Case study

A Caseof Severe CMV Colitis Complicatedwith MegacolonandPerforationinanImmunocompetent Prisoner

ABSTRACT

Aims and introduction: CMV colitis often occurs in immunocompromised patients and those with inflammatory bowel disease, but only occurs occasionally in those without previous medical illness. Here we report on a patient without previous medical illness who presented acutely and was eventually diagnosed as CMV colitis.

Case presentation: A 44 year old prisoner had a one week history of diarrhea and abdominal pain, and presented in septic shock. Abdominal X-rays and CT scan showed marked colon dilatation. Although he had transient clinical improvement with intravenous Meropenem, he experienced clinical deterioration after 2 weeks, including episodes of acute lower gastrointestinal bleeding. Limited sigmoidoscopy revealed friable mucosa with diffuse ulceration. He then developed colon perforation and required partial colectomy, but died of septic shock shortly after. Histopathological examination of the biopsy and colectomy specimens revealed the diagnosis of CMV colitis.

Discussion: CMV colitis most often presents with diarrhea which can be acute or chronic, and may lead to lower gastrointestinal bleeding. Severe CMV colitis may result in toxic megacolon or perforation. Tissue biopsy for histopathological examination and immunostaining is the gold standard for diagnosis of CMV colitis. Once diagnosed, timely treatment with IV Ganciclovir is recommended.

Conclusion: This case highlights that CMV colitis should be considered in the differential diagnosis of severe colitis with colon dilatation, including in immunocompetent patients. Sigmoidoscopy should be considered in such cases to obtain tissue biopsies to confirm the diagnosis**.**

Keywords: Cytomegalovirus, colitis, megacolon, perforation, inclusion bodies

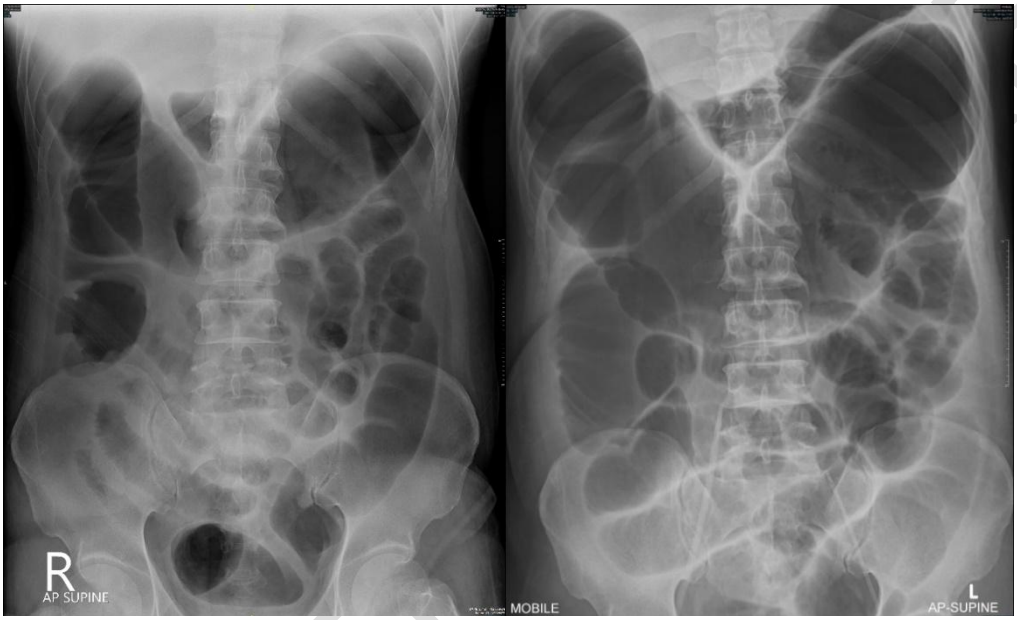
1. INTRODUCTION

Cytomegalovirus (CMV) is a common virus which infects between 60-70% of adults in industrialized countries[1,2]. It is a double-stranded DNA virus from the Herpesvirus family[1]. CMV infection is usually asymptomatic or causes only mild self-limiting symptoms in previously healthy people, with most infections occurring early in life[1,2]. After initial infection, CMV remains in a latent state in the body, but reactivation may then occur in patients who become immunosuppressed[1,2]. The colon is among the commonest sites of CMV reactivation. CMV infection most commonly occurs in immunocompromised patients or those with underlying inflammatory bowel disease[3-8], in whom severe complications may occur. We report a case of severe CMV colitis presenting with toxic megacolon and perforation in a previously healthy prisoner.

