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Gastrointestinal surgical emergencies following kidney transplantation

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Abstract. This study reports major gastrointestinal complications in a group of 416 patients following kidney transplantation. Three hundred and ninety-nine patients received a cadaveric kidney while the other 17 received a living related organ. The immunosuppressive regimen changed somewhat during the course of the study but included azathioprine, prednisolone, antilymphocyte globulin, and cyclosporin. Perforations occurred in the colon ($n = 6$), small bowel ($n = 4$), duodenum ($n = 2$), stomach ($n = 1$), and esophagus ($n = 1$). There were five cases of acute pancreatitis, four of upper gastrointestinal and two of lower intestinal hemorrhage, two of acute appendicitis, one of acute cholecystitis, one postoperative mesenteric infarction, and two small bowel obstructions. Fifty percent of the complications occurred while patients were being given high-dose immunosuppression to manage either the early postoperative period or episodes of acute rejection. Ten percent of the complications had an iatrogenic cause. Of the 31 patients affected, 10 (30%) died as a direct result of their gastrointestinal complication. This high mortality appears to be related to the effects of the immunosuppression and the associated response to sepsis. Reduction of these complications can be achieved by improved surgical management, preventive measures, prompt diagnosis, and a reduced immunosuppressive protocol.

Key words: Kidney transplantation, GI complications – Gastrointestinal complications, kidney transplantation

Introduction

In patients who undergo kidney transplantation, gastrointestinal complications are the second most common events after infection [15]. These complications, which occur in patients with impaired defense mechanisms due to immunosuppression, have a high mortality [17, 23]. Steroids and immunosuppressive agents delay the diagnosis by masking the classical signs of inflammation in response to infection, leading to overwhelming sepsis, and death. The mortality rate of gastrointestinal perforation or sepsis varies on case selection, with higher mortality rates – between 50% and 75% – in major colonic necrosis and perforation [32]. This study documents the pattern of these complications and their outcome in 416 patients undergoing kidney transplantation over a 19-year period.

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Materials and methods

Patient population

From March 1972 to October 1991, 416 patients (250 men, 166 women; median age 31 ± 10 years, range 4–64 years) underwent kidney transplantation in our institution. Seventeen patients received living related kidneys, the remainder cadaveric ones. Forty patients received a second graft (9.6%) and six patients a third one (1.4%). Twelve patients (2.9%) died within 30 days of transplantation of causes unrelated to gastrointestinal complications.

Immunosuppression

Up until 1983, immunosuppressive treatment consisted of azathioprine, prednisolone, and antilymphocyte globulin.

Prednisolone. The first 12 patients transplanted were given prednisolone at a dose of 200 mg, diminishing to 35 mg by the end of the 1st month. After July 1972, prednisolone was started at 60 mg orally, diminishing in 5-mg increments to a dose of 30 mg by the end of the 1st month and, subsequently, to 20 mg at the end of the 1st year. Starting in July 1984, prednisolone was commenced at 55 mg per day; it was subsequently reduced to 25 mg at the end of the 1st month and to 15 mg at the end of the 1st year.

Azathioprine. Azathioprine was started at 5 mg/kg on the 1st day and then adjusted to the white cell count, usually between 1 and 2 mg/kg.

Antilymphocyte globulin. Antilymphocyte globulin (ALG) was administered intravenously at 10 mg/kg per day for the first 15 days and subsequently intramuscularly at 2–3 mg/kg per day on alternate days for another 15 days. Two doses per week were then commenced for the remaining 3 months. As part of a prospective, randomized trial, 15 patients did not receive ALG [20].

Cyclosporin. In 1983, cyclosporin was introduced in place of azathioprine for patients who, during the follow-up, developed diabetes.

aseptic necrosis of the femoral head, Cushing's syndrome, or hepatic failure. It was introduced at 10 mg/kg per day and was tapered to a maintenance level of 6 mg/kg per day, depending on systemic cyclosporin concentration. Ideal cyclosporin levels are in the range of 100–150 mg/ml (plasma RIA). In 1988, cyclosporin was commenced after cessation of ALG, which was itself reduced to only 2 weeks postoperatively at 10 mg/kg per day intravenously.

