HIV associated cytomegalovirus colitis as a mimic of inflammatory bowel disease

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Abstract
Cytomegalovirus (CMV) colitis may cause symptoms and signs identical to those of idiopathic inflammatory bowel disease. Although difficult to diagnose with certainty, the histological finding of cytomegalovirus inclusions in tissue from a case of suspected inflammatory bowel disease is strongly suggestive. CMV colitis is an entity almost entirely confined to cases of severe immunosuppression. The case of a 79 year old widower who was admitted to hospital with symptoms suggestive of inflammatory bowel disease is presented. Despite medical treatment his condition worsened and he developed toxic dilatation of the colon requiring colectomy. Histological examination showed a mild superficial pancolitis, with focal severe inflammation, deep fissuring ulceration, and pseudopolypsis. Abundant CMV inclusions were seen in cells associated with the ulcerating inflammatory tissue. A diagnosis of indeterminate colitis with CMV was made. The patient’s condition worsened after surgery and he died a few days later despite intensive treatment, including antiviral chemotherapy directed against CMV. After death HIV serology was found to be positive. Regardless of the age and perceived lifestyle of the patient, a diagnosis of CMV colitis in someone not known to be immunosuppressed raises the possibility of HIV infection.

Keywords: cytomegalovirus colitis, inflammatory bowel disease.

Case report
A 79 year old widowed farmer presented with a two day history of melena following a course of a non-steroidal anti-inflammatory agent for a flu-like illness. Endoscopy showed prepyloric gastric ulcers, and other investigations suggested a right sided basal lung consolidation. Culture of blood, sputum, stool and urine, viral and atypical pneumonia serology, and a Mantoux test failed to identify a causative organism, and he was treated with antibiotics. In view of the presence of anaemia contributing to his debility he was given a blood transfusion before discharge.

Six weeks later he was readmitted with fever, night sweats, malaise, weight loss, and diarrhoea. Examination showed inguinal lymphadenopathy, non-tender epigastric fullness, bilateral basal chest signs, and peripheral oedema. Investigations showed an erythrocyte sedimentation rate of 53 mm per hour (normal <10), C reactive protein of 127 mg/l (0–8), and serum albumin of 24 g/l (35–50). Haemoglobin was 9·5 g/dl (13·5–18) with a low mean red cell volume of 78·1 fl (81–100). The white cell count was 9·1×10⁹/l (4·0–11), with 81% granulocytes and 15% lymphocytes. Platelets were 303×10⁹/l (150–400). An abdominal x ray and single contrast barium enema showed appearances suggestive of incipient toxic dilatation of the colon, and biopsy samples showed focal severe acute inflammation with crypt abscesses consistent with inflammatory bowel disease.

The patient initially refused surgery. Medical treatment including antibiotics (cefuroxime, metronidazole, gentamycin), corticosteroids, and subsequently cyclosporin failed to control the condition, and emergency colectomy was performed one week later.

The resected colon was dilated and inflamed, with numerous pseudopolyps surrounded by flat mucosa with areas of ulceration. The inflammation extended from the sigmoid to the mid-caecum, and the rectum was spared. Histologically there was deep ulceration between islands of almost normal mucosa. Many ulcers extended into the external muscle and serosal fat. Within the granulation tissue at the base of these ulcers there were abundant endothelial cells and macrophages containing dark intranuclear inclusions suggestive of cytomegalovirus (CMV) infection. This was confirmed with immunohistochemistry. Away from the acutely inflamed areas there was minimal distortion of glandular architecture, and crypt abscesses were only present at the edge of the ulcers. The histological features were not entirely characteristic of either ulcerative colitis or Crohn’s disease, and the specimen was reported as indeterminate colitis with CMV.

The patient’s course was poor postoperatively, requiring transfer to the intensive care unit for ventilatory and renal support. In view of the finding of CMV in the inflamed bowel, the possibility of primary CMV disease was considered, and anti-CMV chemotherapy was included in his aggressive medical treatment.

Despite this he died three days later. After death HIV tests on his previous blood samples confirmed that he had been HIV positive. Subsequently it was found that he had been bisexual and recently living with two young men.
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Discussion

CMV in ulcerative colitis and Crohn's disease
CMV has been recognised as a rare complication of inflammatory bowel disease for many years. Infection is most likely to occur in established cases of severe inflammatory bowel disease, and to be associated with toxic dilatation and a poor prognosis. Berk et al., reviewing the 16 cases published before 1985, found that 10 had required colectomy and seven had died. The significance of the association has not generally been emphasised, as the presence of CMV reflects its known role as an opportunistic pathogen. Some workers have, however, conducted more rigorous searches for the virus in inflamed bowel tissue. Their finding of viral nucleic acid in tissue without the characteristic CMV inclusions has been proposed as evidence of a more frequent association.

