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Gastrointestinal complications in renal transplantation

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Abstract. One wonders whether the use of cyclosporin, histamine receptor antagonists, low doses of steroids, and early diagnosis and treatment actually modify the incidence, morbidity, and mortality of gastrointestinal (GI) and pancreatic complications in renal transplantation. To find out, we reviewed 614 kidney transplant recipients between January 1984 and December 1988. One hundred patients (16.2%) were found to have GI and/or pancreatic complications in the following distribution: 9.6% gastroduodenal, 1.3% pancreatic, 4% colonic, and 0.4% small bowel. None of the patients presenting a gastroduodenal ulcer had perforation or bleeding. Fifty-five percent of the patients with this complication had a past history of esogastroduodenal disease, compared to 19.6% in recipients without gastroduodenal complications. Some 4.4% of the patients had a small bowel or a colonic complication and four died of peritonitis due to bowel perforation. Mortality was 35% in those having intestinal resection and/or perforation with peritonitis. Sixteen percent of patients with colonic complications had a known history of diverticula, compared to 3% for those without colonic complications. The incidence of GI and/or pancreatic complications in renal transplant recipients remains high and has caused 1.1% of the deaths in our series. Mortality is essentially due to upper GI bleeding, peritonitis following perforation, and infectious colitis. Better detection of gastroduodenal and colonic disease before transplantation seems to be mandatory. Prevention with histamine H2 receptor antagonists and early surgical treatment of complicated colonic diverticula help to reduce the morbidity and mortality in kidney graft recipients.

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

The incidence of gastrointestinal (GI) complications in kidney transplantation is relatively high, and their prevention depends on the diagnosis of risk factors during the pretransplant evaluation, the systemic screening of GI ulcers and colonic diverticula, the constant use of preventive antiulcer therapy, and the preservation of the hypogastric artery for colonic blood. These complications may be life-threatening and can, in some situations lead, to graft loss or even patient death. Their impact nowadays is less disastrous because of refined surgical techniques and more selective immunosuppression.

This report describes our experience with GI complications in a group of 614 kidney transplant recipients, all of whom were given cyclosporin-based immunosuppression and prophylactic use of cimetidine.

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Materials and methods

The study involved 614 renal recipients, including two combined transplantations (one kidney-pancreas and one kidney-liver), who were transplanted between January 1984 and December 1988. There were 396 men and 218 women and their mean age was 34.6 years. A total of 578 patients had received a cadaveric kidney while 36 patients had grafts from living related donors.

The pretransplant assessment included a detailed questioning about past history of GI disease and a gastroscopy performed at a mean period of 1 year before transplantation. The diagnosis of peptic ulcer implied an immediate medical treatment, and surgery (selective vagotomy) was performed when other treatment failed. The diagnosis of a gall bladder stone implied a cholecystectomy. A barium enema was systematically given to patients over 50 years of age for colonic diverticula screening. Immediately after transplantation, all recipients were started on 400 mg/day cimetidine (an H2 receptor antagonist) for 2 months. In the postoperative period, gastroscopy was performed on every patient complaining of abdominal pain. Immunosuppression consisted of various combinations of cyclosporin (8 mg/kg p.o.), steroids (2 mg/kg tapered off to 0.20 mg/kg at 3 months), azathioprine, and antilymphocyte globulin (ALG).

We classified our GI complications according to whether they were upper mesocolonic (gastric ulcer, duodenal ulcer, upper GI bleeding, acute gastroduodenal mucosal ulceration, esophagitis, and acute pancreatitis) or lower mesocolonic (small bowel and colorectal complications, such as occlusions, perforations, sigmoiditis, lower intestinal bleeding, and appendicitis).

Table 1. Pattern of GI complications

Minor gastroduodenal complications	3 Duodenitis 26 Gastritis 10 Esophagitis
Stress, bleeding, mucosal ulceration	5 Associated with multivisceral failure
Peptic gastric ulcer	19 Uncomplicated
Peptic duodenal ulcer	33 Uncomplicated
Acute pancreatitis	1 Biological 7 Associated with other abdominal complications
Jejunoileal complications	8 Small bowel obstruction
Colonic complications	1 Intestinal tuberculosis 8 Diverticulitis 1 AIDS + candidosis 1 CMV colitis 2 Nonspecific colitis 5 Polyps with bleeding 1 Colonic angiodysplasia

Results

One hundred recipients were found to have one or more GI complications (Tables 1,2).

