Gastro-intestinal cytomegalovirus infection and extensive colonic ulceration in a renal transplant recipient

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Cytomegalic inclusion disease is a common complication for recipients of organ transplants. In renal transplant recipients, the disease involves the lungs more often than it does the gastro-intestinal tract. We report on a recipient of a cadaveric kidney who had cytomegalic inclusion disease that involved both the upper and lower gastro-intestinal tract, and massive gastro-intestinal bleeding that was caused by a large colonic ulcer. Despite treatment with ganciclovir and cytomegalovirus-specific immunoglobulin, the patient died from subsequent complications.

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Introduction

Cytomegalovirus (CMV) is one of the most common viral pathogens that complicate organ transplantation.[1] In kidney transplant recipients, the organ most frequently involved in CMV infection is the lung. Gastro-intestinal (GI) involvement, although less common, can also occur.[2] We describe a case of cytomegalic inclusion disease that involved multiple sites of the GI tract and massive GI bleeding after kidney transplantation.

Case report

A 47-year-old Chinese man presented to the Department of Medicine at the Princess Margaret Hospital in January 1991 with polycystic kidneys. End-stage renal failure developed in November 1991 and the patient was given continuous ambulatory peritoneal dialysis. Antibodies against CMV were present and in early 1994, he received a cadaveric kidney from a 33-year-old Chinese man who was seropositive for CMV. Because of a relatively long cold ischaemic time, the patient was given immunosuppressive therapy as follows: antithymocyte globulin 0.5 $mg \cdot kg^{-1} \cdot d^{-1}$, azathioprine 1.5 $mg \cdot kg^{-1} \cdot d^{-1}$, and corticosteroid (intravenous methyl prednisolone 500 mg, followed by oral prednisolone 30 mg/d). It is not routine practice at the Princess Margaret Hospital to give prophylactic therapy to CMV-positive recipients. The native kidneys were huge and extended into the pelvis. The surgeons performed a right native nephrectomy and implanted the graft in the right iliac fossa. There was immediate diuresis and the serum creatinine level declined progressively from 1248 μmol/L to approximately 580 μmol/L 3 days later (normal range, 50-110 μmol/L). In view of the adequate graft function, cyclosporin A 10 $mg \cdot kg^{-1} \cdot d^{-1}$ was given 1 day after the operation and antithymocyte globulin treatment was withdrawn 2 days later.

There were no postoperative complications, apart from an episode of urinary tract infection with *Enterobacter* species, which responded promptly to antibiotic therapy. The patient was discharged home towards the end of the second week. The serum creatinine level at the time of discharge was approximately 200 μmol/L and the cyclosporin A level was 377 μg/L (reference range for the first month after transplantation, as determined by monoclonal antibody assay, 300-400 μg/L). After the patient's discharge, the haemoglobin level was between 75 and 88 g/L (normal range, 140-180 g/L; the pretransplant haemoglobin level was 90 g/L); the anaemia was normochromic and normocytic. Tests

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for occult blood, ova, and cysts in the stool gave negative results.

Eight weeks after the transplantation, the patient was re-admitted because of fever and abdominal pain. Abdominal examination revealed signs of peritonitis and rectal examination showed brownish stool. The complete blood count showed a haemoglobin level of 77 g/L; the anaemia was normochromic and normocytic. The white cell count was $2.1x10^9$ /L and the platelet count was $116x10^9$ /L. Chest radiography showed clear lung fields and there was no free gas under the diaphragm. Total serum bilirubin, serum alkaline phosphatase, and serum glutamate pyruvate transaminase levels were 24 μmol/L, 82 U/L, and 24 U/L, respectively (normal ranges, 2-18 μmol/L, 30-120 U/L, and 1-40 U/L, respectively). Laparotomy revealed a 0.5-cm perforated duodenal ulcer and multiple gall stones. Patch repair of the duodenal perforation and cholecystectomy were performed. The patient's condition nevertheless failed to improve; fever persisted and liver function became impaired. One day after the laparotomy, the level of serum bilirubin was 43 μmol/L, that of alkaline phosphatase was 106 U/L, and that of serum glutamate pyruvate transaminase was 14 U/L. The haemoglobin level was 74 g/L and white cell and platelet counts were 8.2×10^9 /L and 166×10^9 /L, respectively. Lung fields remained clear on repeated chest radiographs. Blood culture was negative for all micro-organisms. The presumptive diagnosis was cytomegalic inclusion disease. Cyclosporin A treatment was withheld and ganciclovir 5 mg/kg twice daily and antibiotics were given intravenously.

