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Localisation of CMV ileitis in patients with AIDS using white cell scanning

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Introduction

Cytomegalovirus (CMV) is a major cause of gastrointestinal disease in patients with AIDS. Oesophageal and colonic involvement are well recognised and can be diagnosed using endoscopic techniques. However, post mortem studies suggest that small bowel infection by CMV is more common in patients with AIDS than is currently recognised during life (Ives, 1997). We report two cases of CMV ileitis and one case of HIV-1 enteropathy in which white cell scanning was used to define whether and how much of the ileum was affected by CMV infection, and to then follow the response to therapy.

Case 1: A 38-year-old HIV-1 positive white man presented with campylobacter and salmonella enteritis, cryptosporidial diarrhoea, candida oesophagitis and *Pneumocystis carinii* pneumonia after a visit to Thailand. He responded to conventional treatment and all pathogens cleared from his stool. His CD4 count was 32/μL. During the course of treatment with co-trimoxazole and zidovudine, his white cell count fell to 0.4 x 10^9/L.

Nineteen days after admission, he developed fever, vomiting, abdominal tenderness and severe abdominal pain. A plain abdominal x-ray showed dilated loops of small bowel. A ^{99m}technetium (^{99m}Tc) white cell scan was performed using autologous granulocytes which were isolated, labelled and then re-infused (Peters *et al*, 1986; Danpure & Osman, 1988). Gamma camera images over the first 4 hours showed the accumulation of ^{99m}Tc in the terminal ileum but not in the colon (Figures 1 and 2). A flexible colonoscopy demonstrated normal colonic mucosa and a grossly oedematous ileo-caecal valve. Immunohistochemical stains for CMV antigens of a biopsy from the terminal ileum were positive. Cryptosporidia were also seen. Culture and immunohistochemistry of peripheral blood leucocytes for the early antigen of CMV was positive.

Treatment with paromomycin (White *et al*, 1994) which had been started three weeks earlier resulted in a reduction in the cryptosporidial oocyte count in his stool. However, there was no associated change in his clinical symptoms. Treatment with foscarnet was now started and this resulted in a resolution of his fever, abdominal pain and small bowel obstruction. A follow-up white cell scan showed no localisation of ^{99m}Tc to the ileum and the patient remained well on maintenance CMV therapy.

Case 2: A 41-year-old HIV-1 positive white man with a CD4 of 10/μL developed diarrhoea. Stool microscopy showed numerous cryptosporidial oocysts but no other pathogens. He was treated with paromomycin with complete resolution of his diarrhoea. Four months later, he developed diarrhoea that became so severe (liquid stools 6-20 times/day) that he required regular hospitalisation over a period of 8 months. Control of his abdominal pain required regular opiate analgesia.

Stool microscopy showed only scanty cryptosporidial oocysts and no other pathogens. Gastric and rectal biopsies were positive for CMV antigens on immunohistochemical staining. A colonoscopy revealed such severe inflammation and ulceration of the transverse colon that the procedure had to be abandoned because of the friable nature of the mucosa and because of contact bleeding. The colonic biopsy showed numerous cryptosporidia and large endothelial cells with nuclear inclusions which were typical of CMV infection. Immunohistochemistry for CMV antigens was positive.

There was no response of the diarrhoea to prolonged treatment with paromomycin, ganciclovir, foscarnet, zidovudine and didanosine. Attempts at symptomatic control of his symptoms with opiates, octreotide and pancreatic enzymes were also unsuccessful. An ^{111}indium labelled white cell scan was performed. This showed abnormal uptake in a loop of distal ileum, terminal ileum, ascending colon and at the splenic flexure. Surgical resection of his colon and terminal ileum with a functioning ileostomy was followed by a rapid resolution of his symptoms. Macroscopic and microscopic histopathological findings confirmed the presence of CMV ileitis, CMV colitis and of cryptosporidium (Figures 3-5).

Case 3:
A 46-year-old HIV-1 positive Asian man with a CD4 count of 20/μL was investigated extensively over a period of 2

years for chronic diarrhoea which consisted of 15 liquid stools a day. No pathogens where identified either in the stools, or in gastric or colonic biopsy samples. A small bowel enema showed diffusely thickened folds and a duodenal biopsy showed partial villous atrophy; there were no specific diagnostic features. He had increased faecal fat excretion and reduced pancrealoryl. However, there was no subsequent improvement in his diarrhoea following treatment with oral pancreatic enzyme supplementation. A ^{99m}Tc labelled white cell scan was normal. A clinical diagnosis of HIV enteropathy was made and he was treated with zidovudine. This resulted in the rapid resolution of his diarrhoea.

