Cytomegalovirus Infection Masquerading as an Ulcerative Colitis Flare-Up: Case Report and Review of the Literature

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We report the case of a patient with a case of cytomegalovirus (CMV) colitis, which presented as a flare-up of her ulcerative colitis. Standard treatment for the flare-up, which included intravenous corticosteroids, bowel rest, topical salicylates and ultimately colectomy were not effective. The patient did not improve until therapy with intravenous ganciclovir was initiated.

There have been 26 previous reports of CMV colitis complicating inflammatory bowel disease (IBD). The diagnosis is not frequently entertained and, if not made, leads to a high rate of colectomy (67 percent) and mortality (33 percent). Appropriate antiviral therapy appears to eliminate these complications, thus a high index of suspicion for CMV superinfection in cases of IBD refractory to traditional therapy is warranted.

INTRODUCTION

Cytomegalovirus (CMV) is a herpes virus that is quite prevalent in normal adults, infecting over 40 percent of the population. It is usually responsible for active disease only in immunodeficient patients, although it rarely can cause overt disease in apparently normal hosts. In the gastrointestinal tract, CMV disease may occur from the mouth to the rectum and is generally manifested by mucosal ulceration often associated with bleeding [1].

In this report we present a patient with ulcerative colitis who presented with refractory bloody diarrhea and weight loss that did not respond to standard medical management. A colectomy was performed, and pathologic examination revealed CMV colitis. The patient ultimately improved only after treatment with ganciclovir.

To date, there have been 26 reported patients with CMV colitis complicating inflammatory bowel disease (IBD). Most were not diagnosed prior to undergoing colectomy. Although unusual, it is important to consider CMV in patients with IBD flare-ups refractory to conventional therapy, as appropriate anti-viral therapy may spare the patient non-elective surgery.

CASE REPORT

J.C. is a 56-year-old white female who was in good health until 1992 when she presented to a gastroenterologist with a three-month history of diarrhea. She had no family history of immune disorders and no past history of herpes infections. A work-up revealed brown, heme-positive stool, and flexible sigmoidoscopy showed a normal rectum, with moderate to severe colitis of the sigmoid and left colon, which was felt to be consistent
with Crohn's colitis. She was treated briefly with intravenous corticosteroids, followed by oral steroids for several weeks and was maintained on olsalazine. Three months following this initial presentation, she had a flare-up that was effectively treated with a brief course of IV corticosteroids, and she was discharged on mesalamine by mouth, and by enema, as well as 6-mercaptopurine (6-MP). The 6-MP was discontinued because of leukopenia several months later. She did well on mesalamine for the next several years, not requiring hospitalization or steroid treatment until July of 1995.

In July of 1995, she was admitted with a three-month history of bloody diarrhea uncontrolled with ciprofloxacin or metronidazole (which had been added to her mesalamine), a 15 pound weight loss and epigastric pain radiating to her back. She had a mild increase in her amylase and lipase and was treated with total parenteral nutrition, IV steroids and mesalamine enemas. Colonoscopy on hospital day two revealed severe colitis of the distal 50 centimeters of colon, consistent with ulcerative colitis. Her serum amylase and lipase values rapidly returned to normal, but her diarrhea persisted despite continued IV steroids, 6-MP and antibiotics. Stool cultures for ova, parasites and E. coli were repeatedly negative, as were titers of C. difficile toxin. Because of her blood loss per rectum, she required several transfusions of packed red blood cells. She developed oral lesions and odynophagia approximately 10 days into her hospital course, which were thought to be consistent with candida pharyngitis. Shortly after this, her white blood cell count began to drop, from a high of 15,000 cells/mm³ to a nadir of 1,300 cells/mm³ over the course of seven days. 6-MP was discontinued, but her leukopenia did not improve. She was brought to the operating room three weeks into her hospitalization and underwent an extended left hemicolectomy with colostomy and Hartmann’s pouch. Pathologic examination revealed CMV colitis (Figure 1). She was tested for antibodies to the human immuno-deficiency virus (HIV), which were absent. Treatment with intravenous ganciclovir was initiated at a

Figure 1. a. (left): Photomicrograph of the colon showing intense mucosal inflammation. b. (right): Higher power photomicrograph of colonic mucosa showing intense lymphocytic inflammation and a cytomegalic cell in the center of the field.
dose of 10 mg/kg/day in two divided doses. After two days, her leukopenia improved, and after four days she had a normal white blood cell count. Likewise, her diarrhea, which had persisted, improved over the same period. She required no further transfusions and began tolerating a regular diet. She was discharged from the hospital after four weeks of intravenous ganciclovir therapy, to complete an additional two weeks of IV therapy at home.

DISCUSSION

Cytomegalovirus infection is quite common in normal adults and is generally asymptomatic, with the virus remaining latent in white blood cells for the life of the host [1]. Clinically significant disease occurs in patients with defective cell-mediated immunity, especially transplant patients, AIDS patients and those receiving chemotherapy. Disease is usually a result of reactivation of latent virus, rather than re-infection, thus measuring levels of CMV antibody is often not helpful in establishing a diagnosis. Significant CMV disease may be manifested in a variety of organs, including the retina, the lung and the gastrointestinal tract, and the target organ seems to be specific to the etiology of the immunodeficiency [1].

