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BRIEF REPORT

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Cytomegalovirus infection and colonic perforation in renal transplant patients

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Abstract Cytomegalovirus (CMV) infection in immunocompromised patients is a major cause of morbidity and mortality. A well-documented manifestation of gastrointestinal CMV infection is gastrointestinal haemorrhage. In contrast, CMV-associated intestinal perforation has rarely been reported after transplantation, although it is well documented in AIDS patients. Three patients are reported who received their first cadaveric renal transplant in 1994 and subsequently developed CMV disease. During the course of their CMV illness, which was treated with ganciclovir, each presented with clinical suspicion of peritonitis and proceeded to laparotomy. All three were found to have sigmoid colon perforations with histological evidence of CMV infection. Following bowel resection and defunctioning, two patients made an uneventful recovery and have had the continuity of their bowel restored, but one died of overwhelming sepsis within hours of surgery. The explanation for the apparent clustering of this rare condition in transplant patients is uncertain.

Key words CMV, colonic perforation, kidney transplantation · Colonic perforation, CMV, kidney transplantation · Perforation, colon, CMC · Kidney transplantation, colonic perforation, CMV

Introduction

Cytomegalovirus (CMV) infection in immunocompromised patients is a major cause of morbidity and mortality. In both AIDS patients and transplant recipients, it can induce life-threatening organ-specific disorders such as pneumonitis, hepatitis and gastrointestinal disease. In the gastrointestinal tract of immunocompromised patients, CMV disease usually causes ulcerative lesions that may involve any level from the mouth to the anus. Symptoms usually include fever, abdominal pain, malaise, anorexia, bleeding and diarrhoea [3]. An important and well-documented manifestation of gastrointestinal CMV infection is gastrointestinal haemorrhage [17]. In contrast, CMV-associated perforation in transplant patients has only been reported on one previous occasion [9], although it is well documented in patients with AIDS [8, 11, 19, 21]. The three colonic perforations reported here all occurred within a 6-month period and are the only proven cases seen out of nearly 1300 renal transplants performed at the Oxford Transplant Unit.

Patients

Patient 1

A 58-year-old CMV-seronegative woman with end-stage renal failure secondary to adult polycystic kidney disease received a beneficially matched, CMV-seropositive cadaveric renal transplant. She was placed on a triple immunosuppressive therapy regimen including cyclosporin (10 mg/kg od), azathioprine (1.5 mg/kg od) and prednisolone (10 mg bd). The graft functioned immediately and there were no acute rejection episodes.

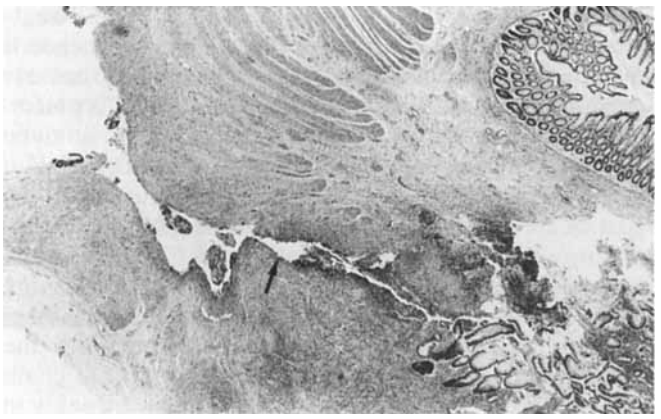

Fig. 1 Sinus tract *(arrow)* lined by granulation tissue extending through wall of sigmoid colon

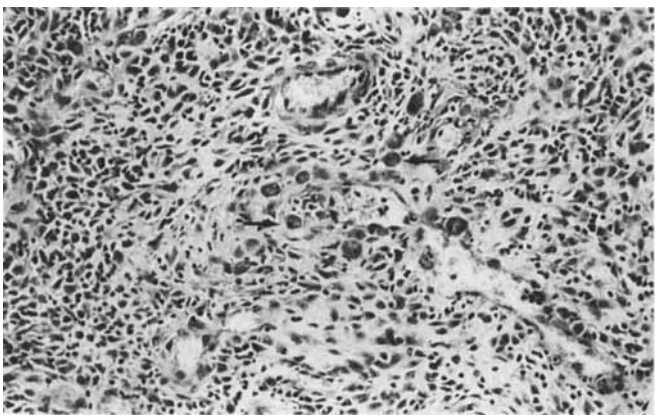

Fig. 2 Granulation tissue with CMV inclusions *(arrows)* within both the stromal and vascular endothelial cells (low power)

