Ulcerative colitis exacerbation associated with cytomegalovirus infection

YK Yee, SW Wong, ML Szeto

There is an increasing prevalence of ulcerative colitis in Hong Kong and cytomegalovirus infection is an important factor in the exacerbation of the disease. We report on a 33-year-old Chinese man with ulcerative colitis in remission, who presented with bloody diarrhoea that failed to respond to an intensive regimen of oral and rectal steroid. Colonoscopy was performed and biopsy specimens showed signs of cytomegalic colitis in association with ulcerative colitis. Administration of ganciclovir and the gradual termination of steroid treatment resulted in remission of the colitis. The clinical course suggested an exacerbation of ulcerative colitis due to cytomegalovirus infection. The relationship between ulcerative colitis and cytomegalovirus is discussed.

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Introduction

Ulcerative colitis (UC) is one type of inflammatory bowel disease. This condition used to be rarely reported in Hong Kong; however, there is now an increasing prevalence of the disease locally. Powell et al first reported the association of cytomegalovirus (CMV) with UC in 1961. Since then, a total of 23 cases have been reported in the literature. Most of the cases were detected during an acute exacerbation of UC, but the coincidental diagnosis of UC and CMV colitis has also been reported. The relationship between CMV and UC is unclear, as is the role of CMV in UC. However, the importance of CMV as an exacerbating factor of UC is neglected by many clinicians. Cytomegalovirus might not be suspected until a histological examination of the colonic biopsy specimen is performed. We report on a patient with an exacerbation of UC complicated by CMV colitis. The role of CMV in the exacerbation of UC, and the diagnosis and treatment of this condition are discussed.

Case report

A 33-year-old Chinese man presented to the Department of Medicine at the Tuen Mun Hospital in May 1996. He gave a history of producing blood-stained diarrhoea, abdominal pain, and low-grade fever during the previous 2 months. Results of the physical examination were normal, but proctoscopy revealed that the rectal mucosa was inflamed. The complete blood picture was normal, as were the results of renal and liver function tests. The stool culture was negative for ova and cysts, and the microscopic examination of stool also showed their absence. Colonoscopy showed that the mucosa was inflamed and that the region from the rectum to the transverse colon was ulcerated; these features were suggestive of UC. The ascending colon was not involved. Results of a colonic biopsy confirmed the diagnosis of UC. The patient was given mesalazine and steroid therapy. The fever subsequently subsided and the diarrhoea improved.

Steroid treatment was gradually terminated over 3 months and mesalazine treatment was maintained at 800 mg twice a day. The patient was well and produced normal stool once daily until March 1997, when he started producing bloody diarrhoea three times daily. Steroid enema and oral prednisolone 60 mg/d were given, but the patient’s condition did not improve. Colonoscopy was performed and showed active colitis from the rectum to the descending colon. A colonic biopsy showed evidence of active UC, distortion and atrophy of colonic crypts, cryptitis, and crypt abscesses. Some stromal and epithelial cells showed cytomegaly and abundant granular cytoplasm, and were positive for CMV on immunohistochemical study. There was no evidence of primary CMV infection or systemic
involvement of CMV, and both CMV pp65 and anti-CMV immunoglobulin (Ig) M were absent.

The dosage of prednisolone was decreased to 15 mg daily and that of mesalazine was increased to 1600 mg twice daily. Ganciclovir was given intravenously for 4 weeks. A colonic biopsy was performed 1 month later and showed the absence of inclusion bodies; however, there were still signs of active UC. Gradual symptomatic improvement was observed subsequently. In October 1997, the patient was well and asymptomatic, and was passing normal stool once or twice daily. Prednisolone treatment was gradually terminated and only mesalazine is currently being given.

Discussion

The prevalence of anti-CMV antibodies is high in the adult population. Cytomegalovirus causes only minor disease in immunocompetent individuals, and the primary infection is usually asymptomatic. In contrast, CMV infection is important in immunocompromised patients because of the high mortality in the absence of antiviral therapy. Reports of CMV infection of the gastro-intestinal tract in immunocompetent individuals are few, although CMV colitis in an immunocompetent individual with UC had been reported as early as in 1961. This disease entity was more commonly reported in patients who were immunosuppressed. The prevalence was 2% to 16% in solid organ transplant recipients and 38% in bone marrow transplant recipients. In contrast to immunocompetent patients, immunosuppressed patients usually present with more systemic symptoms, such as prolonged fever, night sweats, and malaise.

The association between CMV and UC is well recognised: antibodies to CMV are detectable more frequently in UC patients than in a matched control population. Examination of a colonic specimen by using immunofluorescence tests, the demonstration of a cytopathic effect in tissue culture of cells derived from the colon, and detection of characteristic viral particles under the electron microscope also demonstrate the association between CMV and UC. Moreover, viral inclusion bodies have been found in patients with UC at their first presentation and also in individuals with pre-existing UC.

Cytomegalovirus is likely to be more than just a bystander in the colon of patients with UC. Firstly, toxic megacolon—a life-threatening complication of colitis—has been associated with the presence of CMV inclusions in colonic biopsy samples (ie in samples from 5 of 7 patients with toxic dilatation versus only 1 of 39 patients without toxic dilatation). Secondly, CMV colitis frequently responds to ganciclovir therapy. According to Loftus et al, colectomy was not necessary in six patients who received ganciclovir, while three of four patients who did not receive ganciclovir treatment eventually required colectomy. Thirdly, CMV immediate-early genes have been shown to enhance cytokine production in a monocyte cell line. An increased level of cytokine in vivo would lead to pronounced inflammation that would present as an exacerbation of UC.

Steroid treatment might be a risk factor for CMV colitis in patients with UC, but at least one third of these patients give no history of preceding steroid treatment. Rapidly proliferating cells in granulation tissue are susceptible to CMV infection and infected cells are usually found in ulcer beds or areas of granulation tissue; hence, UC might itself be a predisposing condition to CMV infection.

The presence of anti-CMV IgM or a rising titre of anti-CMV IgG suggest primary CMV colitis. Systemic involvement can be confirmed by the detection of CMV antigen in the serum. However, evidence of primary CMV infection or systemic involvement was absent or not reported in many of the reported cases. The diagnosis of CMV colitis in UC still depends on the histological identification of inclusion bodies and CMV antigen in the colonic biopsy sample; serology only screens for the presence of primary or systemic infection. Ganciclovir is usually recommended for CMV colitis in UC as it improves the outcome with a lower incidence of megacolon and colectomy. As far as we know, recurrence of CMV colitis after successful treatment has not been reported. However, our experience in this area is scanty and recurrence is theoretically possible.

As with many reported cases of UC associated with CMV, the deterioration of this patient’s condition was associated with CMV, although the virus was not present in his previous colonic biopsy sample. The improvement of his condition after appropriate antiviral therapy supports the idea that CMV acts as an invader and not just a bystander. The role of CMV in the aetiology of UC is still unclear. Since the clinical presentation and the gross pathological appearance of an exacerbation of UC are non-specific, its diagnosis requires a high index of suspicion. If the patient’s condition deteriorates or if the patient fails to respond to steroid treatment, an early colonoscopic biopsy should be performed to detect any microscopic features...
of CMV colitis (giant cells with cytomegaly, or large pleomorphic nuclei harbouring basophilic intranuclear inclusion bodies).

In summary, CMV acts as an exacerbating factor of UC, in view of its association with UC deterioration and response to ganciclovir therapy. Colonic biopsies should be performed early during an exacerbation. Ganciclovir therapy should be given and steroid treatment gradually curtailed, once the diagnosis is made.

References