Discussion

CMV is a major cause of symptomatic gastrointestinal disease in immunosuppressed patients, particularly those with AIDS. Up to 10% of patients with AIDS will have symptomatic gastrointestinal disease which can be attributed to CMV during life (Francis *et al*, 1989) with post mortem studies showing evidence of gastrointestinal CMV disease in up to 21% (Goodgame, 1993).

Although colonic CMV infection is well documented in the literature, there are only six case reports of CMV disease of the ileum which were diagnosed during life. They include two cases of haemorrhagic ileo-colitis in infants (Kawimbe *et al*, 1991; Dolgin *et al*, 1990) and four cases of terminal ileitis (Wajsman *et al*, 1988; Fernandes *et al*, 1986; Wexner *et al*, 1988; Frank and Raicht, 1984). CMV associated appendicitis has also been described (Dieterich *et al*, 1990). All were diagnosed post-operatively by histological examination of surgical biopsy tissue.

It is often difficult to distinguish small bowel pathology from large bowel pathology on a clinical basis. Small bowel infections typically cause bloating, nausea, abdominal cramps, high volume diarrhoea and early weight loss in contrast to large bowel pathology which usually causes lower abdominal pain, faecal urgency, tenesmus and small volume but more frequent stools. The diagnosis of small bowel pathology is often delayed because of the non-specific nature of the symptoms and signs and because of the inaccessibility of the ileum to endoscopic examination.

White cell scanning has proved to be very useful in patients with Crohn's Disease as a means of identifying areas of inflammation in the ileum (Roddie *et al*, 1988). We have now used this technique to identify sections of the ileum which were actively involved in disease caused by CMV, and to monitor the subsequent response to therapy. The technique can be used successfully even when the patient has a low neutrophil count (ie: $<1 \times 10^9$/L) as is commonly the case in patients with AIDS (Ogg *et al*, 1997). It is likely that the accumulation of granulocytes is secondary to the mucosal inflammation and haemorrhage which is typically seen in the gut of immunosuppressed patients with active CMV infection. The degree of immunosuppression is usually greater in patients with AIDS than in patients with most forms of immunosuppression. The neutrophil labelling technique has the advantage that it can identify both small and large bowel pathology in this group of patients.

Cryptosporidial infections are very common in patients with AIDS. We think that it is most unlikely that the areas of inflammation which were identified in the ileum using white cell scanning could have been due to cryptosporidial infection alone because this organism typically affects the whole of the ileum, the whole of the colon and the gall bladder. Furthermore, diarrhoea did not resolve after treatment with paromomycin and a reduction in the number of oocysts in the stool. A definitive clinical improvement was only seen after treatment for CMV was started.

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Figure legend

Figure 1

Figure 2

Figures 1 and **2** are gamma-camera images of the abdomen obtained at 4 hours after injection of ^{99m}technetium labelled leucocytes from right lateral (Figure 1) and anterior (Figure 2) projections. Intense localisation of cells is seen in loops of small bowel in the right side of the abdomen. Physiological activity is visible in the spleen (top) and bladder (bottom).

Figure 3 shows diffuse granular inflammation and ulceration of the terminal ileum and resembles Crohn's disease.

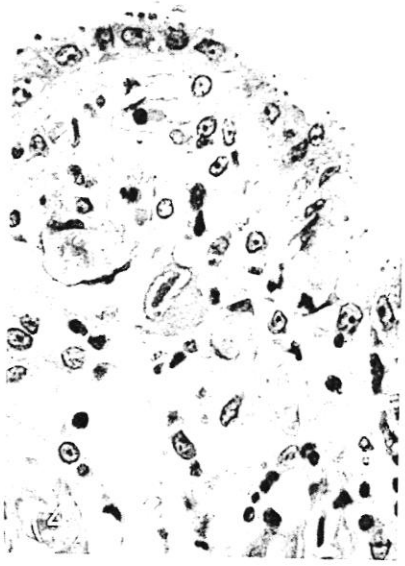

Figure 4 is a high power of the ileal mucosa with surface cryptosporidia and a large CMV infected cell in the lamina propria with typical Cowdry type A inclusions.

Figure 5 is an immunocytochemical stain for CMV (Dako) which shows three positive cells in the muscularis mucosa.