All rejections were treated with intravenous prednisolone, followed by high-dose oral treatment of 120 mg for 3 days, 90 mg for 3 days, 60 mg for 3 days, and 45 mg for 3 days, with subsequent diminution to the prerejection dose. After 1987, failure of this regimen led to "rescue" with the monoclonal antibody OKT3.

Complications

All patients were managed within our institution and any complications resulted in immediate referral to the transplant service. All complications were then diagnosed and managed by that service. Operative, diagnostic, laboratory, and postoperative details were available for all patients presenting with gastrointestinal complications.

Results

In the surviving postoperative patient group of 404 patients, 31 major gastrointestinal complications occurred over the 19-year period.

Perforations

Colon. Table 1 documents the details and outcome of the six colonic perforations. All patients had cadaveric grafts, and two of these were second grafts. Renal function was normal in five cases at the time of perforation with one patient receiving high-dose steroids for irreversible rejection. The perforation in five patients was due to sigmoid diverticulitis, with the other occurring after an attempt to drain a perirenal collection. The drain caused an erosion into the sigmoid. Treatment varied over the years and included: oversewing of perforation and colostomy with subsequent sigmoid resection, a Hartmann procedure, a colostomy with mucous fistula, a cecostomy, and exteriorization of the perforation for the iatrogenic erosion. There was only one perforation diagnosed post mortem.

Small bowel. Perforation of the small bowel occurred in four patients (Table 1). In one patient, the perforation was spontaneous and two were iatrogenic. One was due to erosion of a Tenkoff catheter at the time an acute rejection was being managed by high-dose steroids; the other occurred after an attempt to drain a lymphocele following a second kidney transplant. In both cases, a temporary ileostomy was performed with subsequent closure; both patients survived. The fourth patient developed duodenal and small bowel lymphoma, which led to perforation, peritonitis, and fatal sepsis.

Duodenum. Two duodenal perforations (Table 1) occurred during episodes of high-dose steroid treatment for acute rejection. There was no previous history of ulcer disease, and both patients received regular prophylactic antacids. One patient was treated by oversewing of the ulcer and the other by excision and suture with a highly selective vagotomy. This patient subsequently developed a gastric outlet obstruction that required pyloroplasty.

Stomach. There was one gastric perforation (Table 1) at the lesser curvature that was discovered incidentally during a bilateral nephrectomy and transplantectomy for hypertensive encephalopathy in a patient with recurrence of his original disease. At the time he was receiving high-dose steroids for an acute rejection and had reduced his own intake of antacids. The perforation had been sealed locally by the liver. During the operation, it was mobilized from the liver and oversewn.

Esophagus. One case of esophageal perforation occurred in the lower esophagus secondary to intractable hiccups in a patient with a second kidney and in acute rejection for a third time. Treatment required exclusion, cervical esophagostomy, and gastrostomy because of the size of the esophageal defect.

Hemorrhage

Upper gastrointestinal hemorrhage. Table 2 documents the four patients with upper gastrointestinal hemorrhage. The gastric hemorrhages responded to anti-H2 receptor treatment. The duodenal hemorrhage required, in one case, oversewing of the bleeding ulcer and, in the other, a pyloroplasty and truncal vagotomy. The fourth patient de-