2. CASE PRESENTATION

A 44 year old male with no prior medical illness presented to our emergency department with a 1 week history of watery diarrhea with bowel opening up to 12 times per day, and generalized abdominal pain. This was associated with vomiting for 1 day. He also claimed to have fever for the past 3 days. There was no history of weight loss or appetite loss prior to that. At that time, he was incarcerated in the local prison for 9 months for drug peddling. He admitted to a history of sexual promiscuity with multiple female partners, but denied intravenous drug abuse.

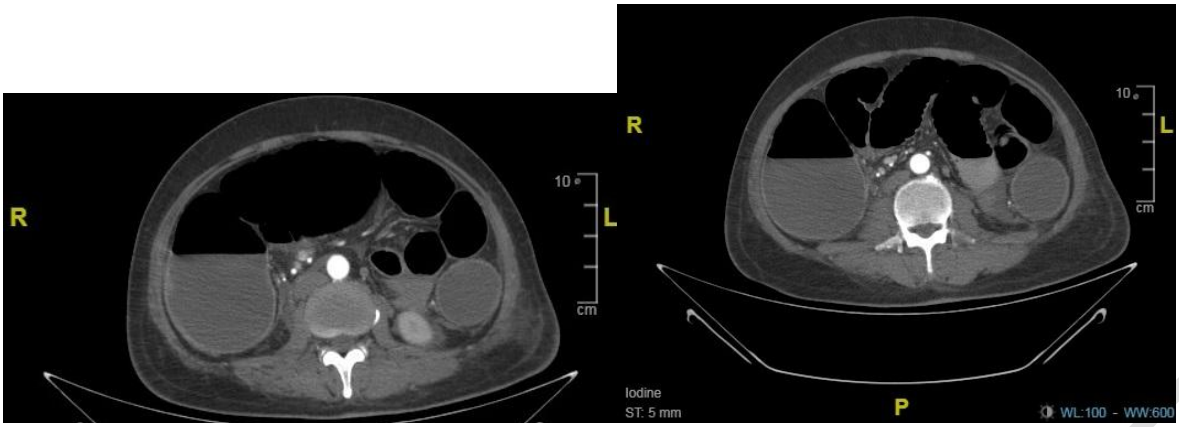
Upon presentation, he was in septic shock with an initial heart rate of 113 beats per minute and blood pressure of 73/59 which required IV Noradrenaline infusion of 0.3 mcg/kg/min. He also had low grade fever of 37.6^0 C. Physical examination revealed a mildly distended and diffusely tender abdomen with sluggish bowel sounds. Initial blood tests revealed a borderline raised white cell count (TWC) of 11.76 x 10^9/L which was neutrophil predominant, raised C reactive protein (CRP) of 248 mg/L, hypoalbuminemia of 22 g/L, hyponatremia (serum sodium of 118 mmol/L), and renal impairment (serum urea of 40.4 mmol/L and creatinine of 386 □ mol/L). He also had lactic acidosis with initial serum lactate of 5.5 mmol/L, pH of 7.35 and bicarbonates 12.4 mmol/L. A plain abdominal X-ray showed loops of dilated and featureless large bowel. He then underwent a contrast enhanced CT abdomen which revealed dilated ascending colon and transverse colon, with enhancing mildly thickened walls in this colon and also distal ileum, but no obstruction. At this point, he was diagnosed as infective enterocolitis, given fluid resuscitation, and started on intravenous Ceftriaxone and Metronidazole.



