Clinical Problems

Ileocolonic Problems after Cadaveric Renal Transplantation

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British Medical Journal, 1972, 1, 99-101

Summary

Fatal colonic complications in five patients after cadaveric renal transplantation were all due to ischaemia of the bowel wall, which in two cases had led to multiple perforation. In two the lesions involved the whole colon and in three they were segmental.

Introduction

Intra-abdominal emergencies are not uncommon in the recipients of renal transplants. Most of the complications have been attributed to immunosuppression, particularly to the use of corticosteroids,[1] or uraemia.[2] We report the cases of five patients with fatal acute ileocolonic disease in a series of 42 cadaveric renal transplants.

Case 1

Four years after developing malignant hypertension a 39-year-old man required haemodialysis for renal failure. Three months later he received a cadaveric renal transplant from an ABO-compatible donor. Dialysis was discontinued during the second posttransplant week and immunosuppressive therapy with azathioprine and prednisone was given. Six weeks after the operation he developed a febrile illness associated with impaired graft function which was treated by increasing the prednisone dosage to 200 mg daily for one week and reducing it thereafter. In retrospect this illness was probably a cytomegalovirus infection and not rejection.

Towards the end of the first posttransplant year the hypertension became more difficult to control despite a low salt diet and methyldopa. Treatment with prednisone 25 mg and azathioprine 150 mg daily held his renal function stable, with a blood urea of 100-130 mg/100 ml and a serum creatinine of 2·0-3·0 mg/100 ml. Eighteen months after transplantation he presented with continuous pain for six hours in the left iliac fossa, the opposite side to the transplant. There was no vomiting or bowel disturbance. Abdominal examination elicited tenderness in the left iliac fossa without guarding or rebound tenderness. Rectal examination was negative. Radiographs of the abdomen showed gas in the small and large bowel down to the rectum and no signs of visceral perforation. His general condition deteriorated rapidly and he died 36 hours after the onset of the illness.

At necrospy the peritoneal cavity was found to contain 500 ml of blood-stained fluid, and multiple fibrinous adhesions were present between loops of small bowel. The sigmoid colon showed many ischaemic areas less than 0·5 cm in diameter involving the full thickness of the bowel wall, several of which had perforated (Figs. 1 and 2). Multiple colonic diverticulae were present but these were not the sites of inflammation or perforation.

Histologically the colonic lesion showed necrosis and thrombosis of submucosal and subserosal vessels. The presence of calcified occluded submucosal vessels indicated previous ischaemia. Clumps of bacteria were present in parts. A small mesenteric artery showed cellular intimal fibrosis associated with a considerable degree of narrowing. The features were those of ischaemic necrosis of the colon associated with mesenteric vascular disease.

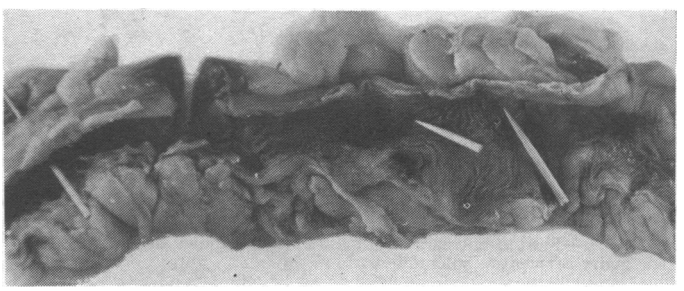

FIG. 1—Sigmoid colon from Case 1. The two right-hand markers point to diverticuli which were not inflamed, infarcted, or the site of perforation. The left-hand marker and the excised area were perforations through segments of infarcted bowel.

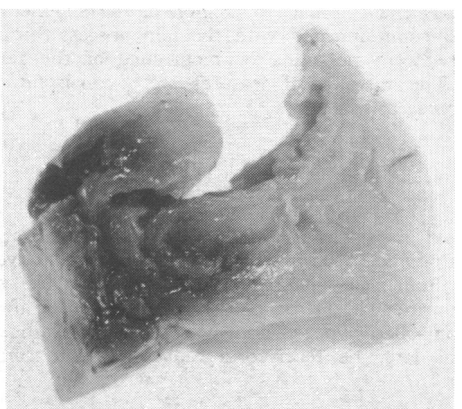

FIG. 2—Close-up view of perforated infarct of the sigmoid colon from Case 1. Note focal nature of lesion.

