

Cytomegalovirus infection in gastrointestinal tract: A case series of three patients and review of literature

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Abstract

Cytomegalovirus disease can involve any site of gastrointestinal tract from oral cavity to rectum. CMV disease most frequently occurs in patients' with immune deficiency, such as the acquired immunodeficiency syndrome, after organ transplantation, after cancer chemotherapy and in patients on immunosuppressive medications. The number of patients with immune deficiency has increased in recent years and has led to a substantial increase in incidence of opportunistic CMV virus. Gastrointestinal CMV infection has also been reported in immunocompetent adults. Symptoms and signs depend on part of the gastrointestinal tract involved. Diagnosis depends either on a positive mucosal biopsy or by serology, quantitative PCR or CMV antigenemia. We report three cases of CMV infection in patients with three different underlying conditions and discuss the clinical features, diagnostic approach and treatment. All patients had positive serology with high viral load on PCR. Histology with immunohistochemistry was positive for CMV in two of the three cases. Ganciclovir response was seen in all patients in respect to clinical improvement, endoscopic resolution of lesions and clearing of the virus load.

Key words

Cytomegalovirus colitis, cytomegalovirus infection, gastrointestinal cytomegalovirus infection

Introduction

Cytomegalovirus (CMV), a member of the herpesviridae family is a double-stranded DNA virus. It is an opportunistic pathogen that frequently causes asymptomatic lifelong latent infection in immunocompetent individuals.^[1] CMV serology is positive in 50–80% of the adult population indicating evidence of past infection.^[2] Gastrointestinal (GI) involvement caused by CMV infection is commonly observed in immune-suppressed patients, e.g., with acquired immunodeficiency syndrome (AIDS), those

receiving immunosuppressive treatment, those receiving chemotherapy, and those receiving frequent blood transfusions.^[3]

CMV infection of the GI tract can occur anywhere in the GI system and is usually characterized by ulcerative lesions.^[4] In immunocompetent individuals CMV infection is asymptomatic or associated with the mild mononucleosis-like syndrome.^[5] In immune-compromised patients, it can present with diarrhea, pain abdomen, or GI bleed depending on the site of involvement. In patients with ulcerative colitis, CMV infection can mimic relapse and its diagnosis requires a high degree of suspicion. An effective antiviral therapy can be offered to the patient, which otherwise would cause higher rates of morbidity and mortality. We report three cases of

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CMV infection affecting GI tract in three different scenarios and also present a brief review of the literature.

Case Reports

Case 1

A 64-year-old male patient was admitted with 3 months history of persisting diarrhea. Stool frequency was 8–10 episodes per day, small in volume, watery, and it was accompanied by colicky pain abdomen. He had a significant weight loss (11 kg in last 3 months). He had no other co-morbidity and was not on any medication. On examination, the patient was dehydrated and had hypotension (systolic blood pressure < 90 mm/hg). His abdomen was distended and revealed generalized tenderness. His blood investigations revealed anemia (8.9 g/dL), mild renal insufficiency (1.33 mg/dL), hypokalemia (3.2 mmol/L), leukopenia (2300 cu/mm³), and hypoalbuminemia (3.0 g/dl).

He was treated with intravenous (IV) fluids and empirical antibiotic (quinolones and metronidazole). Blood cultures and stool studies (including *Clostridium difficile* toxin) were negative. His HIV serology turned out to be positive and CD4 cell count was 38 cells/mm³.

Colonoscopy was done after hemodynamic stabilization, which showed erythema, loss of vascular pattern, and multiple small ulcers throughout the right colon and in the distal ileum [Figure 1a]. Histology demonstrated mixed inflammatory infiltrates in lamina propria with few endothelial cells showing the presence of intra-nuclear viral inclusion which stained positive for CMV on immune-histochemistry [Figure 1b]. IgM and IgG anti-CMV antibodies were positive in high titers, and