Figures 1 and 2: Patient abdominal X-ray on day 1 of admission (left) and day 6 of admission (right) showing grossly dilated and featureless colon

On the second day of admission, as he had worsening abdominal distension and tenderness. He also had hypotension requiring uptitration of IV Noradrenaline infusion to 1.1 mcg/kg/min. As such, his antibiotics were upgraded to IV Meropenem. Haemodialysis was also performed due to persistent metabolic acidosis and uremia. Over the next few days, he developed thrombocytopenia where his platelet count dropped till 41 x 10^9/L, and coagulopathy with a prothrombin time up to 53.8 secs and INR of 4.41. His initial set of blood and stool cultures did not grow any pathogens. He was also found to be hepatitis B surface antigen (HBs Ag) positive, with an ALT of 22 IU/L and HBV DNA viral load of 53 IU/ml, while his anti-HCV and HIV antibodies were non reactive. He underwent a CT mesenteric angiography on day 4 of admission which showed generalized colon and distal ileum dilatation, but no features of mesenteric vessel thrombosis.

Subsequently, he appeared to show transient clinical improvement with reduced abdominal pain, and was able to wean down his IV Noradrenaline infusion and wean off oxygen. However his abdomen was persistently distended with nasogastric tube aspirate of 50-100 mls per shift and sluggish bowel sounds. Abdominal X-ray on day 6 of admission revealed increased dilatation of transverse and ascending colon exceeding 8 cm, indicating megacolon. Thus he was started on total parenteral nutrition for 5 days, until he could tolerate small volumes of nasogastric tube feeding. His TWC decreased to 4.73 x 10^9/L and CRP reduced to 85 mg/L on day 6 of admission, with platelet count, coagulation profile and renal profile improving. On day 10 of admission, his antibiotics were de-escalated to IV Cefotaxime and Metronidazole.



Figures 3 and 4: Patient CT images showing dilated colon, taken on day 4 of admission

However, he then developed persistent high grade fever and tachycardia with hypotension from day 14 of admission, and had diarrhea of 3-5 episodes per day again from day 15. This was associated with leukopenia where his lowest TWC was 3.52 x 10^9/L, and CRP rise to 129 mg/L. Repeat blood and stool cultures did not grow any pathogens, and *Clostridium difficile* antigen was not detected in stool.

On day 20 of admission, he developed haematochezia associated with abdominal pain and lower abdominal tenderness on palpation. His haemoglobin dropped to 7.9 g/dL, necessitating blood transfusion, with deterioration of renal function. After a repeat X-ray to rule out perforation, a limited sigmoidoscopy was performed on day 21 of admission, which showed diffuse ulceration and friable mucosa in sigmoid colon and rectum, including deep ulcers. Biopsies were taken from ulcer edges. Based on these findings which could suggest ulcerative colitis, patient was empirically started on IV Hydrocortisone 300 mg/day.

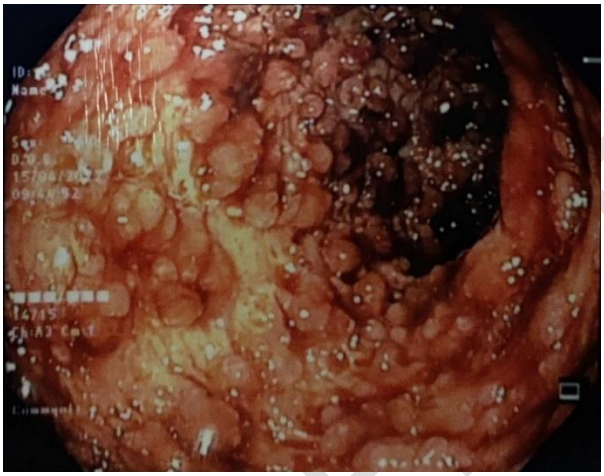


Figure 5. Patient endoscopy image showing many large deep ulcers with fissures in sigmoid colon.