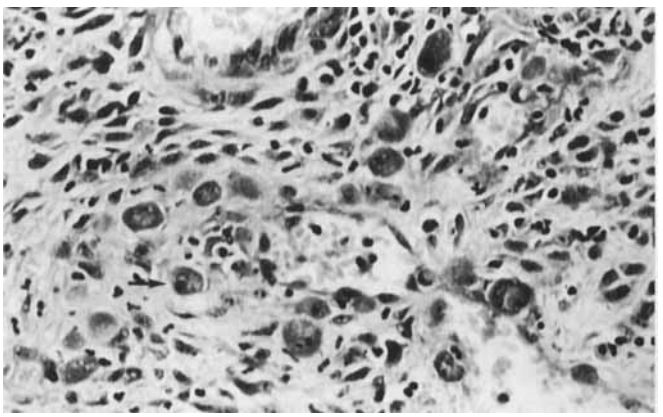

Fig. 3 Granulation tissue with CMV inclusions *(arrows)* within both the stromal and vascular endothelial cells (high power)

Seven weeks later the patient was admitted with a 1-week history of lethargy and mild central abdominal pain. On examination she was pyrexial but her abdomen was unremarkable. Investigations revealed a thrombocytopaenia and raised liver enzymes but no deterioration in renal function. A preliminary diagnosis of primary CMV infection was made and confirmed the next day with a CMV antigenemia test (100 positive cells/50,000 peripheral leucocytes).

The patient was started on intravenous ganciclovir and within 2 days her symptoms settled, her liver function tests improved and her CMV antigenemia count decreased to 60/50,000. However, her azathioprine dose was reduced in response to a developing leucopaenia. On the 6th day of ganciclovir treatment, she developed more severe central abdominal pain but with no signs of peritonism. At this point her white cell count was 3.1×10^9/l with a neutrophil count of 1.8×10^9/l. A plain abdominal radiograph was normal, but a peritoneal lavage performed through the patient's Tenckhoff catheter revealed turbid fluid which, on microscopy, showed a mixed flora of gram-positive cocci and gram-negative bacilli, suggestive of faecal contamination.

At laparotomy a 0.5-cm punched out circular ulcer was found in the sigmoid colon. The diseased segment of sigmoid was resected and a loop colostomy performed to protect the anastomosis. The Tenckhoff catheter was also removed. Histology of the resected sigmoid colon wall revealed many CMV intranuclear inclusions in both macrophages and endothelial cells of the granulation tissue surrounding a sinus extending through to the submucosa, thus confirming CMV infection (Figs. 1–3). An inflamed diverticulum was also found with florid evidence of CMV infection.

Five days after laparotomy the patient's liver enzymes rose significantly and the CMV antigenemia count increased to 100/50,000, despite 11 days of intravenous ganciclovir. Her cyclosporin and azathioprine were stopped because her liver enzymes continued to rise (aspartate aminotransferase 140 IU/l, alkaline phosphatase 1603 IU/l). She remained on a reduced dose of prednisolone with intravenous ganciclovir and oral acyclovir and within 2 days her condition improved. After 4 days the azathioprine and cyclosporin were reintroduced and she was discharged 3 weeks later with excellent graft function. The acyclovir was stopped after 2 weeks, but the ganciclovir was continued at home by her general practitioner for a total of 5 weeks. She remains well after uneventful closure of her colostomy.

Patient 2

A CMV-seropositive, 58-year-old man with adult polycystic kidney disease received a cadaveric renal transplant from a CMV-seropositive donor. He received triple immunosuppressive therapy and was given two 3-day courses of methylprednisolone, 1 week and 8 weeks after transplantation for biopsy proven mild acute rejection.

Ten weeks after transplantation, the patient was admitted with right iliac fossa pain and deterioration in renal function. The CMV antigenemia was negative and he was treated for a urinary tract infection with ciprofloxacin. However, his white cell count was 2.9×10^9/l with a neutrophil count of 2.2×10^9/l. Following initial improvement, he was readmitted 3 days later with worsening pain and a pyrexia (37.8 °C). There were no abdominal signs of peritonism, but there was a pneumoperitoneum on abdominal radiograph and an ultrasound scan revealed a collection in the pelvis.

At laparotomy a localized pelvic abscess and sigmoid perforation were found, as well as several diverticulae. A sigmoid resection with primary anastomosis and defunctioning ileostomy were performed. Histology revealed acute ulcerating and perforating di-

verticulitis of the sigmoid colon with many macrophages and endothelial cells showing intranuclear CMV inclusions. Post-operatively the patient's CMV antigenemia count became 40/50,000 and he was treated with intravenous ganciclovir for 3 weeks. He made an uneventful recovery and remains well after reversal of his ileostomy.

Patient 3

A 66-year-old man with glomerulonephritis who was CMV-seronegative underwent renal transplantation with a beneficially matched cadaveric renal graft from a CMV-seropositive donor. He was given triple immunosuppressive therapy and had an uneventful post-operative course without any evidence of rejection.

Ten weeks after transplantation the patient was admitted with symptoms suggestive of active CMV infection including fever and moderately severe dysphagia and epigastric pain, despite taking omeprazole. His CMV antigenemia count was 50/50,000 and his liver enzymes were raised. Upper gastrointestinal endoscopy revealed oesophagitis and a gastric mucosal biopsy showed CMV inclusions. He was treated with intravenous ganciclovir for 2 weeks and was discharged with a CMV antigenemia count of 0/50,000 and normal liver enzyme levels.