Upper mesocolonic complications

Nineteen patients had a peptic gastric ulcer with neither perforation nor bleeding, diagnosed by fibroscopy and medically treated with nonabsorbable antacids and cimetidine after a delay of 195 ± 375 days (range 1–360 days); all were cured. Two patients had associated acute pancreatitis, which also completely resolved under medical therapy. Fifty-six percent of these patients had a past history of GI disease, such as peptic ulcers, esophagitis, or acute mucosal ulcerations.

Thirty-three patients had a peptic duodenal ulcer with neither perforation nor bleeding after a delay of 214 ± 348 days (range 5–1050 days) and they were all successfully medically treated. Sixty-one percent had a past history of GI disease: 1 patient had a previous gastrectomy with an anastomotic line recurrence, 12 patients had a history of ulcer, 8 patients had a history of acute gastroduodenal mucosal ulceration and 1 had esophagitis.

Thirty-nine patients had an acute esogastroduodenal mucosal ulceration, all medically treated after a delay of 136 ± 298 days (range 2–1230 days). Eight of these patients had a past history of peptic ulcer, three of whom were operated before transplantation (one vagotomy, one vagotomy plus ulcer suture, and one gastrectomy). In eight cases there was a history of gastroduodenal mucosal ulceration and in four cases a history of esophagitis.

Eight patients presented an acute pancreatitis that was only biological in one case and associated with other complications in the seven remaining recipients: one hemorrhagic colonic angiodysplasia, two gastric ulcers, two duodenal ulcers, and two colonic diverticulitis with one perforation managed by colectomy-colostomy, followed by a septic shock and a bacterial hepatitis (this patient died).

Among the 557 kidney recipients who had no gastroduodenal ulcer, 19.6% (109 patients) were found to have had a past history of gastroduodenal ulcers.

Five patients were found to have upper GI bleeding on a stress gastric mucosal ulceration with other life-threatening complications: cirrhosis with portal hypertension, septic shock with lower limb ischemia, septic pulmonary embolism, postoperative hemorrhagic shock, and CMV colitis. All five of these recipients died of multivesical failure.

In contrast, no patient developed gall bladder disease after the transplantation.

Inframesocolonic complications

Three patients had a jejunoileal complication after a delay of 262 ± 243 days (range 15–500 days). Two intestinal obstructions (adhesive band constriction) were referred to our department late and therefore had delayed surgery (ileal resection plus ileostomy); they died of peritonitis. The third patient had a perforation, which was correctly managed by intestinal resection plus ileostomy.

Twenty-five patients had a colonic complication after a delay of 700 ± 546 days (range 23–144 days). There were 13 cases of colonic diverticular disease, including 8 sigmoid diverticulitis; 7 were medically treated by diet and antibiotics and, in one case, a blank laparotomy was done. One patient had a bleeding sigmoid diverticulum, treated uneventfully by colectomy. Four patients perforated their colonic diverticulum and were managed by colectomy-colostomy. Two of them died, one patient was operated on the 8th day for peritonitis, and another had an acute necrotizing pancreatitis with bacterial hepatitis (the same patient referred to earlier with acute pancreatitis).

Five recipients had septic colitis: one case of AIDS with colonic candidosis (the patient died), one case of CMV colitis with upper GI bleeding (the patient died), one case of perforated intestinal tuberculosis with perineal fistula (the patient died) [5], and two cases of nonspecific colitis which were medically treated.

Five recipients had minor GI bleeding secondary to a colonic polyp, and they were treated successfully by endoscopic resection.

One patient had a colonic angiodysplasia, which was treated by endoscopic electrocoagulation. There was also one case of ulcerated rectitis.

Sixteen percent (4/25) of the patients with colonic complications had a past history of diverticula, compared to 3% (18/589) among those who had no colonic complications.

The mean graft survival in our series was 83% at 1 year, 80% at 2 years, 76% at 3 years, 72% at 4 years, and 69% at 5 years.

Discussion

Serious complications involving the alimentary tract are commonly reported following organ transplantation and may be associated with significant morbidity and mortality. The genesis of these complications is multifactorial.

