CASE REPORT

Protracted severe systemic cytomegalovirus disease in an immunosuppressed patient with ulcerative colitis

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ABSTRACT

A 33-year-old man with ulcerative colitis presented with 5-day history of fever, night sweats, abdominal pain and increased stool frequency. He was on mesalazine M/R 1 g once daily, 6-mercaptopurine (6-MP) 75 mg once daily and prednisolone 40 mg once daily. Examination revealed fever and tachycardia. Blood examinations identified a persistent leucopenia, C reactive protein of 23 mg/L and an initial alanine transaminase of 855 IU/L. Flexible sigmoidoscopy revealed well-demarcated, punched-out ulcers in the proximal rectum and distal sigmoid, with histology pathognomonic of cytomegalovirus (CMV). CMV DNA PCR was 51 140 copies/mL. Despite prompt withdrawal of 6-MP, steroids and initiation of intravenous ganciclovir on day 2 of admission, his systemic illness, diarrhoea and fever persisted until day 19 of antiviral therapy. Other copathogens and lymphoma were ruled out on serology and CT scan, respectively. After an unusually prolonged course of antiviral therapy, the patient made a full clinical recovery, bloods normalised and there were two consecutive undetectable CMV DNA PCRs.

BACKGROUND

Cytomegalovirus (CMV) is a herpesviridae virus of high prevalence within the general population, whereby approximately 70% of adults have lifelong latent infection.¹ Although generally asymptomatic in the immunocompetent, CMV can have severe systemic consequences for patients who are immunocompromised (ie, HIV, chemotherapy, disease-modifying antirheumatic drugs, immunosuppressive drugs after organ transplants, glucocorticoids). In particular, patients with inflammatory bowel disease (IBD) on

immunosuppressive therapies can develop pancolitis, hepatitis, bone marrow failure, retinitis and, potentially, death. Ever since the description of its association with ulcerative colitis (UC) by Powell *et al*² the exact role and management of systemic CMV in UC has been the subject of much debate. The European Crohn's and Colitis Organisation guidelines in 2014 state that antiviral therapy should be initiated and immunomodulators (ie, azathioprine, mycophenolate) should be considered for discontinuation in patients with severe steroid-resistant colitis and positive CMV morphology on colonic biopsy.³ However, in the rarer form of severe systemic CMV disease (with multiorgan involvement and positive CMV PCR >2000 copies/mL), immunomodulation therapy must be discontinued immediately. The guidelines do not advocate screening for CMV before initiating immunomodulators nor do they recommend ongoing surveillance once established on the treatment.

Severe, primary systemic CMV infection is rarely seen in clinical practice in patients with UC. However, this case encompasses the full range of risk factors (age >30 years, presence of ulcers at endoscopy, recent treatment with corticosteroid and/or immunomodulators) previously described by McCurdy *et al*⁴ Unlike the majority of cases of IBD and CMV, in which CMV is confined to the colonic mucosa, this case highlights severe, multiorgan systemic CMV with high serum levels (>50 000 copies/mL), hepatitis, colitis, bone marrow failure and septicaemia. Despite promptly discontinuing steroid/immunomodulator therapy and initiating intravenous antiviral

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therapy as per guidelines,³ the septicaemia and multi-organ involvement persisted for 2 weeks longer than has been reported in the literature (ie, 3–7 days). The case highlights the importance of prolonged antiviral therapy, regular endoscopic assessment (eg, UC flare vs persisting CMV ulceration) and key non-invasive markers of clinical improvement (decreasing stool frequency, temperature, CMV PCR and improving markers of bone marrow function).

CASE PRESENTATION

A 33-year-old man of South Asian ethnicity with known left-sided UC presented to hospital with a 5-day history of fever, night sweats, malaise, crampy abdominal pain and increased stool frequency (8×/day, including nocturnal). He had recently returned from holiday in Dubai. His immediate family had recently suffered from flu-like symptoms and had made a complete recovery. He has had three flares of UC since diagnosis 5 years prior, with surveillance colonoscopy revealing the extent of disease to the proximal transverse colon. He has no other medical/surgical history, no relevant family history and abstains from alcohol and smoking. Prior to admission he was well established on mesalazine M/R 1 g once daily and 6-mercaptopurine (6-MP) 75 mg once daily and had taken treatment dose oral prednisolone for 10 days.

Observations revealed tachycardia (115 beats per minute), blood pressure of 98/60 mm Hg and respiratory rate of 16/min, oxygen saturations of 98% on room air, blood glucose of 4.6 mmol and swinging fever of 38.9°C. Cardiorespiratory, neurological, and joint and soft tissue examinations were unremarkable. Abdominal examination revealed mild generalised tenderness, but no evidence of guarding or rebound. Per rectum examination was unremarkable.