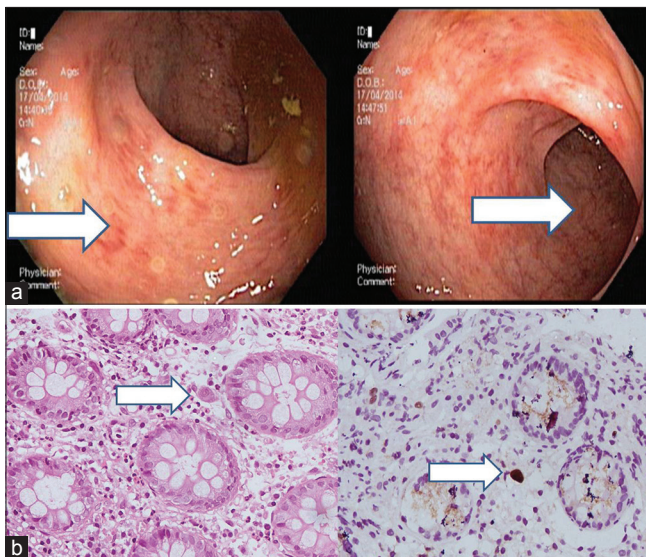


Figure 1: (a) Colonoscopy is showing erythema, loss of vascular pattern, and multiple small ulcers throughout the right colon and in the distal ileum. (b) Microphotograph is showing characteristic cytomegalovirus intranuclear inclusion in endothelial cell (H and E, ×40) with immunohistochemistry positive for cytomegalovirus

quantitative polymerase chain reaction (PCR) for CMV was positive (4800 copies/ml).

Based on these findings, a diagnosis of CMV infection affecting the small intestine and colon was made and IV ganciclovir (5 mg/kg/12 h) was started. Highly active antiretroviral therapy (HAART) (emtricitabine, tenofovir, and efavirenz) was also started simultaneously. Diarrhea improved significantly over the next 2 weeks. Ganciclovir dose was reduced to (5 mg/kg/day) after 3 weeks of treatment. Colonoscopy was repeated 6 weeks after starting antiviral therapy which revealed complete resolution of the lesions. Quantitative PCR for CMV was repeated, and it became negative. Biopsies from repeat colonoscopy showed only mild nonspecific inflammation with no histopathological evidence of CMV infection. Maintenance antiviral therapy was stopped after 3 weeks after complete resolution of lesions. No long-term maintenance therapy was given.

Case 2

A 19-year-old young male with steroid dependent ulcerative colitis who was on azathioprine (125 mg/day) for 6 months presented with complaints of bloody diarrhea and fever of 2 weeks duration. The provisional diagnosis was a flare of underlying ulcerative colitis or superadded bacterial infection. His laboratory parameters revealed leukopenia (2700 cu/mm³), anemia (8 g/dL), high ESR (59 mm), and positive CRP (14 mg/l). Colonoscopy showed edema, friability, granularity, and spontaneous hemorrhages throughout the colon except caecum [Figure 2], and biopsy revealed features compatible with chronic ulcerative colitis.

Azathioprine was stopped and he was started on antibiotics and IV steroid therapy. His stool for *C. difficile* toxin assay was negative on three occasions. IgM for CMV serology turned out to be positive and quantitative PCR for CMV was also positive with high levels of viremia (4577 copies/ml). Although the immunostaining of colonic biopsy for CMV was negative, a diagnosis of CMV viremia exacerbating CMV colitis was considered. Steroids and antibiotics were stopped, and IV ganciclovir started at a dose of (5 mg/kg/12 h). The patient gradually showed improvement in pancytopenia, fever, and frequency of stools. IV ganciclovir was replaced by oral ganciclovir. On

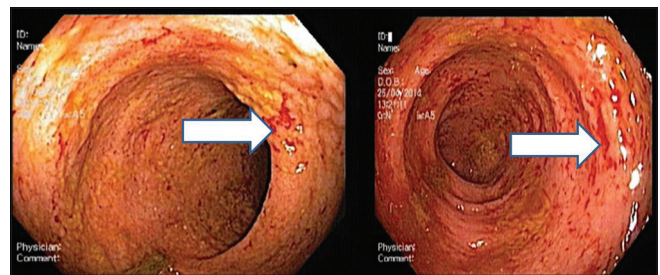


Figure 2: Colonoscopy is showing edema, friability, granularity, and spontaneous hemorrhages in the colon

follow-up at 1-month, repeat CMV DNA PCR was negative. Maintenance antiviral therapy was continued for 8 weeks and then stopped. Subsequently patient was started on 5ASA and is doing well at 6 months follow-up.

Case 3

A 55-year-old male presented with complaints of black tarry stools associated with pain abdomen and giddiness since 5 days. He was diagnosed to have diffuse large B-cell lymphoma 3 months back and had received his first cycle of chemotherapy (R-CHOP) 5 days prior to commencement of these symptoms. He had no history of upper GI bleed, fever, or rash. He had no other co-morbidities and gave no history of intake of nonsteroidal anti-inflammatory drugs. On examination, salient clinical findings were tachycardia, pallor, and pedal edema. His laboratory parameters revealed low hemoglobin (7.6 g/dL), high total leukocyte count (12700 cu/mm³), mildly elevated serum creatinine (1.52 mg/dL), hypernatremia (165 mEq/L), and hypokalemia (3.2 mEq/L). His coagulation profile was normal and HIV serology was negative.

