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ORIGINAL ARTICLE

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Severe gastrointestinal complications after 1,515 adult kidney transplantations

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Abstract We studied, retrospectively, the occurrence of severe gastrointestinal (GI) complications after kidney transplantation. After 1,515 consecutive adult kidney transplantations performed on 1,445 patients during 1990–1999 at our centre, 147 (10%) severe post-transplantation GI complications were found. Ten percent of the complications were fatal. The median follow-up time was 6.2 years. The main complications were gastroduodenal ulcers and colon complications. GI malignancy developed in 13 patients (0.9%). The complication rate for the first post-transplantation year was 4.8%. Delayed graft function, high age and polycystic kidney disease were risk factors. Five-year patient survival rate was significantly lower in patients with a first-year complication than in those with later or no GI complications (68% vs 88%). Graft survival with deaths censored was the same in both groups. In conclusion, severe GI complications during the first post-transplantation year remain a high risk factor also for long-term patient survival.

Keywords Immunosuppression · Kidney transplantation · Gastrointestinal complication

Introduction

Immunosuppressive treatment predisposes organ transplantation patients to various gastrointestinal (GI) problems. Before the use of modern ulcer medicines, bleeding or perforated gastric ulcers were common in kidney transplantation patients. Colon perforations caused by diverticulitis or intestinal paralysis have been reported to be frequent, and, in those patients, the outcome may more often be fatal. The cause of uraemia, e.g. diabetes mellitus, polycystic kidney disease, SLE or amyloidosis, can predispose immunosuppressed patients to many GI complications [1, 2, 3].

Immunosuppressive medication, especially corticosteroids, can hide symptoms, which results in delay in diagnosis and treatment of serious GI conditions. Azathioprine and corticosteroids, as well as hypercalcaemia due to secondary or tertiary hyperparathyroidism in kidney transplantation patients, can cause post-transplantation pancreatitis, and it is reported that patients on long-term immunosuppression are prone to develop gallstones [4, 5, 6, 7]. It is also known that long-term immunosuppression increases the risk of malignancies. The standardised incidence rate for cancer is 3.3-times higher in Finnish kidney transplantation patients than in the general population [8].

During immunosuppressive treatment many opportunistic infections are common in the GI tract. Cytomegalovirus (CMV), one of the most important post-transplantation pathogens, can cause ulceration, erosion and mucosal haemorrhage in the GI tract [9]. On the other hand, we have previously shown that *Helicobacter pylori* infection, associated with peptic ulcer disease in the immunocompetent population, does not

result in significant post-transplantation gastroduodenal problems in kidney transplantation patients [10].

The aim of this study was to examine the frequency and characteristics of post-transplantation GI complications in Finnish kidney transplantation patients. We also wanted to find possible risk factors for those complications.

Patients and methods

During 1990–1999, 1,515 (1,478 cadaveric, 37 living donated) kidney transplantations were performed on 1,445 adult patients (880 men, 565 women). Two patients, who died on the day of transplantation from non-GI causes, were excluded from this study. Of the transplantations 1,284 (85%) were first kidney transplantations, 194 (13%) were second, 32 (2%) were third and five (0.3%) were fourth kidney transplantations. During the study period 68 (5%) patients received two kidney grafts and one patient received three.

The study was divided into two 5-year periods: from 1990 to 1994 and from 1995 to 1999. At the time of transplantation the median age of all patients was 45.1 years (range 16–76 years); during the first 5-year period, 1990–1994, it was 42.3 years (range 16–70 years) and during the second, 1995–1999, 47.6 years (range 16–76 years). The median follow-up time was 6.19 years (range 7 days–12 years). The pre-transplantation work-up included abdominal ultrasound screening and further examination of patients with GI complaints. Cholecystectomy, in cases of gallstones, and colon resection, for symptomatic diverticular disease, were prerequisites for acceptance to the waiting list. All patients were on maintenance dialysis before the transplantation. Other characteristics of the patients are shown in Table 1.