Table 1. Perforations

	Sex	Age (years)	Original disease	Time after transplantation	Etiology	Outcome
Colon	M	57	Glomerulonephritis	13 years	Sigmoid diverticulis	Alive
	M	49	Familial nephropathy	6 years	Sigmoid diverticulis	Died of sepsis
	M	37	Glomerulonephritis	2 months	Sigmoid diverticulis	Died of sepsis
	M	59	Polycystic kidney	3 weeks	Sigmoid diverticulis	Died of sepsis
	M	29	Chronic pyelonephritis	16 days	Sigmoid diverticulis	Died of cardiac arrest
	F	28	Chronic pyelonephritis	2 months	Iatrogenic	Alive
Small bowel	F	64	Polycystic kidney	3 months	Iatrogenic	Alive
	M	30	Glomerulonephritis	15 days	Spontaneous	Alive
	F	39	Glomerulonephritis	27 days	Iatrogenic	Alive
	F	41	Polycystic kidney	3 months	Spontaneous (lymphoma)	Died
Duodenum	M	44	Unknown	15 days	Peptic ulcer	Alive
	F	9	Glomerulonephritis	36 days	Peptic ulcer	Alive
Stomach	M	46	Hypertensive nephritis	30 days	Peptic ulcer	Alive
Esophagus	M	25	Chronic pyelonephritis	6 months	Boerhaave's syndrome	Died

Table 2. Hemorrhages

	Sex	Age (years)	Original Disease	Time after transplantation	Pathology	Treatment	Outcome
Upper	F	28	Chronic pyelonephritis	8 days	Prepyloric ulcer	anti-H2	Healing
	F	31	Polycystic kidney	31 months	Acute fundic gastritis	anti-H2	Healing
	F	54	Glomerulonephritis	8,5 years	Duodenal ulcer	Suture, vagotomy, pyloroplasty	Healing
	M	57	Glomerulonephritis	15 years	Hepatic veno-occlusive disease	Liver transplant	Died of sepsis
Lower	F	46	Unknown	55 days	Rectitis	Sulfasalazine	Healing
	F	34	Hypertension	39 months	Sigmoid aphtoid ulceration		Healing

Table 3. Acute pancreatitis

Sex	Age (years)	Original disease	Time after transplantation	Suspected etiology	Treatment	Outcome
M	54	Toxic nephropathy	2 weeks	Obesity	Cholecystectomy and drainage	Alive
M	23	Chronic pyelonephritis	7 weeks	–	Cholecystostomy and drainage	Died of sepsis
F	33	Glomerulonephritis	2 months	–	Cystogastrostomy	Alive
M	28	Glomerulonephritis	6 months	Hypercalcemia	Necrosectomies	Died of sepsis
F	30	Hypertensive nephritis	10 months	Hypercalcemia	Medical	Alive

veloped veno-occlusive liver disease following treatment with azathioprine. He subsequently developed portal hypertension with fundal gastric varices and hemorrhage. This was successfully controlled by conservative medical treatment; however, due to further variceal bleeding, a portocaval shunt was attempted. During the operation, a small atrophic liver was found and the decision was made to perform a hepatic transplant. During the post-transplant hospitalization, the patient developed an infection and died 6 weeks postoperatively.

Lower gastrointestinal hemorrhage. Table 2 also shows the two patients with lower gastrointestinal hemorrhage due, in one case, to ulcerating rectal disease and, in the other, to sigmoid ulceration. One of these patients was undergoing treatment for acute rejection at the time of the hemorrhage. There was no evidence of cytomegalovirus infection or Crohn's disease in either patient. Both patients were successfully managed medically.

Pancreatitis

Five patients developed severe pancreatitis, but in none of them was it associated with cholelithiasis or abnormal alcohol intake. The suspected etiology in each case is shown in Table 3. Three of these patients were hospitalized and undergoing treatment for acute rejection at the time of the pancreatitis attack. Only one patient was managed without surgery. In four patients, surgery was performed and included: a cholecystectomy and drainage of the prepancreatic space, a cholecystostomy and drainage of the prepancreatic space, a cystogastrostomy, and elective necrosectomy.