After initial resuscitation, he underwent upper GI endoscopy, which was normal, and colonoscopy which showed black tarry stool throughout the colon. In view of persistent melena, double balloon enteroscopy was done which showed actively bleeding jejunal ulcers at approximately 50 cm from the DJ flexure. Multiple biopsies were taken and adrenaline was injected to achieve hemostasis [Figure 3a]. The possibilities considered were GI lymphoma, drug induced ulcerations, or ulcers secondary to opportunistic infections. His bleeding stopped and he started passing yellow color stools after 48 h. Histopathology from the ulcer revealed granulation tissue within lamina

propria along with intra-nuclear and intra-cytoplasmic inclusions of CMV, which stained positive for CMV on immunohistochemistry (IHC) [Figure 3b]. IgM for CMV was positive in high titers and quantitative PCR for CMV was positive (2979 copies/ml).

Hence, the final diagnosis was CMV induced jejunal ulcer bleed as a complication of chemotherapy given for diffuse large B-cell lymphoma. He was started on IV ganciclovir at a dose of (5 mg/kg/12 h) for 2 weeks and later continued with oral ganciclovir at half the dose for 4 weeks. On follow-up at 1-month, repeat CMV DNA PCR was done which detected no target virus.

Discussion

Human CMV is a DNA virus, a member of herpesviridae family. It can exist as a commensal in GI system. CMV disease can involve any site in the GI tract, from the oral cavity to the rectum. CMV infection usually occurs in immune-compromised hosts such as recipients of organ transplants and patients with AIDS.^[6] Reports of CMV in immunocompetent patients has emerged in recent years with more and more cases being reported with time.^[4,5,7] CMV infection still tends to occur predominately in immune-compromised patients.

Cytomegalovirus infects columnar epithelial cells, endothelial cells, myocytes and fibroblasts, and causes tissue destruction and ulceration.^[8] The most common site of involvement in GI tract is a colon.^[9,10] The reason for the predilection of colonic involvement is not known. In our series, two patients had colonic involvement and one had small bowel involvement. All the patients were immune-compromised with (AIDS, on chemotherapy, and on azathioprine).

Endoscopically, CMV involvement of GI tract manifest as ulcerations and erosions. GI CMV can mimic a variety of conditions including ischemic colitis, pseudomembranous colitis, inflammatory bowel disease, and even carcinoma.^[11] CMV has also been implicated as a cause of esophagitis,^[12] gastritis,^[3] Ménétrier's disease (protein-losing hypertrophic gastropathy),^[13] ileitis,^[14] and colonic obstruction.^[15]

CMV GI disease is a serious complication in patients with AIDS. Patients with advanced HIV infection, particularly in those with CD4 count < 50/mm³, are at high risk to develop a life-threatening complication following CMV infection.^[16] Our first patient had AIDS with CD4 count of 39 cell/mm³. The median survival reported in patients with HIV after CMV infection is 4 months with CMV colitis and 8 months after CMV esophagitis, even with ganciclovir therapy.^[17] However, the prognosis has improved with the availability of effective HAART. In a study done by Salzberger *et al.*,^[18] the number of new cases of CMV-related GI disease have significantly declined after the introduction of ART; 61 cases were

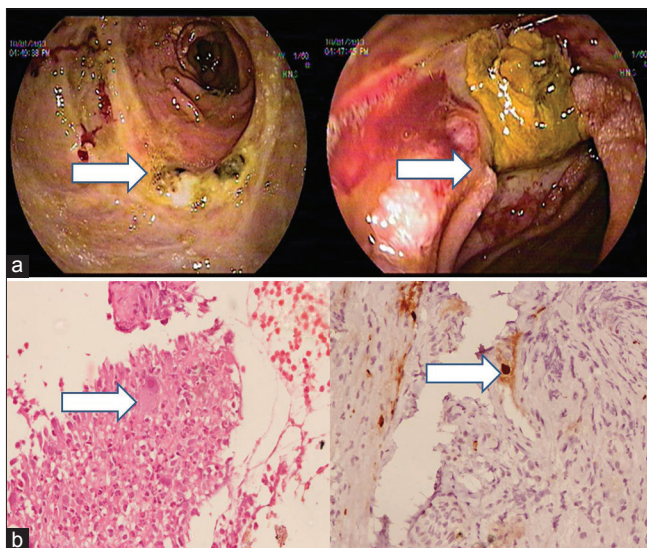


Figure 3: (a) Enteroscopy is showing actively bleeding jejunal ulcers at approximately 50 cm from the DJ flexure. (b) Microphotograph is showing characteristic cytomegalovirus intra-nuclear inclusion (H and E, $\times 40$) with immunohistochemistry positive for cytomegalovirus

diagnosed between 1994 and 1995 and 9 cases were diagnosed between 1998 and 2001.