Ninety-five percent of the patients had cyclosporine-based maintenance immunosuppression and 4% had tacrolimus as the main immunosuppressive medication. Rejections were treated with high-dose methylprednisolone for 5 days, and, if this treatment failed, with plasmapheresis or monoclonal antibody OKT 3. Ranitidine 150 mg or omeprazole 20 mg was used, during at least the first postoperative month, as ulcer prophylaxis, and acetylsalicylic acid (ASA) 50–100 mg as thrombosis prophylaxis.

At transplantation 82% of the patients were CMV seropositive. Ganciclovir was used as CMV prophylaxis in 73 (5%) of the kidney recipients during rejection or due to donor CMV-positive/recipient CMV-negative combination. CMV infection was diagnosed from peripheral blood by a monoclonal antibody against CMV-specific antigen (pp65) [11]. Symptomatic CMV infection was treated with intravenous ganciclovir.

Delayed graft function (DGF) was defined as serum creatinine concentration higher than 500 μmol/l throughout the first post-transplantation week or the need for more than one dialysis session in the first week or oliguria of less than 1,000 ml/24 h for more than 2 days [12].

Kidney transplantation patients in Finland are followed up by local nephrologists reporting to the Finnish Kidney Transplantation Registry. Data on GI complications were gathered from the patients' hospital records at the transplantation centre, from the nephrologists' regular follow-up reports and from the Finnish Kidney Transplantation Registry. Gastroduodenal ulcers, severe GI infections and perforations, pancreatitis, cholecystitis and malignancies diagnosed by clinical, radiological and endoscopic methods were considered as severe GI complications. All gastroduodenal ulcers were verified by oesophago-gastroduodenoscopy (OEGD).

Ethics

The study was approved by the Ethics Committee of Helsinki University Hospital.

Statistics

The variables were compared by Mann–Whitney U test, chi-squared test or Fisher's exact test, and multivariate

Table 1 Characteristics of 1,515 kidney transplantation patients during 1990 to 1999 (*Tx* kidney transplantation, *NS* not significant, *CAPD* continuous ambulant peritoneal dialysis)

Characteristic	Tx with GI complication ($n=134$)	Tx without GI complication ($n=1,381$)	Significance
Age in years at the time of Tx (median, range)	52.8 (19.9–71.5)	44.6 (16.1–76.3)	$P<0.01$
Gender (% female/% male)	41/59	40/60	NS
BMI (median, range)	24.0 (13.4–30.7)	23.4 (14.2–34.0)	NS
Mode of dialysis (% haemodialysis/% CAPD)	60/40	56/44	NS
Cause of uraemia			
Polycystic kidney disease	31	195	
Other kidney disease	71	712	$P<0.01$
Diabetes mellitus	18	363	
Systemic disease other than diabetes mellitus	14	111	

analysis was done with general regression model Statistica (data analysis software system version 6, StatSoft, 2003). Significance was established at $P<0.05$. Patient and graft survival was evaluated with the life-table method and compared by the log-rank test.

Results

Altogether 147 (10%) GI complications were found in this material (Table 2). All the GI complications were seen in transplantations from cadaveric donors. Thirteen patients had two GI complications. Median time from transplantation to complication was 0.93 years (range 2 days–11 years). During the follow up 261 (18%) patients died. Of the deaths, 15 (6%) were due to GI complications. The fatal GI complications in relation to the time from transplantation are shown in Fig. 1. Other causes of death were: cardiovascular, cerebral and infectious diseases, diabetic complications and non-GI malignancies.

Patients with GI complications were older at the time of transplantation than patients without any complication (median 52.8 vs 44.6 years, $P<0.01$) (Table 1). In the age category 16 to 19 years ($n=21$) the complication rate was 4.8%; from 20 to 39 years ($n=522$) it was 5.9%; from 40 to 59 years ($n=767$) 9.4%, and in patients over 60 years ($n=205$) it was 14.6%. Patients with polycystic kidney disease were found to have GI complications significantly more often than patients with other causes of uraemia (14% vs 8%, $P<0.05$). Diverticulitis was more common in patients with polycystic kidney disease than in other patient groups (3.5% vs 0.9%, $P<0.01$).