INVESTIGATIONS

Initial investigations revealed haemoglobin of 111 g/L, platelet count of 302×10^9 /L, white cell count (WCC) of 2.3×10^9 /L (differential including neutrophils 1.9×10^9 /L, lymphocytes 0.3×10^9 /L), ferritin of 1777 ng/mL and C-reactive protein of 23 mg/L. Urea and electrolytes included a sodium of 128 mmol/L, potassium 4.4 mmol/L, urea 5.0 mmol/L, creatinine 80 μ mol/L, alongside estimated glomerular filtration rate (eGFR) of >90 mL/min/1.73 m². Liver function tests were abnormal with an alanine transaminase of 855 IU/L, alkaline phosphatase of 122 IU/L, bilirubin of 12 μ mol/L and albumin of 35 g/L. Chest X-ray and abdominal ultrasound were normal. Abdominal X-ray revealed a degree of left-sided colonic thumb printing and mural thickening, with no evidence of bowel dilatation. Urine, blood and stool cultures were negative after 48-hour culture, with the latter being negative for *Clostridium difficile* toxin. Serology was negative for hepatitis A, B, C, E viruses, HIV and previous tuberculosis infection. IgG was positive for Epstein-Barr virus,

but was equivocal for CMV. CMV DNA PCR was initially 51 140 copies/mL. 6-MP metabolites for TGN and MMPN-6 were 372 and 6799 pmol/ 8×10^8 cell, respectively, with the latter representing toxicity >5700 pmol/ 8×10^8 cell.

Index flexible sigmoidoscopy on day 2 of admission revealed well-demarcated, punched-out ulcers in the proximal rectum and distal sigmoid (figure 1A), with background Mayo 1 continuous colitis. Histology was pathognomonic of CMV infection with large cells, with hyperchromatic nuclei bearing intranuclear basophilic amorphous inclusions surrounded by clear halos (figure 1B,C). Due to persistent night sweats, fever and pancytopenia, a CT of the thorax, abdomen and pelvis was performed, which revealed evidence of mild pancolitis, but no evidence of lymphoma or intra-abdominal collections (figure 1D). Repeat flexible sigmoidoscopy on day 8 was performed to assess whether the predominant mucosal injury was CMV or UC flare, of which the former was still the main finding.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis on presentation was a severe flare of UC, infective gastroenteritis, tuberculosis or opportunistic primary CMV infection exacerbated by 6-MP-induced immunosuppression. The working diagnosis throughout was systemic CMV with colitis, hepatitis and bone marrow suppression.

TREATMENT

Initially the patient was started on intravenous fluids with electrolyte replacement, prophylactic low molecular weight heparin, intravenous 100 mg hydrocortisone four times a day and intravenous metronidazole 500 mg three times a day on the admissions unit. After specialist gastroenterology input on day 2 and CMV positivity, the 6-MP was stopped and intravenous ganciclovir 300 mg twice a day was given. Hydrocortisone was subsequently stopped on day 3 after the findings of flexible sigmoidoscopy strongly indicating CMV colitis over UC. After 19 days of intravenous ganciclovir, the patient was switched to oral valganciclovir 900 mg twice a day until there were two sequential negative CMV PCR results.

OUTCOME AND FOLLOW-UP

Despite early withdrawal of immunosuppression and starting intravenous ganciclovir, the patient remained symptomatic with swinging fever, night sweats and type 5–6 stools with a frequency of 4–5×/day until day 19 of the admission (figure 2). However, in parallel with his clinical improvement on day 19, his alanine transaminase (ALT), WCC, neutrophil and lymphocytes normalised, alongside a significant decrease in his CMV titres to undetectable levels on PCR. Interestingly, these improvements coincided with undetectable TGN levels, low MMPN levels of 317 pmol/ 8×10^8 cell

Figure 1 (A) Well-demarcated, punched-out mucosal ulcers in the distal sigmoid colon on flexible sigmoidoscopy. (B) H&E stain ($\times 40$) of colonic mucosa highlighting cytomegalovirus (CMV) inclusion bodies (black arrow). (C) Positive CMV immunohistochemistry (brown stains). (D) CT scan highlighting left-sided colitis, but absence of significant lymphadenopathy.

and the development of host IgG to CMV. The patient was successfully discharged after a 24-day admission, having returned to his baseline bowel habit on oral valganciclovir and oral mesalazine. On review in outpatient clinic, he remained well with undetectable CMV PCR and on maintenance 5-ASA therapy.