On day 23 of admission, he had further episodes of haematochezia, and had worsening abdominal tenderness and distension with guarding. Hemoglobin dropped further to 6.2 g/dL, and there was worsening coagulopathy and lactic acidosis. An urgent abdominal X-ray showed diffuse large bowel dilatation with double wall sign, indicating pneumoperitoneum. He was referred to Surgical team, and a CT mesenteric angiography was then performed which showed extensive pneumoperitoneum indicating perforated viscus, but no active bleed into bowel visualized. After blood and fresh frozen plasma transfusions, urgent laparotomy was performed. During surgery, long segment perforation of 5 cm in descending colon and a smaller perforation in transverse colon was noted, with friable and diffusely ulcerated colon wall. Primary closure of the perforation failed due to fragile colon wall, and thus a partial colectomy till mid transverse colon with stoma creation was performed. Following that, he developed fungemia with septic shock, persistent lactic acidosis and oliguric acute kidney injury. He rapidly deteriorated despite support with multiple vasopressors, antibiotic change to Meropenem, addition of Anidulafungin, and haemofiltration on day 24. He died of septic shock on day 25.

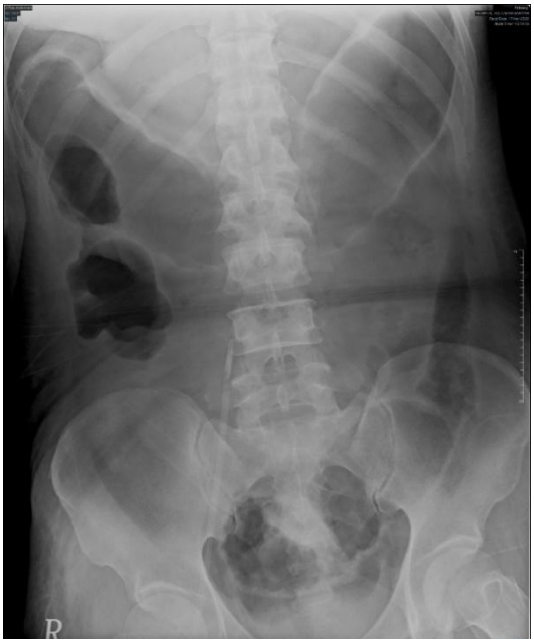


Figure 6: Abdominal X-ray taken on day 23 showing double wall sign

Figure 7. Partial colectomy specimen of left and transverse colon showing deep ulcers, fissuring and perforations.

Posthumously, histopathological examination of his colon biopsy showed fibrogranulation tissue with mixed inflammatory cell infiltration, occasional CMV inclusion bodies (these highlighted on haematoxylin and eosin staining) and positive CMV immunostaining, indicating CMV colitis. Subsequently, examination of his colon resection specimen showed several perforations with the perforated edges displaying transmural necrosis with granulation tissue formation, associated with extensive mucosal ulceration including deep fissuring ulcers, and pseudopolyps of intervening mucosa. There was heavy ulcer infiltration by mixed inflammatory cells, many CMV inclusions are seen at the ulcer bases, and CMV immunostaining was positive. This confirms the diagnosis of severe CMV colitis.

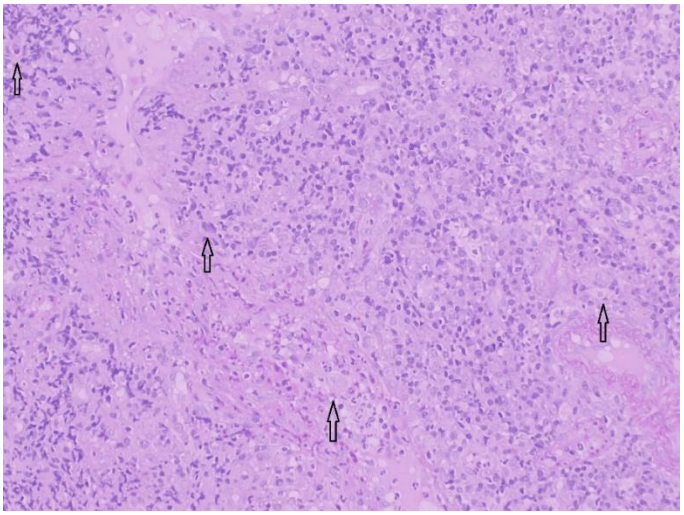


Figure 8. Occasional CMV inclusion bodies identified (arrows), with a background of mixed inflammatory cell infiltration, on histopathology.