In the multivariate analysis the variables included age at the time of transplantation, gender, BMI, mode and length of dialysis, cause of uraemia, the number of transplantations, donor and recipient CMV status, cold ischaemia time and onset of graft function. Age was the only significant risk factor for GI complications as a whole. In the biggest subgroup, gastroduodenal ulcers, none of those factors was significant, whereas age and polycystic kidney disease were risk factors for colon complications.

Ten patients were on dialysis treatment at the time of complication. Five of them had DGF at that time and were on immunosuppressive therapy. In five patients graft loss had occurred, dialysis treatment had restarted and immunosuppressive treatment had ended a median 2.4 months (range 8 days–22 months) before the complication occurred. In those patients immunosuppression

Table 2 Gastrointestinal complications in 1515 kidney transplantation patients during 1990–99

Complication	Number ($n=147$)	Median time after transplantation (range)
1. Gastroduodenal ulcers	57	0.6 Years (4 days–11.2 years)
Perforated	3	
Bleeding	16	
Uncomplicated	38	
2. Colon complications	31	0.4 Years (2 days–7.1 years)
Diverticulitis with perforation	8	
Diverticulitis without perforation	12	
Other colon perforations	8	
Colitis	3	
3. Biliary complications	18	3.7 Years (11 days–10.8 years)
Cholecystitis with perforation	2	
Cholecystitis without perforation	15	
Suppurative cholangitis	1	
4. Pancreatitis	13	0.9 Years (4 days–6.2 years)
5. Mechanical bowel obstruction	5	0.3 Years (4 days–1.8 years)
6. Appendicitis	4	0.7 Years (109 days–1.2 years)
Perforated appendix	2	
No perforation of appendix	2	
7. Other	6	0.6 Years (62 days–5.9 years)
Bleeding oesophageal varices	1	
Liver abscess	1	
Mesenterial thrombosis	2	
Rectal prolapses	1	
Perforated Meckel's diverticulum	1	
8. Gastrointestinal malignancies	13	3.3 Years (138 days–10.8 years)
Pancreatic carcinomas	2	
Gastric carcinomas	3	
Carcinoid tumours	2	
Lymphoma	1	
Cholangio-carcinoma	1	
Colon carcinomas	4	