Case 2

Soon after a left nephrectomy and radiotherapy for renal adenocarcinoma a 32-year-old woman developed impaired function of her right kidney. After four years chronic haemodialysis was started because of uraemia and hypertension. Three months later she received a cadaveric renal transplant and standard immunosuppression with azathioprine and prednisone. There were no recognized rejection episodes and renal function was excellent. Four months after transplantation she complained of left loin pain but there were no abnormal clinical signs. The pain was intermittent and the loin became slightly tender during the en-

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suing weeks. Six weeks after the onset of the pain she was admitted to hospital with a rigor (temperature 104°F; 40°C). A chest radiograph showed bilateral basal effusions and her urine contained pus cells. The temperature settled rapidly with antibiotics and increased steroid dosage.

Three weeks later the left loin became tender and swollen with cutaneous oedema. Needle aspiration of the left loin produced faecal fluid. A barium-enema film showed a large paracolic abscess (Fig. 3). At operation there were three colonic perforations in the region of the splenic flexure. A transverse colostomy with drainage

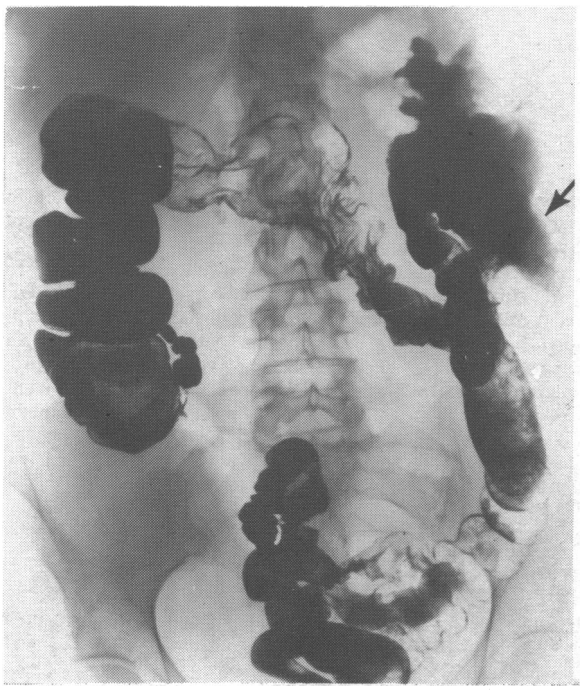

FIG. 3—Barium-enema film of Case 2. Arrow shows large abscess cavity adjacent to splenic flexure.

of the abscess was performed. Twelve days postoperatively she had a massive haematemesis and melaena from a duodenal ulcer and died despite vagotomy and pyloroplasty.

At necropsy the colon in the region of the splenic flexure was necrotic and communicated with the loin abscess through several holes. There were no signs of recurrence of the renal adenocarcinoma. The histological features were consistent with those of ischaemic necrosis.

Case 3

A 19-year-old man was found to have proteinuria at a routine medical examination. Renal biopsy showed proliferative glomerulonephritis. Four years later he was azotaemic. He was treated with azathioprine without benefit. At the age of 25, after a period of poorly-controlled hypertension, he started chronic haemodialysis. Two months later he received a cadaveric renal transplant. He

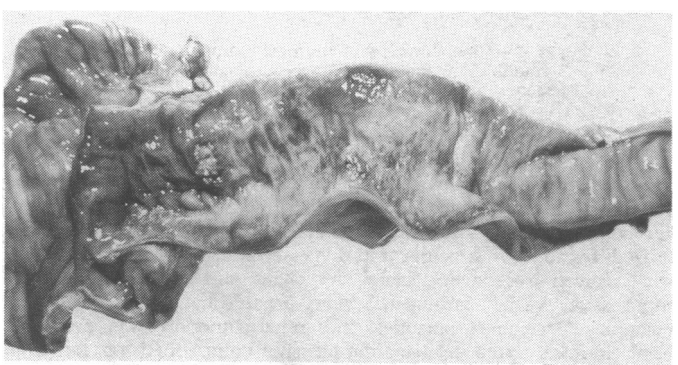

FIG. 4—Ileocaecal region of Case 3. The caecum is to the left and the ileum to the right. The mucosa is grossly oedematous, with areas of ulceration.

was treated for two rejection episodes during the first six weeks. The blood urea never fell below 90 mg/100 ml and the prednisone dosage was always over 50 mg daily.