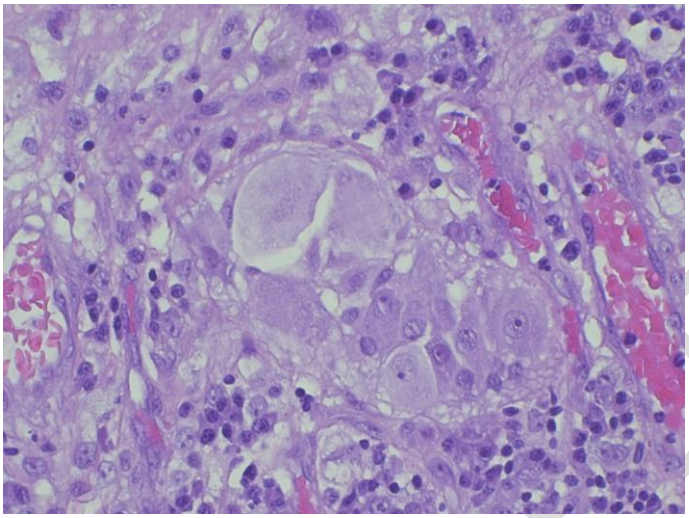


Figure 9. Close-up of CMV inclusion body.

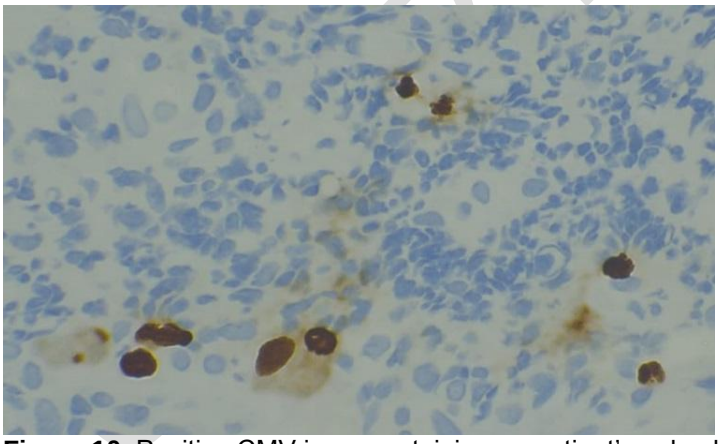


Figure 10. Positive CMV immunostaining on patient's colon biopsy sample

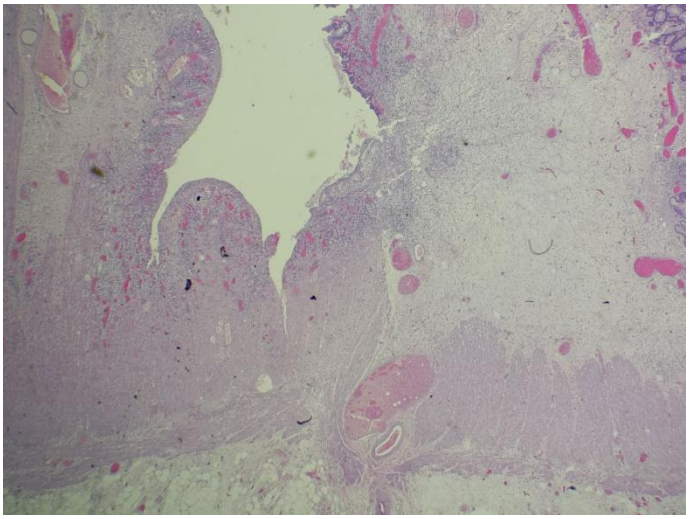


Figure 11. Microscopy of colon resection specimen showing deep ulcer with transmural inflammatory infiltrate and areas of necrosis