Six weeks later the patient was readmitted with similar symptoms. His CMV antigenemia count had risen to 50/50,000 and he was also diagnosed as having bacterial septicaemia. Despite intravenous ganciclovir and antibiotics, his condition deteriorated rapidly and he developed abdominal pain with ascites. At laparotomy he had peritonitis, but no perforation could be found despite an extensive search. His azathioprine was stopped due to leucopaenia (2.5×10^9/l with a neutrophil count of 1.6×10^9/l). Following a brief period of general improvement, the patient's condition suddenly worsened a week later and a CT scan showed pelvic collections. He was re-explored and a sigmoid perforation with faecal peritonitis was found. A Hartmann's procedure was performed but the patient died from overwhelming sepsis hours later. Histology of the resected segment of bowel showed evidence of CMV infection. Granulation tissue at the site of the perforation contained CMV inclusions within stromal and endothelial cells.

Discussion

CMV disease of the gastrointestinal tract has been reported in 2 %–16 % of transplant patients [3]. Intestinal perforation has been recognised in transplant patients for many years [7, 13], but on only one occasion has CMV been considered and proven to be the primary diagnosis [9]. These perforations were thought to be caused by maintenance high-dose steroids and irradiation treatment. Gastrointestinal haemorrhage with signs of colitis, namely diarrhoea and rectal bleeding, is the usual pattern of serious CMV involvement of the lower gastrointestinal tract. However, the patients reported here did not present in this way and all had minimal clinical signs of perforation, although patient 1 was probably diagnosed relatively early following peritoneal lavage through the Tenckhoff catheter.

The prevention and treatment of active CMV infection in transplant patients has received much attention recently [2, 5, 16]. It appears that ganciclovir is the treatment of choice for CMV infection, particularly since it can now be given orally. However, it remains unclear whether prophylactic or therapeutic treatment is preferential [6, 15]. Prophylactic intravenous ganciclovir given for 100 days has been shown to be more effective than prophylactic acyclovir in liver transplantation [22]. In most cases, therapeutic treatment using ganciclovir rapidly improves the clinical symptoms of CMV infection, but patient 1 developed the colonic perforation having already taken ganciclovir for a week. In our unit a surveillance regimen has been adopted where both the CMV antigenemia count and CMV polymerase chain reaction (PCR) detection are measured twice weekly in patients who are likely to develop CMV infection. Patients who develop primary CMV infection and who have previously received anti-rejection treatment and any patients who develop evidence of organ involvement are given ganciclovir as soon as either of the surveillance tests turn positive. Both tests are considered highly sensitive for the detection of active disease [20]; yet, in patient 2, the CMV antigenemia count and PCR test did not become positive until late in the clinical disease process.

The explanation for the apparent cluster of CMV-associated colonic perforation is uncertain. Two of our three patients had primary disease, which is recognised to be more severe, in general, than reinfection or reactivation [10, 18], but the vast majority of primary CMV in our unit has not been associated with this complication. None of the patients received antilymphocyte therapy with ATG or OKT3, which is recognised to increase the risk of serious CMV disease [1], and it is not possible to implicate a virulent viral mutant because there was not a common viral source (two primary infections from temporally and spatially separated donors and a reinfection/reactivation).

In each case there was a clear association between the CMV infection and perforation, but although a causal link seems likely, this has not been established beyond any doubt. In two of the three cases, the histology of the resected colonic segment revealed florid CMV infection as well as concomitant pathology, namely diverticulitis. Some authors suggest that CMV may have an affinity for sites of pre-existing ulceration [9, 14], although it has also been suggested that microscopic evidence of CMV inclusions in the endothelial cells with related small vessel vasculitis lends strong evidence that the virus is likely to be responsible for the ulceration [3]. All three specimens revealed CMV inclusions within the endothelial cells of the granulation tissue.

Prevention of CMV infection in the light of the severity of the complications would obviously be desirable. The risk of CMV disease would be reduced if seropositive donors were only used for CMV-seropositive recipients, but this would dramatically reduce the availability

of well-matched organs for CMV-seronegative recipients. Ganciclovir has been successfully used in the management of both prophylactic and therapeutic CMV treatment and has been shown to be cheaper and more effective than CMV immunoglobulin administration [12]. It is unknown whether prophylactic ganciclovir administration would have prevented the serious complications of CMV disease reported here, although no significant difference has been shown between prophylactic and therapeutic ganciclovir in liver transplantation [4]. Also, since relapses of CMV disease are well recognised after ganciclovir treatment [3] and one patient suffered colonic perforation during a relapse after ganciclovir, it seems unlikely that this will provide the whole answer to the prevention of serious CMV disease.

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