Six weeks after transplantation he was admitted to hospital with a sudden attack of persistent upper abdominal pain. He was hypotensive and there was epigastric guarding. In view of the high steroid dose a perforated peptic ulcer was suspected. There was no radiological evidence of this. Treatment with intravenous fluids and antibiotics was given. Blood cultures grew *Clostridium welchii*, but despite massive doses of antibiotics he died.

At necropsy the peritoneum contained 300 ml of clear, straw-coloured fluid. There were fibrinous adhesions over the bowel wall. The terminal ileum, caecum, and ascending colon showed external serosal congestion and oedema. The mucosa was congested and oedematous with patchy ulceration, the whole giving a rather cobblestone appearance (Fig. 4).

Histologically the intestinal sections showed necrosis, oedema, haemorrhage, and necrosis of the muscularis mucosa. There was also necrosis of the walls of vessels. Clumps of Gram-positive bacilli were noted on the surface. The features were those of an ischaemic lesion in the form of ischaemic necrosis associated with *Clostridium welchii* proliferation.

Case 4

A woman aged 39 received a cadaveric renal transplant after a seven-year history of pyelonephritis associated with gross vesicoureteric reflux. Twice-weekly haemodialysis had been performed for four years before transplantation. She suffered from severe renal osteodystrophy and chronic bronchitis but was normotensive. Two months before operation she had a single small haematemesis not associated with indigestion. Barium-meal examination showed spasm of the first part of the duodenum. In view of these findings conservative treatment was indicated and it was not regarded as a contraindication to transplantation.

Six days after transplantation she vomited a small amount of blood and later passed a large melaena stool. Her condition deteriorated during the ensuing five days. She became unconscious, with the clinical signs of an intercerebral bleed. She started to pass blood in the urine and from the vagina, though haematological examination showed no deficiency of clotting factors. She died 11 days after transplantation and permission was granted for only a limited necropsy. This showed a moderately dilated large bowel containing a large volume of altered blood. Macroscopically there were many shallow ulcers throughout the colonic mucosa.

Histological examination showed multiple foci of ulceration associated with haemorrhagic fibrinoid necrosis of mucosal and submucosal vessels. Some of the vessels showed necrotizing angiitis and phlebitis. A few areas of regenerating epithelium were noted in the mucosa. All these findings were consistent with a diagnosis of ischaemic colitis. There was no evidence of a systemic angiitis.

Case 5

A 34-year-old man had been diagnosed in 1965 as suffering from chronic renal failure due to polycystic disease. Home dialysis was complicated by repeated problems due to clotting of his arteriovenous shunts. He was therefore admitted to the transplant programme. The first graft, inserted in April 1970, failed to function and was removed and home dialysis was reinstituted. In January 1971 a second transplant operation was performed. Histological examination of the biopsy specimen taken 30 minutes after completing the anastomosis showed an increased number of polymorphs in the glomerular capillaries due to graft rejection. A second biopsy 12 days after transplantation confirmed a severe acute rejection reaction. The second graft was therefore removed and immunosuppression stopped. After this he had diarrhoea associated with mild colicky abdominal pain and some vomiting. The stools consisted of fluid faeces not containing blood, and no abnormal organisms were found on bacteriological examination. His condition deteriorated and he died six weeks after the second transplant operation.

At necropsy it was found that almost the entire mucosa had been sloughed from the large bowel; in several areas the serosa was deeply congested but there was no perforation.

Comment

Five cases of acute colonic problems after transplantation are presented to illustrate their similarities and differences. The cause and duration of renal failure was different in each case. None of the patients had a history of bowel upset before treatment, and though constipation is common in patients on dialysis these five were not unusually affected. Gastrointestinal complications in patients receiving corticosteroids and adrenocorticotrophic hormone have been recognized for more than two decades.[3] The incidence of peptic ulceration in patients on corticosteroids was estimated to be 31% compared with 5% in control groups. Usually there are reports of a single or a few cases, with bleeding being more common than perforation.[4-7]

The total dose of steroids given to transplanted patients depends on the time since operation and the number and severity of rejection episodes. Though the doses used in this series may appear large (see Table) they did not differ significantly from those given to other patients treated in this or other units over the same period. Further, Cases 2, 4, and 5 received steriods for only six, three, and two weeks respectively. The interesting feature of Cases 1 and 2 was the multiplicity of the perforations, for though colonic perforations have been described due to steroid therapy[8 9] they were all solitary lesions (Fig. 5).

