cytotoxic T cell response acts to clear these cells; however, if this process is compromised the virus can then disseminate causing overt disease.¹⁹ A tantalising hypothesis to explain the presentation with colitis is that our patients had an initial gastroenteritis or flare of inflammatory bowel disease resulting in an acute inflammatory response delivering monocytes to the colon. Maturation of these cells into macrophages then induced active viral replication, which subsequently evaded the immune response (likely permitted by iatrogenic immunosuppression with corticosteroids and ciclosporin in case No 1).

These two patients highlight the fact that CMV infection in the bowel may be patchy, and that there are limits to the sensitivity of sigmoidoscopically acquired biopsies in its diagnosis. The endoscopist is therefore cautioned to obtain multiple samples and the histopathologist to examine all tissue layers. Between 37% and 73% do not demonstrate inclusion bodies with routine histological staining.^{20–21} Similarly, the sensitivities of immunohistochemistry, PCR and culture may range from 78% to 93%, 60% to 100% and 45% to 78%, respectively.²¹ While serology is highly sensitive for primary CMV infection, false negatives may occur in patients with reactivation disease, infection limited to the tissues without viraemia and early in the course of the illness. Nonetheless, it is extremely rare in patients who are CMV IgG negative, and a positive IgM as well as features of an acute mononucleosis-like illness (pharyngitis, lymphadenopathy and/or splenomegaly and hepatitis) are highly suggestive. In individuals in whom there is a high clinical index of suspicion, CMV should be extensively sought using

Learning points

- CMV infection can precipitate flares of inflammatory bowel disease
- CMV colitis can arise in immunocompetent individuals
- There are limits to the sensitivity of current diagnostic modalities
- Colitis may be patchy, introducing sampling error at endoscopy
- There is a case for empirical antiviral therapy in patients in whom clinical suspicion is high

Key messages

- Consider CMV colitis in patients with inflammatory bowel disease whose clinical course is at variance with their clinical and/or pathologically identified diagnosis, particularly in those who deteriorate with escalating immunosuppression.
- In patients with an atypical clinical course, seek advice from an expert gastrointestinal histopathologist.
- Consider empirical anti-CMV therapy on an individual case by case basis.

a combination of all of these modalities, and antiviral treatment considered even in the face of negative investigations. This will include patients with inflammatory bowel disease not improving despite immunosuppression and others with potential immune compromise.

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References

1. Maher MM, Nassar MI. Acute cytomegalovirus infection is a risk factor in refractory and complicated inflammatory bowel disease. *Dig Dis Sci* 2009;54:2456–62.
2. Galiatsatos P, Shrier I, Lamoureux E, *et al.* Meta-analysis of outcome of cytomegalovirus colitis in immunocompetent hosts. *Dig Dis Sci* 2005;50:609–16.
3. Schreiber A, Härter G, Schubert A, *et al.* Antiviral treatment of cytomegalovirus infection and resistant strains. *Expert Opin Pharmacother* 2009;10:191–209.
4. Staras SA, Dollard SC, Radford KW, *et al.* Seroprevalence of cytomegalovirus infection in the United States, 1988–1994. *Clin Infect Dis* 2006;43:1143–51.
5. Matsuoka K, Iwao Y, Mori T, *et al.* Cytomegalovirus is frequently reactivated and disappears without antiviral

- agents in ulcerative colitis patients. *Am J Gastroenterol* 2007;**102**:331–7.
6. **Karakozis S**, Gongora E, Caceres M, *et al.* Life-threatening cytomegalovirus colitis in the immunocompetent patient: report of a case and review of the literature. *Dis Colon Rectum* 2001;**44**:1716–20.
 7. **Rafailidis PI**, Mourtzoukou EG, Varbobitis IC, *et al.* Severe cytomegalovirus infection in apparently immunocompetent patients: a systematic review. *Virol J* 2008;**5**:47.
 8. **Paya CV**, Wilson JA, Espy MJ, *et al.* Preemptive use of oral ganciclovir to prevent cytomegalovirus infection in liver transplant patients: a randomized, placebo-controlled trial. *J Infect Dis* 2002;**185**:854–60.
 9. **Crumpacker CS**. Ganciclovir. *N Engl J Med* 1996;**335**:721–9.
 10. **St Clair MH**, Miller WH, Miller RL, *et al.* Inhibition of cellular alpha DNA polymerase and herpes simplex virus-induced DNA polymerases by the triphosphate of BW759U. *Antimicrob Agents Chemother* 1984;**25**:191–4.
 11. **Terry BJ**, Mazina KE, Tuomari AV, *et al.* Broad-spectrum antiviral activity of the acyclic guanosine phosphonate (R,S)-HPMPG. *Antiviral Res* 1988;**10**:235–51.
 12. **De Clercq E**, Naesens L, De Bolle L, *et al.* Antiviral agents active against human herpesviruses HHV-6, HHV-7 and HHV-8. *Rev Med Virol* 2001;**11**:381–95.
 13. **Venturi C**, Bueno J, Gavalda J, *et al.* Impact of valganciclovir on Epstein–Barr virus polymerase chain reaction in pediatric liver transplantation: preliminary report. *Transplant Proc* 2009;**41**:1038–40.
 14. **Hierro L**, Díez-Dorado R, Díaz C, *et al.* Efficacy and safety of valganciclovir in liver-transplanted children infected with Epstein–Barr virus. *Liver Transpl* 2008;**14**:1185–93.
 15. **Adams LA**, Deboer B, Jeffrey G, *et al.* Ganciclovir and the treatment of Epstein–Barr virus hepatitis. *J Gastroenterol Hepatol* 2006;**21**:1758–60.
 16. **Knösel T**, Schewe C, Petersen N, *et al.* Prevalence of infectious pathogens in Crohn's disease. *Pathol Res Pract* 2009;**205**:223–30.
 17. **Smyth RL**, Sinclair J, Scott JP, *et al.* Infection and reactivation with cytomegalovirus strains in lung transplant recipients. *Transplantation* 1991;**52**:480–2.
 18. **Taylor-Wiedeman J**, Sissons P, Sinclair J. Induction of endogenous human cytomegalovirus gene expression after differentiation of monocytes from healthy carriers. *J Virol* 1994;**68**:1597–604.
 19. **Sinclair J**, Sissons P. Latency and reactivation of human cytomegalovirus. *J Gen Virol* 2006;**87**(Pt 7):1763–79.
 20. **Mentec H**, Leport C, Leport J, *et al.* Cytomegalovirus colitis in HIV-1-infected patients: a prospective research in 55 patients. *AIDS* 1994;**8**:461–7.
 21. **Kandiel A**, Lashner B. Cytomegalovirus colitis complicating inflammatory bowel disease. *Am J Gastroenterol* 2006;**101**:2857–65.