Table 2. Gastrointestinal complications (stress, mucosal ulceration excluded)

	Number	Age (years)	Sex M/F	Past abdominal history	Acute rejection	Delay (days)	Medical treatment	Surgical treatment	Death
Minor gastroduodenal complications	39	38 ± 11	25/14	+	32/39	136 ± 298	39	0	0
Peptic gastric ulcer	19	43 ± 12	16/3	+	15/19	195 ± 375	19	0	0
Peptic duodenal ulcer	33	39 ± 11	25/8	+	25/33	214 ± 348	33	0	0
Acute pancreatitis	8	47 ± 10	7/1	+	6/8	706 ± 490	7	1	1
Jejunoileal complications	3	36 ± 7	2/1	+	3/3	262 ± 243	0	3 resection ileostomy	2
Colonic complications	25	46 ± 10	20/5	+ +	20/25	700 ± 546	19	5 resection colostomy	3

One hundred of the 614 kidney recipients in our study group were found to have GI complications. In spite of preventive measures taken by an H2 receptor antagoinist, 9.6% of these patients had a gastroduodenal ulcer, which is slightly more than what is reported in the literature. This incidence is comparable to that reported by Musola et al., who also found a 25% rate of endoscopic abnormalities among hemodialysed patients and 36% among kidney transplant recipients not treated with an H2 receptor antagonist [25, 29].

Stuart et al. had a 5% incidence of gastroduodenal perforation with a 50% mortality rate [38]. The 4.7% complication rate decreased to 0.8% after the systematic use of an H2 receptor antagonist. In Garvin et al.'s study [12], the prophylactic use of antacids plus an H2 receptor antagonist reduced mortality from 22% to 0%. We believe that the introduction of cyclosporin and consecutive steroid reduction, associated with preventive H2 receptor antagonist, helped to significantly lower the mortality rate due to gastroduodenal ulcers; this mortality reached 50% in previous historical publications [14, 22]. Corticosteroid sparing maintenance immunosuppression seems to give fewer GI complications with a lower mortality rate [7, 23]. The transient toxic effect of an H2 receptor antagonist on the glomerular blood flow does not contraindicate its use in transplant recipients [3, 25, 28].

On the other hand, acute mucosal gastroduodenal ulcerations occurred in 6.3% of all cases, which shows that H2 receptor antagonists reduce ulcer morbidity but do not change the vulnerability of the mucosa after renal transplantation.

The presence of a past GI history (56%–61% of our cases) is a risk factor when compared to the group with no GI antecedents (19.6%). Spanos et al. [37] showed that cases with a past GI history had a 70%–80% chance of recurrence after transplantation. Feduska and colleagues suggested that these patients should be operated before transplantation, but this attitude has changed [8]. In our series, we only operated on ulcers that were resistant to medical treatment, but our results show that in cases with a past history of peptic ulcer, H2 receptor antagonist prevention is inadequate and that a pump proton inhibitor must be used.

As for pancreatitis, our incidence rate of 1.4% is comparable to those reported in the literature [1, 9, 10, 27, 31, 35]. Two patients had an acute necrotizing pancreatitis and several were associated with other complications (colonic diverticulitis, gastroduodenal ulcer, biliary stone). Only one patient in this group died because of infectious hepatitis.

The 4.5% incidence of inframesocolonic complications in our population is high: 0.5% involved the small bowel, 2.7% severe colonic complications (diverticulitis, septic colitis, and perforation), and 1.3% minor colonic problems (polyp bleeding, rectitis, angiodysplasia). Historical series have shown a 3.8% incidence [4, 15, 16, 20, 24, 26]. No acute appendicitis was encountered among our GI recipients with complications, probably due to the mean population age (34 years) and the naturally low incidence of this complication at this age [36, 39].

No ischemic colitis was found and this may perhaps be related to the non-use of the hypogastric artery for arterial anastomosis in the case of a retransplant [11].

The most severe complications in this group were intestinal obstructions and perforations. Increased colonic complications and colonic ischemia were noticed by Bailey et al. [2] and Gomella et al. [13] among immunosuppressed and end-stage renal disease patients. In our study, 18% of the patients who were over 50 years of age and had a known colonic diverticulum showed a complication related to their diverticular disease. This is much higher than the 1% incidence shown by Carson et al. [4].

Colon perforation is the most lethal of all GI complications. In intestinal perforation, our mortality rate due to peritonitis reached 20% [15, 24]. In the series of Pollak et al. on 542 kidney recipients, peritonitis was present in 4.4% of the cases, with a 66% mortality rate. The best results are obtained when early surgery is performed without primary anastomosis but with colostomy in the case of bowel resection [6, 20, 24, 30, 33, 40]. Colonic perforations may complicate kidney transplantation at a variable delay, as shown in our population (1 month to 2 years) and in others [15]. In the study by Flanigan et al., the colonic complications incidence was 0.51% among 587 renal transplant recipients (2 ischemic colitis, 2 pseudomembranous colitis), and of the 2539 cases compiled from numerous literature series, the GI complications incidence was 2.2%, with a 1% ischemic complication. 0.6% colonic diverticulitis, and a 70% mortality rate [11]. In the Cleveland Clinic series, Church et al. report 1.1% colonic

perforation with a 61% mortality rate [6]. Among the 800 renal transplant patients studied by Carson and colleagues, there was a 1.6% colonic perforation, mostly on the sigmoid [4]. The timing was, in 70% of the cases, during the first 3 months following transplantation.