Nine days after the laparotomy, the patient suddenly passed fresh blood per rectum. An urgent colonoscopy was performed and showed multiple bleeding ulcers. The bleeding was so extensive that a second laparotomy was performed on the same day. During the operation, a 12.0- by 3.5-cm longitudinal bleeding ulcer was found over the transverse colon near the mesenteric border (Fig 1) and multiple smaller ulcers were found in the ascending colon. The base of the longitudinal ulcer was greenish and had pseudopolyps. There was no perforation of the colon, and the terminal ileum and appendix were unremarkable. A right hemicolectomy and ileocolic anastomosis were performed.

Microscopic sections of the colonic ulcers showed the presence of cellular debris and neutrophilic infiltration. The ulcer base was composed of granulation tissue. Large cells that had large and irregular nuclei; occasional eosinophilic nuclear inclusions, and abundant amphophilic cytoplasm were seen in the submucosa, especially in the endothelium and around the capillaries in the colonic mucosa (Fig 2). Review of the cholecystectomy specimen also showed inclusion bodies in the gall bladder wall. The results of the patient's polymerase chain reaction assay were subsequently found to be positive. The anti-CMV antibody titres showed a 16-fold increase and the urine culture was positive for CMV. These features were compatible with those of cytomegalic inclusion disease. The patient's condition remained poor after the second laparotomy, and he was hypotensive and required inotrope infusion; mechanical ventilation was continued postoperatively. Treatment with CMV-specific immunoglobulin (Cytotect Biotest; Biotest Pharma GmbH, Dreieich, Germany) 100 U/kg on alternate days was given. Serial chest radiography showed progressive diffuse mottling of both lung fields. Transbronchial biopsy samples showed the presence

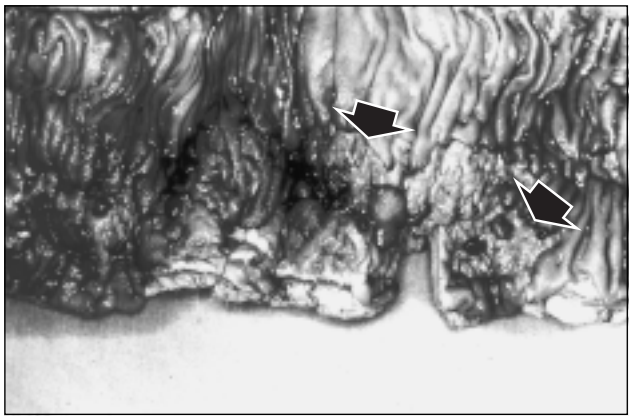

Fig 1. Gross picture of resected specimen from transverse colon showing large longitudinal ulcer (arrows)
The ulcer base was greenish yellow and pseudopolyps were present

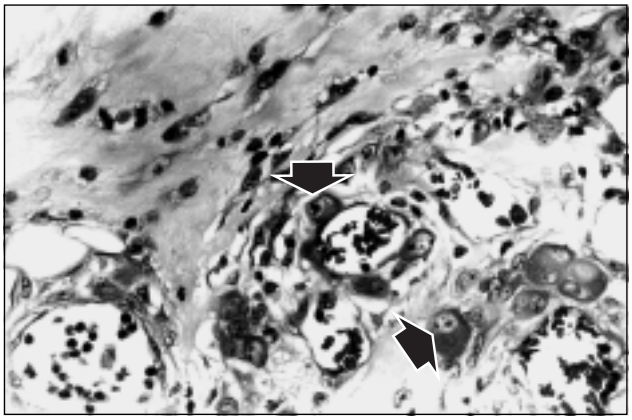

Fig 2. Photomicrograph of section from colonic mucosa showing cytomegalic inclusion disease
A small venule in the colonic mucosa has markedly enlarged endothelial cells owing to the presence of nuclear and cytoplasmic inclusion bodies (arrows) [H&E, x400]

of *Pneumocystis carinii* in the alveoli. Despite intravenous co-trimoxazole therapy, the patient died 12 weeks after the kidney transplantation.