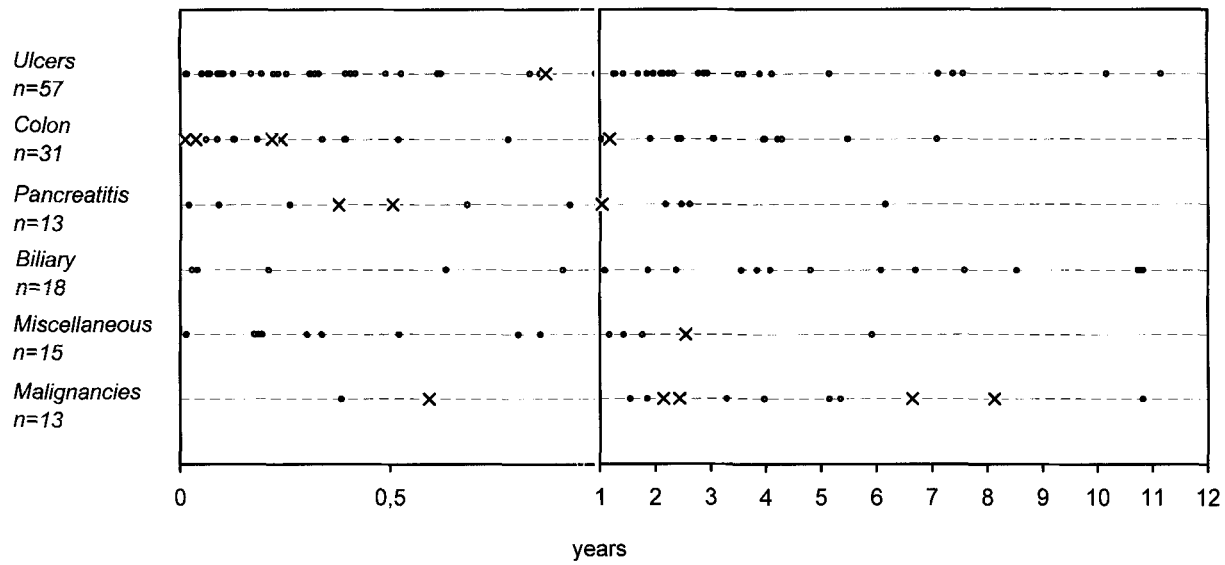

Fig. 1 GI complications in relation to the time of transplantation in 1,515 kidney transplantations during 1990 to 1999. (*x* fatal GI complication)

had lasted for a median of 8 years (range 4 days–11 years). In the patient group without GI complications, immunosuppression had lasted a median 5.7 years (range 1 day–12 years).

Seventy five (51%) of all the verified GI complications in 70 patients occurred during the first postoperative year (Table 3). The first-year GI complication rate in the whole material was 4.8%. During the first 5-year period (1990–1994) the first-year rate of GI complications was 4.0%, and during the second period (1995–1999) it was 5.8% (not significant). Five-year patient survival rate in patients with a first-year complication was 68% compared to 88% in those with later or no GI complications ($P < 0.001$). Graft survival with deaths censored was the same in both groups. The two biggest groups of GI complications during the first year were gastroduodenal ulcers (44%) and colon complications (23%). There were ten cases of ulcer bleeding, two ulcer perforations and 12 colon perforations, including six with diverticulitis. Eight (11%) of the GI complications occurring during the first year were fatal, four colon perforations among them (Fig. 1). Probable predisposing factors to complications are listed in Table 3. DGF preceded a GI complication in 33 of 70 (47%) transplantations compared to 455 of 1,445 (31%) transplantations without a GI complication during the first post-transplantation year ($P < 0.05$).

During the follow-up period there were 57 gastroduodenal ulcers, with bleeding or perforation in 19 (33%) of them (Table 2). *Helicobacter pylori* infection was associated with an ulcer in 21% of the patients, and CMV was detected in biopsies of four patients. Half of the colon perforations were caused by diverticulitis. Causes for the other colon perforations were ischaemic colitis in two, pseudo-obstruction in two and iatrogenic rectum perforation in connection with fibroscopy in one patient. In three patients no underlying cause was known.

Biliary complications were distributed evenly throughout the follow-up period. None of the patients died of biliary complications. Three of the 13 cases of pancreatitis were fatal, two of them during the first post-transplantation year.

Of the 1,445 patients included in this study 13 (0.9%) developed a GI malignancy during the follow-up period (Table 2). Two of the malignancies occurred during the first year after the transplantation; one male patient developed a MALT-type lymphoma of the jejunum 7 months after the transplantation, and one female patient had a small sigmoid cancer (carcinoma in adenoma) 4.6 months after the transplantation.

Table 3 First year post-transplantation GI complications in 1515 kidney transplantations and factors predisposing to them

Parameter	Number (%) ($n = 1,515$)	DGF	Rejection therapy	CMV infection
Transplantations with GI complication during the first year	70 (5)	33* (47)	7 (10)	9 (13)
Transplantations without GI complication during the first year	1,445 (95)	455 (31)	349 (24)	144 (10)

*$P < 0.05$

Discussion

Serious GI complications occurred after 147 (10%) of 1,515 kidney transplantations performed on 1,445 consecutive adult patients, who received transplants between 1990 and 1999. GI complications had not been the focus of interest in the 1990s. We could not find any comparable single-centre or large-registry report on GI complications of patients who had undergone transplantation in the 1990s. In studies from the earlier years the frequency of GI complications has varied between 8% and 37% [13, 14, 15].