Clinical features of CMV colitis in AIDS are low-grade fever, weight loss, anorexia, malaise, and abdominal pain, or diarrhea. In a patient with HIV, diagnosis of CMV GI disease is based upon the following triad: Clinical symptoms of GI disease, visualization of characteristic lesions on endoscopy, and intra-nuclear or cytoplasmic inclusions on biopsy.^[19] Our patient had severe nonbloody diarrhea with characteristic endoscopic findings and biopsy showed CMV inclusion bodies and IHC was positive.

Treatment for CMV infection in AIDS is recommended for 21–42 days or until signs and symptoms have resolved. AIDS guidelines recommend withholding therapy for mild disease if ART is to be initiated soon or can be optimized.^[20] The initiation of ART in CMV disease should be delayed for at least 2 weeks in patients with CMV retinitis or other neurological disorder for preventing IRIS.^[20] If there is no evidence of CMV retinitis, HAART can be initiated simultaneously. The old literature on CMV in AIDS recommends long-term ganciclovir maintenance therapy in patients with AIDS.^[21] Availability of effective HAART has significantly improved the treatment of CMV infection. According to AIDS guidelines^[20] long-term maintenance therapy is not recommended for CMV GI disease unless there is concurrent retinitis or recurrent GI disease after induction therapy has been discontinued. In our patient, we achieved a complete response after ganciclovir, and thus, no long-term maintenance therapy was given.

CMV infection can occur with a number of underlying hematological diseases including nonHodgkin's lymphoma, multiple myeloma, acute myeloid leukemia, and myeloproliferative disorders. In patients with hematological malignancies, CMV infection is most frequently seen in stem cell transplant recipients.^[22] Severe GI CMV disease has been reported in patients receiving chemotherapy for malignancies, particularly those receiving steroids.^[23,24] In a study, in patients with hematopoietic cell transplantation 79% (15/19) patients developed CMV disease in the GI tract.^[25] Our patient was treated with R-CHOP regimen containing steroids, after which he developed bleeding from jejunal ulcer due to CMV infection. Clinicians dealing with hematological malignancies should be aware of CMV infection, especially for patients receiving rituximab and steroids.^[23]

CMV infection has been reported to cause a relapse in patients with ulcerative colitis. The natural course of UC in patients with CMV reactivation might be worse than that in CMV negative patients because severe inflammation itself can cause a poor outcome. In a study done by Kim *et al.*,^[26] the cumulative colectomy ($P = 0.025$) and disease flare-up rates ($P = 0.048$) were significantly higher in the CMV-positive group. Eleven patients who were successfully treated with ganciclovir in the initial treatment, three patients (27.3%) experienced

CMV reactivation, and six patients (54.5%) experienced poor outcomes such as the need for colectomy or a steroid-dependent state.^[26] In one study, 21% of resected surgical specimen of ulcerative colitis tested positive for CMV.^[27] Hence, it is unpredictable how these patients will respond in future and a close monitoring is required throughout.

CMV infection has been reported in steroid resistant UC. In one study, CMV infection was detected in 16 of 47 patients (34%) with intractable ulcerative colitis.^[28] It is suggested that cytokines such as interferon- γ and tumor necrosis factor- α that are frequently elevated in patients with inflammatory bowel disease can promote the reactivation of a latent CMV infection. This, in turn, is known to cause additional cytokine release, particularly of interleukin-6, a fact that may lead to exacerbation of the inflammatory bowel disease.^[9] Treatment with azathioprine in addition to corticosteroids is another factor significantly associated with CMV infection.^[29] This is not surprising as CMV colitis is a well-known complication of immunosuppression such as AIDS, transplantation, and malignancies during treatment with chemotherapy and corticosteroids.

It is difficult to make a diagnosis of CMV infection complicating ulcerative colitis based on clinical features or endoscopic appearance. Another common pathogens such as *C. difficile* can cause similar symptoms. We ruled out *C. difficile* infection by testing three stool samples as our suspicion was high. It is recommended that in inflammatory bowel disease patients repeated stool testing for *C. difficile* toxin should be done.^[30] In real life situations, a high degree of suspicion is required for identifying CMV infection and whenever in doubt examinations to confirm CMV infection should be performed as soon as possible. Suzuki *et al.*^[31] reported specific endoscopic findings which predicted CMV infection in UC patients including irregular ulcers (sensitivity 100%), wide mucosal defect (specificity 95%), punched out ulceration, and longitudinal ulceration (sensitivity and specificity 70%). Our patient had no specific feature on colonoscopy suggestive of CMV over underlying UC, and the histology was also not suggestive of CMV infection. In patients who have negative histology for CMV, blood examination for the detection of plasma quantitative real-time PCR assay for CMV may enable diagnosis of CMV infection with a high sensitivity,^[31] as was in our case.