DISCUSSION

This is a rare case of systemic, multiorgan CMV infection in a young patient with UC and immunosuppressed with 6-MP and steroids. The clinical course, high CMV DNA PCR, lack of CMV IgG positivity and infective contact history suggest that this was a primary infection of CMV. A recent meta-analysis has shown that in a subgroup of patients with steroid-refractory UC (ie, failure to respond to intravenous corticosteroids) and a colonic tissue diagnosis of CMV, there is a significant lower risk of colectomy (OR 0.20; 95% CI 0.08 to 0.49) with early antiviral therapy.⁵ In addition, a potential association between severity of viral load (>2000 copies/mL) and risk of colectomy at 6 months has been proposed.⁶ Although there is evidence to suggest that CMV activation in UC might

not require antiviral therapy, this mainly relates to a study cohort that has low CMV DNA PCR values in the absence of positive colonic biopsy specimens.⁷ In contrast, the current case had all the poor prognosticators of high initial CMV DNA PCR $>50\,000$ copies/mL, punched-out ulceration on sigmoidoscopy, septicaemia and positive colonic immunohistochemistry for CMV. Current guidelines do not advocate serological testing for past CMV infection (ie, IgG) prior to 6-MP or azathioprine use, largely based on the fact that there is no evidence to suggest CMV prophylaxis would benefit those who have never been exposed to CMV. However, prior knowledge of the presence or absence of CMV IgG in a patient being considered for immunosuppressive therapy may heighten awareness of superimposed CMV infection in the presence of UC, and subsequently translate into early disease recognition and antiviral treatment.

The disease course in this man was unusually protracted, and he had persistent symptomatic fever (mainly nocturnal) that extended into the third week of treatment with intravenous ganciclovir, despite early discontinuation of steroids and 6-MP (figure 2).

Figure 2 Flow chart highlighting the pattern of body temperature, cytomegalovirus (CMV) DNA titres, total white cell count (WCC) and lymphocytes after commencing intravenous antiviral therapy.

The vast majority of reported case studies indicate clinical response within 3–5 days of antiviral therapy,⁸ hence the reason for cross-sectional imaging and quantiferon serology in the current case to exclude important differentials including lymphoma and tuberculosis, respectively. Interestingly, the prolonged clinical illness corresponded approximately with time taken to clear serum 6-MP metabolite levels, with recorded levels after 3 weeks of <100 and 317 pmol metabolite/ 8×10^8 cells for TGN and MMPN, respectively. It is not usual to measure serial 6-MP metabolite levels in an inpatient setting; however, in this case it aided with understanding the prolonged nature of the CMV disease and bone marrow suppression. Bone marrow suppression and fever are recognised complications of ganciclovir; however, in the current case the leucopenia was attributed to the CMV, as there was improvement in the leucocyte count after initiation of ganciclovir therapy.

This case emphasises the importance of early discontinuation of immunosuppression and initiation of intravenous antiviral therapy in patients with significant systemic CMV disease and underlying IBD. It also highlights the need to prolong the course of antiviral therapy, beyond 14 days in our case, until there is clear evidence that there has

been both a localised colonic (ie, normalisation of stool frequency and consistency) and systemic (ie, persistent apyrexia, normalisation of bone marrow and liver function tests) response. In addition, it highlights the need for re-evaluation of left-sided colonic mucosa if there is a delayed symptomatic response to antiviral therapy, to ensure that the individual's UC is not active with the prompt withdrawal of immunosuppression. The optimal duration of intravenous antiviral treatment after resolution of clinical signs is uncertain in both the IBD literature and in the solid-organ transplant setting, in which there is more experience with opportunistic CMV disease. Serial PCR of CMV DNA offers an objective measure of the degree of viraemia and may aid with deciding the duration of treatment. In the solid-organ transplant guidelines, the clinical response as well as PCR measurements are used, and at least 14 days full-dose treatment is recommended, with a longer duration of treatment if there is not a prompt fall in viral load.⁹ Due to the severity of illness in this case and the prolonged fever, we opted to switch to oral valganciclovir after symptomatic improvement on day 19 of treatment and awaited two serial undetectable CMV DNA levels (ie, 7–14 days apart) prior to discontinuing the valganciclovir as an outpatient.

In keeping with transplantation guidance, we elected to monitor CMV DNA levels at monthly outpatient visits to detect early recurrence.

The high number of reported rates of emergency colectomy in patients with active CMV and UC,^{5 10} which was avoided in this case, highlights the pressing need for expert consensus and a clear stepwise medical management pathway in patients with severe CMV on the background of IBD, which at present is limited by a lack of prospective study.³ There needs to be clarity with regard to when to stop antiviral therapy (ie, treatment targets, stopping rules, duration of undetectable CMV load required), monitoring post severe CMV disease and guidance as to when immunosuppression can be safely reintroduced in patients with UC.

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Competing interests None declared.

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