All Finnish kidney transplantations are performed at one centre, and detailed post-transplantation follow-up data are sent regularly from the nephrological units to the Finnish Kidney Transplantation Registry. During the 10-year study period the immunosuppressive treatment, surgical techniques and postoperative care changed little. Further, pre-transplantation requirements for GI examinations were unchanged.

The first-year GI complication rate was 4.8%. The small increase in the first-year complication rate in this series, might, in later years, be associated with the increase in the median age of the recipients during that time.

It is of notice that half of all the GI complications occurred during the first post-transplant year, when the doses of immunosuppressive medication are highest. Over a half of the gastroduodenal ulcers and colon complications were seen during the first year. Our study did not show an association between GI complications and preceding rejection therapy or CMV infections. On the other hand, DGF increased the risk of GI complications during the first year.

Before the use of proton-pump inhibitors and H2 blockers, over 40% of gastroduodenal ulcers were fatal in immunosuppressed patients [16, 17]. In this series the frequency of gastroduodenal ulcers was 4% during a median 6-year follow-up time. The result is in parallel with Troppmann's earlier study, where also patients from the 1980s were included [18]. All except one of the ulcers were treated successfully. That was probably because OEGD was easily available for transplantation patients with upper gastroduodenal symptoms and because of the effective ulcer prophylaxis and treatment used.

The incidence of colon perforations in kidney transplantation patients was 1%, comparable with earlier values, which varied from 1%–2% [19, 20]. Half the perforations were caused by diverticulitis. Although they were few in number, 25% of these complications were fatal. The diagnosis was often delayed because immunosuppressive drugs might have masked symptoms and affected the patients' responses to the septic condition. All fatal colon perforations in our series occurred during the first year after the transplantation.

Patients with polycystic kidney disease are reported to have an increased incidence of GI complications after kidney transplantation and to have a higher incidence of colon diverticular disease than others [1, 21, 22]. Our results were in accordance with these findings: patients with polycystic kidney disease had GI complications more often, especially diverticulitis.

Permanent immunosuppressive medication exposes kidney transplantation patients to malignancies. In a Finnish study the incidence of cancer in kidney transplantation patients was 16% after 15 years after kidney transplantation and 22% after 20 years. The standardised incidence rates for colon and small bowel carcinoma were significantly increased, the values being 11.8 and 3.9, respectively [8]. Two of the malignancies in our study were diagnosed during the first postoperative year; the MALT-type lymphoma could probably be explained by the use of high-dose immunosuppressive medication early after transplantation, and the small sigmoid carcinoma was probably missed in pre-transplantation examinations. This emphasises the importance of the screening of the pre-existing cancer before and after transplantation, as recommended by the EBPG expert group on renal transplantation [23, 24].

In conclusion, 10% GI complications were found after kidney transplantation during a median 6-year follow-up period. Half of them occurred during the first post-transplantation year. GI perforations were found to be especially serious complications in this patient group. High age, DGF and polycystic kidney disease increased the risk of GI complications. These results demonstrate the importance of meticulous pre-transplantation screening of GI disorders in elderly patients that are waiting for kidney transplantation.