Mean Daily Doses of Prednisone and Azathioprine after Renal Transplantation

Case No. ..	1	2	3	4	5
Prednisone (mg) ..	24	25	69	75	78
Azathioprine (mg) ..	151	110	46	73	75

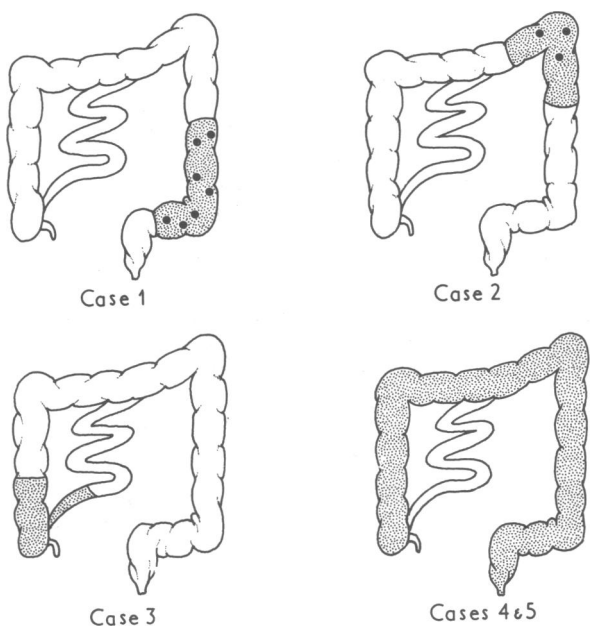

FIG. 5—Areas affected by ischaemic colonic lesions. Sites of perforation are shown for Cases 1 and 2. Only Cases 4 and 5 presented bowel symptoms.

Azathioprine can cause gastrointestinal side effects[2] but there have not been any reports of colonic perforation attributed to the drug. A similar lesion was reported in a series of 11 renal transplant patients who received prednisone, antilymphocyte globulin, and cyclophosphamide, not azathioprine, for immunosuppression.[10] Prednisone and azathioprine have been used in combination to treat the nephrotic syndrome and ulcerative colitis but there is no report of colonic perforation in these series. Azathioprine with or without prednisone is therefore probably not aetiologically significant. Only one of the patients had any evidence of fungal infection or cytomegalic disease.

Uraemia can cause bowel symptoms, particularly diarrhoea, but only two of the five patients had raised blood urea levels. Three of the patients did not at any time complain of a bowel disturbance.

One patient (Case 2) had received radiotherapy to the left renal bed which would of necessity have included the splenic flexure, where the perforations were to occur more than four years later. Though it must be considered, irradiation was unlikely to be the cause of her colonic perforations because of the long time interval and the rarity of this complication in other patients receiving this therapy. It may have rendered this part of the colon more susceptible to further ischaemia.

Hypovolaemia is a cause of intravascular thrombosis leading to colonic perforation in atherosclerotic patients, but it can be regarded as a factor only if the complication occurs within one week of hypotension. Though these patients in common with others on haemodialysis suffered from periods of low blood pressure during dialysis only Case 4 had such episodes in the week before presentation.

Unlike the colonic lesions described after aortic surgery these lesions cannot be attributed to surgical interference with the inferior mesenteric or middle colic arteries. The principal aetiological factor appears to be vascular disease associated with endarteritis or fibrosis and arterial occlusion. It is difficult to explain why the colon suffers more than other organs, for necropsy findings in these five patients failed to show gross changes in any other organ comparable to those found in the colon. All patients undergoing renal transplantation have arterial degeneration and often hypercholestrolaemia in advance of their years, the five reported cases being no worse than average. Three of the five patients were intermittently hypertensive. Histologically the lesions were very similar in that there was extensive necrosis of the bowel wall with thrombosis of small arteries and veins.

We have been unable to explain why colonic problems developed in these five patients out of a series of 42 renal transplants, but we wish to draw attention to the possibility in patients with abdominal symptoms and rapid circulatory collapse. Urgent investigation including sigmoidoscopy and contrast radiography and laparotomy is indicated when the diagnosis is entertained as neither we nor Penn[1] have noted any survivors of this complication.

We would like to thank Dr. P. Hollingworth for performing the necropsies on these patients.

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