Our policy concerning colonic diverticula screening is applied to patients older than 50 years. The high incidence of colonic complications (16%) in cases of known diverticula may lead us to change our attitude and to perform this screening earlier, on patients over 40 years of age, and to evaluate patients on the waiting list if they are in the fifth decade. When a colonic diverticulum is diagnosed before transplantation with no symptoms, we remain watchful, but if the patient has experienced clinical symptoms before transplantation, a colectomy is indicated [11, 15].

In our colonic perforation group, diagnosis was suspected with one or more of the following signs: abdominal pain, fever (66%), increased white blood cell count (75%), tenderness (66%), and pneumoperitoneum (33%). Our only concern was to have the minimum delay and to perform surgery as soon as possible. The 61% mortality rate in the Carson et al. series was strictly related to treatment delay: when given within 24 h, 66% of the patients were alive, compared to 16% when the delay was longer than 24 h. Another criterion was renal function: a 66% success rate was possible when creatinine was less than 250 µmol/l versus 14% when creatinine was greater than 250 µmol/l [4]. Koneru et al. had almost the same results concerning treatment delay: 86% of their patients were alive when the delay was less than 24 h versus 25% when the delay exceeded 24 h. Our perforation rate in colonic diverticula is high: 30% compared to 1% in the Carson et al. series [18].

Thus, colonic and small bowel complications should be highly suspected, even when the patient shows minor symptoms. The clinical criteria may be very poor in the case of bad renal function and high doses of steroids. A plain abdominal X-ray and a CT scan using colonic opacification with hydrosoluble contrast material and/or peritoneal dialysis will confirm perforation and lead to ~~an~~ emergency surgery [19, 40]. If the plain abdominal X-ray and CT scan do not show a perforation or colonic diverticulum, colonoscopy will identify ischemic or pseudomembranous colitis [11, 17, 32, 34]. We again insist on ~~the fact~~ that surgery should be performed as quickly as possible under a broad spectrum of antibiotherapy and reduction of immunosuppression [4, 6]. Only simple procedures are allowed: resection, colostomy, and peritoneal washing. We do not believe that pretransplant diagnosis of colonic diverticula justifies surgery before transplantation unless a past history of diverticulitis has been proven.

The past history of our population with GI complications shows a high rate of gastroduodenal pathology before the transplantation (56% in the case of peptic ulcer) and a high rate of colonic pathology (18% in the case of colonic complications). This high rate of gastrointestinal complications can be explained by the fact that in no case was the past GI history a contraindication for kidney transplantation. Table 2 shows that in this population the rate of acute rejection during the first 3 months (78%) was identical to that of patients without complications. These gastrointestinal complications were not related to acute rejection, as shown by their mean delay after the transplantation. CMV infection can cause esophagogastrointestinal ulceration, and the incidence of CMV disease was 15% in the total population, with only two CMV gastrointestinal complications.

By contrast, Table 2 also shows that complications generally described during the first 6 months were mainly gastroduodenal [21], while the more life-threatening ileal and colonic complications happened 1 or 2 years later, usually outside the transplant department. This explains the delay before surgery and the high mortality rate of colonic complications in our series compared to others. Transplantation should involve an educational program for the physician who will later be responsible for all of these recipients.

To sum up, 100 patients with GI complications were detected among 614 kidney transplant recipients (16.2%) over a 4-year period. Of these complications, 9.6% were gastroduodenal, 1.3% involved pancreatitis, 0.5% small bowel, and 4% were colonic. The mortality rate was 11/614 (1.7%) and mainly due to peritonitis, which is the most life-threatening complication. Mortality increased to 35% in cases of perforation plus peritonitis and upper stress GI bleeding in the case of multiorgan failure.

We conclude that the surgical management of abdominal complications after kidney transplantation should be prompt. The magnitude of the procedure should be correlated with the stability and status of the patient. Frequent use of peritoneal dialysis and diagnostic laparotomy are recommended in every doubtful case since the morbidity of negative exploration is much lower than that of an undiagnosed complication. Prevention depends essentially on pretransplantation screening of colonic diverticula and gastroduodenal ulcer disease, combined with special prevention with antiproton therapy.

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