Discussion

Although the success rate of transplantation has risen in the past few decades, the incidence of cytomegalic inclusion disease has remained unchanged due to the use of potent immunosuppressive drugs. The manifestation and severity of GI cytomegalic inclusion disease during organ transplantation can vary. In patients with heart or heart-lung transplants who develop cytomegalic inclusion disease, GI involvement often occurs. Kaplan et al[3] found that among 101 patients with heart or heart-lung transplants, 10 had GI cytomegalic inclusion disease. Eight patients had non-specific symptoms of the upper GI tract, one patient had perforated pyloric ulceration, and one had intractable haemorrhage from the caecum. None of the 10 patients had disseminated organ involvement and all were given ganciclovir. The patient who had caecal haemorrhage died from a fungal infection, whereas the other patients survived.

In renal transplant patients with cytomegalic inclusion disease, the lung is the most frequently affected organ, and GI involvement is much less common. The incidence of colonic complications in renal transplant recipients was reported to be 2.3% by Archibald et al,[4] who reviewed 12 such studies. Complications included perforation of diverticuli, spontaneous perforation, pneumatosis cystoides intestinalis, ischaemic colitis, infarction, pseudomembranous colitis, ulceration, and faecal impaction. The role of CMV in these lesions is not known. Foucar et al[5] reported that among 964 recipients of renal transplants, six had CMV colonic ulceration. The six patients presented with GI bleeding from haemorrhagic ulceration that involved the ascending and transverse colon. The pretransplant CMV status of the patients and donors was not mentioned, however. Widespread organ damage due to CMV was found during the post-mortem examination and involved the lungs, liver, central nervous system, small intestines, and kidney.[5]

Compared with reactivation/reinfection, primary infection with CMV usually leads to more severe disease. The patient in this case report, however, tested positive for antibodies against CMV and had received a kidney from a donor who was seropositive for CMV, thus illustrating that reactivation/reinfection can be equally fulminant. In the series of Foucar et al,[5] which preceded the ganciclovir era, none of the patients with GI cytomegalic inclusion disease survived. In the series of Kaplan et al,[3] all patients with upper GI tract cytomegalic inclusion disease responded to ganciclovir treatment, whereas the patient who had caecal haemorrhage died. The patient in this case report received a cadaveric renal transplant and presented first with an upper GI complication in the form of perforated duodenal ulceration. Although a biopsy sample was not taken from the duodenum during the patch repair, histological examination of a sample that was removed from the gall bladder during the same operation showed CMV inclusion bodies. The duodenal ulceration was also likely to be the result of cytomegalic inclusion disease. Furthermore, the patient subsequently had massive lower GI bleeding that was caused by extensive colonic ulceration. The lesion was similar to those described by Foucar et al,[5] in that the ulceration started distal to the ileocaecal junction and extended to the ascending and transverse colon. The patient failed to respond to both ganciclovir and anti-CMV immunoglobulin. Despite appropriate therapy, lower GI tract cytomegalic inclusion disease is associated with a poor outcome.[3-5]

We have described a CMV-seropositive patient who developed GI manifestations of cytomegalic inclusion disease and extensive colonic ulceration that caused massive GI bleeding. The GI manifestation included cytomegalic inclusion disease of the gall bladder and probably also duodenal involvement that caused perforation of the duodenal ulcer. Although this was a reactivation/reinfection of a CMV infection, the patient died despite treatment with ganciclovir and anti-CMV immunoglobulin.

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