3. DISCUSSION

CMV infection of the gastrointestinal (GI) tract is usually associated with immunocompromised state. CMV infection of almost every part of the GI tract have been reported. The majority of CMV infection of the GI tract is thought to be due to reactivation of latent infection, although primary infection may occur in severely immunocompromised patients[2]. Clinically manifested CMV disease in HIV infected patients usually presents in those with a CD4 count < 100 / □ L, with colitis being observed in 7.3% of these patients[3]. CMV infection of the GI tract often occurs in solid organ transplant recipients[4] and stem cell transplant recipients[5], who will have received intensive immunosuppressive therapy. Corticosteroid use within the last 1 month was also found to be associated with CMV colitis[6]. Use of anti-TNF necrosis alpha inhibitors was also reported to be associated with CMV colitis[7]. Localized mucosal immunosuppression can also lead to reactivation as CMV colitis, such as in underlying inflammatory bowel disease (IBD). In this setting, superimposed CMV infection was found to occur in 4.5% of patients with new onset ulcerative colitis (UC)[8], 13.8% in severe UC[9], and 25-27.3% in steroid refractory UC[9,10]. CMV colitis in immunocompetent patients who do not have underlying inflammatory bowel disease has been reported in the literature[11-13] but is uncommon.

Among the symptoms often reported in CMV colitis are acute diarrhea, chronic diarrhea, and often bloody diarrhea[1,6,14, 15]. Concurrent fever has also been reported[6,15]. Some cases presented with acute lower gastrointestinal bleeding[14,15]. Findings seen on colonoscopy include mucosal inflammatory changes, friable mucosa, isolated or multiple discrete ulcers, aphthous ulcers, exudates, and mucosal sloughing[14,16]. Deep fissuring ulcers and pseudopolypoidal appearance have been reported in immunocompromised patients with CMV colitis[17], although these findings are more commonly seen in IBD. These findings may be superimposed on pre-existing IBD[18]. Toxic megacolon and perforation are complications of severe CMV colitis[14,15], and have been occasionally reported in immunocompetent patients[12]. These complications may be fatal.

Tissue biopsy is the gold standard for definitive diagnosis of CMV colitis[15,18,20]. CMV colitis is diagnosed by the presence of typical “owl-eye” intranuclear inclusion bodies in enlarged cells which can be seen on H&E staining, as well as positivity for CMV immunostaining[1,14]. Detection of CMV DNA through PCR in tissue biopsies and in the blood is also used to diagnose CMV infection[15,20]. However, in this case as patient had diffusely dilated colon and of ill condition, a gentle limited sigmoidoscopy will suffice due to increased risk of perforation. According to the 3rd European Consensus on Diagnosis and Management of Ulcerative Colitis, a flexible sigmoidoscopy should confirm the diagnosis of severe colitis and exclude CMV infection[18].

Once diagnosed, IV Ganciclovir at a dose of 5 mg/kg every 12 hourly for 2-3 weeks is the treatment of choice[19]. The 2014 European Evidence-based Consensus also recommends Ganciclovir for 2–3 weeks as the therapy of choice for CMV infections in IBD patients[20]. After 3–5 days, a switch to oral Valganciclovir for the rest of the 2- to 3-week course may be considered[20].

This case highlights that in non-resolving acute infective colitis despite adequate duration of broad spectrum antibiotics, a colonoscopy, or sigmoidoscopy if patient is unfit for colonoscopy, has a role to ensure that other forms of colitis such as CMV colitis in this case, or ulcerative colitis are not missed. The possibility of CMV colitis should be kept in mind in patients who have toxic megacolon. Timely treatment is recommended once CMV colitis is diagnosed, to avoid poor outcomes as in our patient.

4. CONCLUSION

Severe CMV colitis in immunocompetent patients is rare, but can lead to complications of megacolon, septic shock and perforation. This case highlights that CMV colitis should be considered as a differential diagnosis in severe infective colitis with colon dilatation, even in immunocompetent patients. High index of suspicion is important, and after abdominal imaging, careful sigmoidoscopy with biopsies should confirm the diagnosis. Early diagnosis with early initiation of antiviral treatment once CMV infection is confirmed, is recommended.

CONSENT

We declare that informed consent was obtained from the patient's next-of-kin for the publication of this case report and the accompanying images.

ETHICAL APPROVAL

This is not applicable for this article.

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