Appendicitis

Two female patients, aged 20 and 42 years, developed acute appendicitis 10 months and 38 months, respectively, after cadaveric transplantation. One was suffering from chronic rejection. Both underwent surgery within 24 h of presenting symptoms. Their postoperative recovery was uneventful.

Cholecystitis

Cholecystitis occurred in one 42-year-old male patient 6 months after receiving a cadaveric transplant. He was treated by cholecystectomy.

Obstruction

Obstruction of the small bowel occurred in two patients. A 40-year-old female developed an obstruction 6 years after a cadaveric graft due to adhesions from previous abdominal surgery. Surgical release of the adhesions led to an uneventful recovery. A 64-year-old male developed an incarcerated inguinal hernia with obstruction 6 weeks after receiving a cadaveric graft and he was treated by a surgical repair (Shouldice).

Mesenteric infarction

Sixteen years after cadaveric kidney transplantation, a 49-year-old female developed a ruptured renal artery aneurysm, which was initially managed by embolization and the following day by a transplant nephrectomy. Two days later, she developed a mesenteric infarction with necrosis of the left colon and left transverse colon, as well as of the distal 70 cm of the terminal ileum. She underwent total colectomy and resection of the ischemic ileum with formation of a rectal stump and ileostomy. She died 10 days later from irreversible multiorgan failure.

Discussion

Ten deaths occurred in the group of patients with 31 gastrointestinal complications, resulting in a 30% mortality rate. This emphasizes the serious, and often life-threatening, nature of such complications in patients receiving immunosuppression following renal transplantation. Similar

Table 4. Gastrointestinal (GI) complications. $P > 0.05$ (chi^2 test)

Etiology	Pred + Aza ($n = 295$)	Cyclosporin ($n = 121$)	
Perforation:			
Esophagus	1	–	
Stomach	1	–	
Duodenum	2	–	
Small bowel	1	3	
Colon	6	–	
Hemorrhage			
Upper GI	3	1	
Lower GI	2	–	
Appendicitis	1	1	
Cholecystitis	1	–	
Intestinal obstruction	1	1	
Mesenteric infarction	1	–	
Acute pancreatitis	4	1	
Total	24	7	P > 0.05

results ranging from 30% to 75% have been reported by others [30]. These complications occurred in 30% of the patients during the first 3 months after transplantation, which corresponds to the period of high-dose immunosuppression. In addition, 20% of the patients developed their gastrointestinal complications during high-dose steroid immunosuppression for acute rejection.

The introduction of cyclosporin virtually revolutionized the field of kidney transplantation, preventing acute and chronic rejection while minimizing infectious diseases [18]. Nevertheless, since the systematic introduction of cyclosporin in 1988, there has not been a lower incidence of major gastrointestinal complications, and this despite the fewer episodes of acute rejection and the lower doses of prednisolone used ($P < 0.05$; Table 4).

The most severe and frequent gastrointestinal complication in our patient population was colonic perforation. This was secondary to diverticular disease in five out of six cases. This complication is often masked by the accompanying steroid treatment [1, 26, 33], and the delay in diagnosis may in part explain the high mortality observed in four of the six cases. Renal transplantation patients have a predisposition to constipation due to ingestion of aluminum-containing antacids, inactivity, dehydration, and electrolyte imbalance [4, 11, 24]. Moreover, it is known that young uremic patients have a high incidence of diverticular disease [3, 16], as illustrated by two of our six patients aged 29 and 37 years old. This is alleged to be due to decreased tissue strength, autonomic nervous system dysfunction, or chronic constipation in these uremic patients.

The incidence of colon perforation in an immunosuppressed group of patients is higher than that in a group that has not been immunosuppressed. In a recent study in patients with complicated diverticular disease, there was a strong association between corticosteroid or nonsteroidal anti-inflammatory drugs and the most serious complications [6]. Many of the immunosuppressive agents exert an action that is capable of adversely altering gastrointestinal function and gastrointestinal histological integrity [31].