Gastrointestinal CMV disease may occur from mouth to rectum, with non-specific gross lesions consisting of erosions, ulcerations and mucosal hemorrhage. Microscopically, submucosal vasculitis or microvascular thrombosis is often present, as was the case in our patient. Tissue necrosis may also be a prominent feature. Diagnosis is made histologically by identifying large cells with intranuclear and intracytoplasmic inclusions; culture of lesions or biopsy specimens is neither sensitive nor specific [1]. Immunohistochemical staining for CMV antigen, in situ hybridization for mRNA, and the polymerase chain reaction for CMV DNA may improve sensitivity, although these may be positive in the latent state.

There have been a total of 26 reported cases of CMV colitis complicating inflammatory bowel disease [2-16]; our patient represents the 27th. The vast majority of cases (24) have been in patients with ulcerative colitis; one patient [10] had Crohn's ileocolitis, and one [3] had indeterminate colitis. Although initially diagnosed with Crohn's colitis, our patient has clinical and pathologic manifestations more consistent with ulcerative colitis.

Fourteen of the previously reported cases had their diagnosis of CMV colitis less than six months after the diagnosis of inflammatory bowel disease (Figure 2). This raises the possibility that the patients may not have had inflammatory bowel disease at all, but in fact had primary CMV colitis. In at least four patients, however, [4, 13, 15] ulcerative colitis symptoms persisted after adequate treatment for and resolution of CMV infection. This leads to a more intriguing speculation, that CMV infection somehow plays a role in the onset of ulcerative colitis, as proposed by Orvar and colleagues [4]. Other investigators [17, 18] have also sought for a link between CMV or other viral infections and IBD, but no study has been able to convincingly demonstrate a causal relationship. It is known, for example, that CMV infection in tissue culture causes induction of MHC class I surface antigen expression [19], as well as cytokine production in monocytes [20]. Thus CMV infection in colonocytes may trigger an autoimmune response in the susceptible host, which leads to the clinical and pathologic manifestations of ulcerative colitis. Others [3, 4] have suggested, and we concur, that a screening for viral infections be undertaken as part of the initial work-up in patients presenting with new onset inflammatory bowel disease. Additionally, it is prudent to have a high index of suspicion for CMV superinfection in a patient who presents with a flare-up of inflammatory bowel disease that is not promptly responsive to standard management.

The clinical sequelae of delayed or missed diagnosis of CMV colitis may have considerable significance. As reported by Loftus et al., of five patients with primary CMV
Figure 2. The duration of inflammatory bowel disease (IBD) prior to diagnosis of cytomegalovirus (CMV) colitis. The numbers represent patients, with percentages in parentheses.

Figure 3. The length of steroid therapy prior to the diagnosis of cytomegalovirus (CMV) colitis in 27 patients with inflammatory bowel disease. The numbers represent patients, with percentages in parentheses.
colitis initially diagnosed with inflammatory bowel disease and treated with corticosteroids, four died [2]. Of the 27 patients (including ours) with inflammatory bowel disease and CMV superinfection, 14 required colectomy. Six patients were correctly diagnosed on colonoscopic biopsy and treated appropriately with ganciclovir; in none of these patients was colectomy necessary [2, 4, 14-16]. Thus, untreated CMV infection in the setting of inflammatory bowel disease carries a 67 percent colectomy rate. Patients with documented CMV colitis who are on corticosteroids may also respond simply to steroid withdrawal [3]. All patients who received ganciclovir treatment survived without requiring colectomy, but seven of the 21 patients (33 percent) who did not receive ganciclovir died, four after undergoing colectomy.

It is commonly stated that a major predisposing factor for patients with IBD in developing CMV colitis is corticosteroid immunosuppression. Although this is undoubtedly true in some of the case reports, five patients were on no corticosteroid therapy at the time of their diagnosis. Additionally, 16 patients (including ours) had been on steroids for less than three months and seven for less than one month (Figure 3). Thus, the majority of patients were not receiving long-term steroid therapy. Therefore, there may be some undefined factor that predisposes patients with IBD to develop CMV infection. Cytomegalovirus has a known propensity to invade rapidly growing tissue [21], such as granulation tissue in an ulcer bed, which may be present in patients with IBD. This has led some to conclude that CMV is not pathogenic in these cases [5], but rather an "innocent bystander," which does not alter the course of the disease. In their series, Eyre-Brook and Dundas [5] found CMV in three of 12 patients requiring urgent colectomy, but in none of 14 patients undergoing elective resection and concluded that CMV did not alter the course of the ulcerative colitis. However, none of the three patients in this report received appropriate antiviral therapy. It would seem, given the success in avoiding colectomy in patients with CMV colitis and IBD adequately treated with ganciclovir, that this conclusion is not supported. Cooper and colleagues [11] have identified an association between CMV, ulcerative colitis and toxic megacolon. Cytomegalovirus inclusion bodies were identified in five of seven patients with ulcerative colitis requiring emergent colectomy for toxic megacolon [11]. The other reported cases of CMV in IBD do not include any with toxic megacolon, however.

In summary, therefore, although CMV infection complicating or initiating inflammatory bowel disease appears to be uncommon, it may be under-diagnosed. If missed, however, it carries with it a substantial morbidity in terms of emergency colectomy and prolonged hospitalization and a mortality of 33 percent. Additionally, the concept that CMV or other viral infection may play a role in the etiology of inflammatory bowel disease is an area which merits further investigation.

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