References

1. Andreoni K, Pelletier R, Elkhammas E, et al. Increased incidence of gastrointestinal surgical complications in renal transplant recipients with polycystic kidney disease. Transplantation 1999; 67:262–266.
2. Logan A, Morris-Stiff G, Bowrey D, Jurewicz W. Upper gastrointestinal complications after renal transplantation: a 3-yr sequential study. Clin Transplant 2002; 16:163–167.
3. Padilla B, Pallak V, Pesce A, Kant S, Gilinsky N, Deddens J. Pancreatitis in patients with end stage renal disease. Medicine 1994; 73:8–20.
4. Alberu J, Gatica M, Cachafeiro-Vilar M, et al. Asymptomatic gallstones and duration of cyclosporine use in kidney transplant recipients. Rev Invest Clin 2001; 53:396–400.
5. Fernandez-Cruz L, Targarona E, Cugat E, Alcaraz A, Oppenheimer F. Acute pancreatitis after renal transplantation. Br J Surg 1989; 76:1132–1135.
6. Frick T, Fryd D, Sutherland D, Goodale R, Simmons R, Najarian J. Hypercalcemia associated with pancreatitis and hyperamylasemia in renal transplant recipients. Am J Surg 1987; 154:487–489.
7. Mallory A, Kern F. Drug-induced pancreatitis: a critical review. Gastroenterology 1980; 78:813–818.
8. Kyllönen L, Salmela K, Pukkala E. Cancer incidence in a kidney-transplanted population. Transplant Int 2000; 13 [Suppl 1]:394–398.
9. Goodgame R. Gastrointestinal cytomegalovirus disease. Ann Intern Med 1993; 119:924–935.
10. Sarkio S, Rautelin H, Kyllönen L, Honkanen E, Salmela K, Halme L. Should Helicobacter pylori infection be treated before kidney transplantation? Nephrol Dial Transplant 2001; 16:2053–2057.
11. The T, van der Berg A, Harmsen M, van der Bij W, van Son W. The cytomegalovirus antigenemia assay; a plea for standardization. Scand J Infect Dis Suppl 1995; 99:25–29.
12. Kyllönen L, Salmela K, Eklund B, et al. Long-term results of 1047 cadaveric kidney transplantations with special emphasis on initial graft function and rejection Transpl Int 2000; 13:122–128.
13. Bardaxoglou E, Maddern G, Ruso L, et al. Gastrointestinal surgical emergencies following kidney transplantation. Transpl Int 1993; 6:148–152.
14. Benoit G, Moukarzel M, Verdelli G, et al. Gastrointestinal complications in renal transplantation. Transpl Int 1993; 6:45–49.
15. Meyers W, Harris N, Stein S, et al. Alimentary tract complications after renal transplantation. Ann Surg 1978; 4:535–542.
16. Ahonen J, Eklund B, Lindfors O, Kuhlbäck B, Lindström B. Peptic ulceration in kidney transplantation. Proc Eur Dial Transplant Assoc 1977; 14:396–400.
17. Owens M, Passaro E, Wilson S, Gordon H. Treatment of peptic ulcer disease in renal transplant patients. Ann Surg 1977; 186:17–21.
18. Troppmann C, Paplois B, Chiou A, et al. Incidence, complications, treatment and outcome of ulcers of the upper gastrointestinal tract after renal transplantation during the cyclosporine era. J Am Coll Surg 1995; 180:433–443
19. Church J, Braun W, Norvick A, Fazio V, Steinmuller D. Perforation of the colon in renal homograft recipients Ann Surg 1986; 203:69–76.
20. Stelzner M, Vlahakos D, Milford E, Tilney N. Colonic perforations after renal transplantation. J Am Coll Surg 1997; 184:63–69.
21. Dominquez Fernandez E, Albrecht K, et al. Prevalence of diverticulosis and incidence of bowel perforation after kidney transplantation in patients with polycystic kidney disease. Transpl Int 1998; 11:28–31.
22. Scheff R, Zuckerman G, Harter H, Delmez J, Koehler R. Diverticular disease in patients with chronic renal failure due to polycystic kidney disease. Ann Int Med 1980; 92:202–204.
23. The EBPG expert group on renal transplantation. European best practice guidelines for renal transplantation (part 1). Nephrol Dial Transplant 2000; 15 [Suppl 7]:6–7.
24. The EBPG expert group on renal transplantation. European best practice guidelines for renal transplantation (part 2). Nephrol Dial Transplant 2002; 17 [Suppl 4]:31–36.