Diverticulitis remains the most common cause of colon perforation in renal transplant recipients, and it is associated with high mortality. Polycystic kidney disease [34] has also been reported to have a high incidence of diverticular disease and was present in one of our patients. CMV virus has also been implicated as causing colon perforation [9, 13]. However, this was not found to be present in our group. We disposed of the serology of only two patients (complement-fixing antibody < 1 : 8). For the other patients, bowel perforation appeared at a time when diagnosis of CMV disease was done by culture alone. Nevertheless, CMV was not identified in undamaged colonic mucosa.

Iatrogenic causes of perforation occurred in three of our patients (two small bowel, one colonic). Two of these followed erosion of the bowel wall from drains placed intra-abdominally. It may be that impaired healing mechanisms in such patients lead to a higher than expected incidence of drain-induced perforations [15].

Duodenal perforations were associated with periods of high-dose steroids for acute rejection in both cases. A case can be made for increased antiulcer medication during periods of treatment of rejection to perhaps reduce this complication. We routinely use 30 ml antacid every 2 h in such patients.

Gastrointestinal hemorrhage has been reported to occur in over 20% of all patients following renal transplantation [22, 27]. Bleeding is a notably lethal complication, although in our series only one of the six patients died. Factors contributing to gastrointestinal hemorrhage in post-transplant patients include: gastric hypersecretion, hypergastrinemia, the suppression of platelet factor III in azotemia, immunosuppression-induced thrombocytopenia, the use of platelet inhibitors (e.g., azathioprine), anticoagulants for the treatment of rejection, and the use of heparin for dialysis when renal function is impaired [2, 14, 19, 25, 36]. We recommend prophylactic surgery for patients with known ulcer disease prior to transplantation [7, 37]. We have reported this in 79 patients in a transplanted group of patients with no subsequent symptomatic ulcer disease [21]. CMV infections of the gastrointestinal tract in transplant patients usually manifest themselves as focal areas of erythematous erosions and ulcerations, in addition to moderate diarrhea, weight loss, and severe gastroenterocolitis with intestinal or colonic perforation [5, 9, 10]. However, these findings were not present in our group of patients.

Pancreatitis following renal transplantation is reported to occur in 0.4%–7.0% of all cases and to have a mortality of 20% [8, 38]. Etiological factors suggested include immunosuppressive medications, viral infections, postoperative hyperparathyroidism, and vasculitis [12, 28, 29, 35]. In our group, the use of azathioprine and prednisolone may have predisposed patients to pancreatitis. However, hypercalcemia was also present in two patients and hyperlipidemia in another. Of interest is the lack of the classical causes of cholelithiasis or alcohol.

The two patients with acute appendicitis fortunately presented early and were successfully treated without any further event. The preoperative diagnosis was suggested by a thorough history and physical examination. These two women underwent an abdominal ultrasound examination with additional pelvic scanning to search for pathological pelvic characteristics. Plain abdominal films were

normal. The high index of suspicion of appendicitis led us to early surgical removal of the inflamed appendix. The diagnosis of cholecystitis was also suggested by history, physical examination, laboraty findings (elevated white cell count and liver enzymes), and ultrasonography. These abdominal emergencies do not appear to be particularly related to post-transplant patients [32].

An appreciation of the range and severity of gastrointestinal complications following kidney transplantation is important if a reduction in the associated mortality is to be achieved. Iatrogenic causes in our group could have been prevented, and this illustrates the great care that is required in placing and using drains in steroid-treated patients. Furthermore, 50 % of the surgical emergencies occurred during the first 3 months following transplantation, which is a critical period and requires constant vigilance.

Finally, attention should be focused on the prevention or early diagnosis of complications during treatment of acute rejection, when 20 % of our group experienced a gastrointestinal emergency. It is to be hoped that improved immunosuppressive regimens will reduce the incidence of acute rejection and the associated complications.

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