In a study using the polymerase chain reaction Wakefield et al. showed CMV DNA in 66% of Crohn's tissue and 81% of ulcerative colitis, compared with 29% of biopsy specimens without inflammatory bowel disease. These findings have been interpreted as suggesting the CMV may be a cause of inflammatory bowel disease. The relation is clearly multifactorial, complicated by the fact that CMV is a common secondary pathogen, and that mononuclear cells carrying the virus in its latent phase may concentrate viral DNA at sites of inflammation. Thus the virus might be detectable in a case of ulcerative colitis because of secondary infection, because of passive carriage by inflammatory cells, or conceivably because it has caused the disease.

Diagnosis of CMV colitis
Before the advent of the acquired immune deficiency syndrome CMV colitis was a rare entity confined to cases of renal transplant or other significant immunosuppression. The distinction from secondarily infected ulcerative colitis is suggested by such a history.

Grossly the pattern of ulceration, which tends to consist of well circumscribed, punctuate lesions penetrating deep into the bowel wall, may not match the classic picture of ulcerative colitis or Crohn's disease. Histologically the virus is visibly present, with striking numbers of intranuclear inclusions in the inflammatory tissue. The absence of clear features of Crohn's disease or ulcerative colitis is helpful, though primary CMV colitis should always be considered if unequivocal CMV inclusions are seen. Although the ulcers may be surrounded by essentially normal tissue, in the more severe cases the intervening mucosa may be inflamed and superficially ulcerated to the extent of pseudopolyp formation and toxic dilatation.

A complicating factor, shown by this case, is that CMV inclusions are most abundant in and around vessels at the base of ulcers. Small superficial biopsy specimens may, therefore, not contain the most characteristic histological feature. Despite these difficulties, the histological finding of CMV inclusions in biopsy tissue is the most reliable diagnostic test, particularly as coexisting immunosuppression may make the interpretation of viral serology difficult.

CMV colitis in HIV disease
As larger numbers of people have become immunosuppressed through infection with HIV, CMV colitis has become increasingly common, with HIV accounting for almost all the reported cases. Frequently CMV is seen as a comparatively late complication of HIV infection, with almost all patients simultaneously suffering the effects of other opportunistic pathogens. In one study of 44 cases AIDS had already been diagnosed a median time of 16 months previously. Mortality, even with maximal medical and surgical treatment, is high.

In patients with HIV disease CMV may coexist with other infective agents within the bowel, or with other AIDS related conditions such as Kaposi's sarcoma. Cryptosporidium spp, Isospora belli, herpes simplex types 1 and 2, Mycobacterium avium-intracellulare and the many organisms associated with the gay bowel syndrome are frequent opportunistic pathogens in the HIV positive subject. Whether or not another pathogen is present when CMV is found, there is often a history of previous unusual infection. In cases such as these the diagnosis of CMV colitis can be comparatively straightforward. A good description of the pathology of AIDS in the bowel and elsewhere is given by Millard and Esiri.

This case does not fit into the usual pattern of HIV associated CMV colitis. An elderly, widowed farmer with no previous history of unusual infection and with a normal lymphocyte count was not suspected as having HIV. The CMV inclusions were not present in the initial biopsy. Such a pattern of presentation was in favour of idiopathic inflammatory bowel disease. Examination of the resected colon did not support this diagnosis, however, and the colitis seems to have been caused by primary CMV infection in the presence of HIV.

There are several points raised by this case. One is that patients suffering a first episode of 'inflammatory bowel disease' who have CMV inclusions in the diseased bowel are probably suffering CMV colitis, and that such a diagnosis raises the possibility of HIV infection.

Perhaps of equal relevance is the reminder provided by this case that HIV associated disease can occur in patients who, by most accepted criteria, would be considered to be at very low risk of infection. The categorisation of patients into high and low risk groups provides false reassurance to the surgeon, the pathologist, and all those who may be exposed to fresh human tissue.

2 Berk T, Gordon SJ, Choi HY, Cooper HS. Cytomegalovirus infections of the colon: a possible role in exacerbations of