There are several methods of detecting CMV infection: Histology including IHC, serology, CMV culture, quantitative PCR for CMV from plasma, and CMV antigenemia.^[2] The gold standard for CMV detection is an examination of formalin-fixed, paraffin-embedded tissue, and IHC.^[32] Histological examination is a relatively easy method but lacks sensitivity without IHC (10–87%).^[2,29] Typical CMV inclusions on routine staining have “owl’s eye” nuclear inclusions (Cowdry bodies) and eosinophilic inclusions in the cytoplasm of enlarged cells.^[33] In addition, Schwartz and

Wilcox have described the three types of atypical inclusions in GI CMV.^[34] In two of our patients, HPE from the colonic biopsy and small bowel biopsy was the primary mode of diagnosis and was substantiated by PCR confirmation. In the third case, a high quantitative PCR in addition to nonresponse to conventional treatment clinched the diagnosis.

Quantitative PCR for the CMV genome is very sensitive, but the false-positive rate is relatively high. In a retrospective study of 81 solid organ transplant recipients (mostly kidney and liver transplant recipients) with GI symptoms who underwent GI biopsies and quantitative plasma PCR testing, 20 cases of biopsy-proven gastrointestinal disease were identified. The sensitivity and specificity of PCR for diagnosing CMV GI disease taking histology as the gold standard was 85% and 95%, respectively.^[35] In our series, CMV DNA was positive in all three cases.

CMV PCR on GI biopsies complements IHC and has the potential to identify additional patients who may benefit from anti-CMV therapy.^[32] In a study by Kishore *et al.*,^[29] the authors concluded that PCR of rectal biopsy was the most sensitive method for detection of CMV. Although we had not done PCR for CMV in tissue samples in our patients, they all tested positive for serum CMV PCR and IgM antibody for CMV.

The mortality rate of untreated CMV GI disease is high. Three classes of drugs are approved for the treatment of CMV, all of which target the DNA polymerase: Ganciclovir (and the prodrug valganciclovir), foscarnet, and cidofovir. Patients with CMV disease should be treated with induction dose of ganciclovir or foscarnet for 14–21 days, followed by maintenance dose for at least 3–4 weeks. Ganciclovir (5 mg/kg) should be administered every 12 h for 14 days followed by half the dose for maintenance. Foscarnet (60 mg/kg) should be administered every 8 h intravenously for 14 days, followed by maintenance at 90 or 120 mg/kg every day. In a placebo-controlled study, ganciclovir resulted in greater treatment success for CMV colitis in AIDS patients (63% when compared with 37%), improved endoscopic scores, and decreased dissemination of CMV disease.^[34] Foscarnet has been shown to induce remission in 67% of patients who were unresponsive to ganciclovir.^[36]

In our series, all the three patients responded well to treatment with ganciclovir. The recommended duration of therapy for CMV GI disease varies from 3 to 6 weeks. This is based upon expert opinion and no clear guidelines are available. We determined the duration of therapy according to the patient's response to treatment. For example, a patient who improves symptomatically within 1-week of treatment may require 3–4 weeks of induction therapy while a patient who is slower to respond should be treated for the full 6 weeks. The patients who have persistent symptoms after 6 weeks of treatment may have an alternative diagnosis and/or CMV drug resistance. It should also be noted that any presumed benefit of specific

antiviral treatment in severe cases of CMV infection should be weighed against the potential toxicity of therapy. While adverse-effects associated with the administration of antiviral treatment against CMV were not reported in our cases, one should be aware that ganciclovir can cause myelosuppression, central nervous system disorders, hepatotoxicity, irreversible infertility (inhibition of spermatogenesis), or teratogenesis, whereas foscarnet can cause disturbances in mineral and electrolyte homeostasis, as well as nephrotoxicity.^[9]

Conclusion

CMV can affect any site in GI and has a predilection for the colon. Immuno-compromised individuals are the most commonly affected. CMV infection should be actively looked for in refractory ulcerative colitis patients. Prompt diagnosis and treatment can improve outcome in this otherwise fatal condition.

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Conflicts of interest

There are no conflicts of interest.

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