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Incidence of intraabdominal infection in a consecutive series of 40 enteric-drained pancreas transplants with FK506 and MMF immunosuppression

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Abstract Although the introduction of FK506 and MMF has markedly improved patient and graft outcome after pancreas transplantation, this procedure is still associated with a high surgical complication rate. The aim of the following study was to retrospectively analyze a series of 40 consecutive pancreas transplants with enteric drainage with regard to intraabdominal infection (IAI). Between March 1997 and December 1998 a total of 40 whole pancreas transplants were performed. Prophylactic immunosuppression consisted of an intraoperative single shot ATG (Thymoglobulin), FK506, MMF, and prednisone. The mean observation period was 14.6 (5–26) months. Overall incidence of IAI was 27.5% ($n = 11$) leading to pancreatectomy in 5 patients (12.5%). In the remaining 6 patients the graft could be rescued by necrosectomy and radical drainage of the abscess (5 patients) or percutaneous drainage (1 patient). Pancreatectomy or local infection did not alter kidney graft function in the 11 patients with simultaneous pancreas kidney transplantation. In 10 patients no evidence for leakage at the site of enteric anastomosis was present, one duodenal leak occurred due to ischemia. IAI in the early postoperative period was the predominat risk factor for graft loss. An early and invasive diagnostic approach is recommended to maximize the chance of graft rescue.

Key words Pancreas transplantation · Enteric drainage · Intraabdominal infection

Introduction

Simultaneous pancreas kidney (SPK) transplantation has evolved as an effective treatment modality for patients with end-stage nephropathy due to type I diabetes mellitus. As of the end of 1998, more than 11000 pancreas transplants worldwide have been reported to the IPTR with a 1-year patient, pancreas and kidney graft survival for SPK transplant cases of 94, 83, and 90%, respectively [1]. This improvement in graft outcome was mainly achieved by a reduction of technical failures and more powerful immunosuppression. Various maintenance immunosuppressive regimens including new substances such as tacrolimus (FK506, Tac) and MMF (Cellcept) resulted in dramatic improvement of pancreas graft survival in solitary pancreas transplant recipients, whereas this effect was less pronounced in SPK transplant patients. Although the majority of transplant centers use bladder drainage (BD) for the diversion of the pancreatic juice, an increasing proportion of SPK transplants is being performed with the more physiologic enteric drainage (ED), leading to changing patterns of posttransplant technique-related complications. While BD is associated with a high incidence of urological complications, including urinary tract infections, dehydration, hematuria, metabolic acidosis, and reflux pancreatitis in the long term, enteric diversion bears an increased risk of serious early infectious complications. In addition, the advantage of monitoring the pancreas transplant by assessment of urine amylase activity after

BD is lost. In this article we report on our experience with ED in a consecutive series of 40 pancreas transplants, focusing on intraabdominal infections (IAI) in the immediate postoperative period.

Patients and methods

Donor and recipient demographics

Between March 1997 and December 1998, 40 patients (22 men, 18 women) with a mean age of 39.1 ± 7.9 years (range 26.6–55.4) underwent pancreas transplantation. In 38 (95%) cases the pancreas was grafted together with the kidney from the same donor (SPK). Two (5%) patients received a pancreas sometime after kidney transplantation, in one case as a retransplant. The mean number of HLA mismatches for class I and II antigens was 3.2 ± 0.65 and 1.59 ± 0.59, respectively. The mean donor age was 30.45 ± 9.63 years (range 10–47), 4 donors were over 45 years old, and the mean overall BMI was 22.9 ± 1.9. Mean cold ischemia time (CIT) for the kidney transplants was 12.2 ± 3.0 h and for the pancreas transplants 11.7 ± 2.7 h. All pancreas transplants were enterically drained.

Perioperative antimicrobial prophylaxis

All patients underwent selective small bowel decontamination prior to surgery using neomycin, AmphoB, and tobramycin. Peri- and postoperative antibiotic prophylaxis consisted of ampicillin and clavulanic acid at a dose of 2.2 g t.i.d. until postoperativeday (p.o.d.) 3. Routine swabs were taken from the perfusion solution, the transplant ureter, and the transplant duodenum. Prior to wound closure, the abdomen was extensively irrigated with neomycin-containing saline and a silicone drain was placed into the Douglas pouch. The majority of patients received Octreotide at 100 µg t.i.d. subcutaneously, starting preoperatively until the end of the 1st postoperative week.

Immunosuppression

All patients received MMF at 1 g b.i.d. orally starting at the time of admission to the hospital. A rapid steroid-tapering regimen was applied reaching a dose of 25 mg at the end of the 1st postoperative week. After p.o.d. 21 prednisone was further tapered every other week by 2.5 mg and finally maintained at a daily dose of 5 mg. MMF was usually given at a dose of 1 g b.i.d. and reduced in case of gastrointestinal side effects. MMF was switched to azathioprine at 1.5 mg/kg body weight daily in case of MMF side effects resistent to dose adjustment. A single shot ATG (Thymoglobulin; Sangstat) at 3–4 mg/kg body weight was started at the beginning of surgery. No further anti T-cell antibodies were used. Patients received oral Tac at 0.08 mg/kg per day twice daily, starting 6 h after revascularization. The Tac dose was adjusted to achieve whole blood trough levels of 10–12 ng/ml for the first 3 months after transplantation, 8–10 ng/ml for 6–12 months, and 6–8 ng/ml thereafter. All patients had weekly testing for cytomegalovirus (CMV) antigen (pp65) and CMV-seronegative recipients of CMV-seropositive organs ($n = 7$) were treated prophylactically with a 14-day course of intravenous ganciclovir followed by 3 g orally for 12 weeks.

Table 1 Kaplan-Meier patient, kidney, and pancreas survival

Time (months)	Patients		Kidney		Pancreas	
	Number	Survival (%)	Number	Survival (%)	Number	Survival (%)
1	40	100	37	97.4	36	90
6	36	100	33	97.4	31	85
12	24	100	22	97.4	21	85
24	2	100	2	97.4	2	85

Statistical analysis

Data are reported as mean ± SD. Patient survival was calculated from the date of transplantation until death, graft survival rates were censored for graft failure or patient death. Survival curves were generated using the Kaplan-Meier method. Groups were compared using the non-parametric Mann-Whitney *U*-test and Spearman correlation.

Results

Patient and graft survival

The mean follow up was 14.6 (range 5–26) months. Overall 1- and 6-month, and 1- and 2-year actuarial kidney graft survival was 97.4%. All patients are currently alive (100%). One kidney graft was lost due to early arterial thrombosis. Patients were discharged with a mean serum creatinine ($n = 37$) of 1.16 ± 0.28 mg/dl and after a follow up of 1 year creatinine was 1.23 ± 0.24 mg/dl (P = NS; $n = 22$). Overall 1- and 6-month, and 1-year pancreas graft survival was 90, 85, and 85% (Table 1). Of the 40 pancreas grafts, 34 (85%) are currently functioning. The six graft losses occurred in six SPK transplant patients, one due to acute rejection and five due to severe IAI necessitating pancreatectomy.

Incidence of IAI

Eleven out of the 40 patients (27.5%) developed IAI with a mean onset of 12.1 days (range 3–22). Patient characteristics of the IAI group and those patients who did not develop IAI (no IAI, $n = 29$) are depicted in Table 1. Clinically patients presented with severe abdominal pain in the right lower quadrant and signs of local or diffuse peritonitis associated with fever and elevated CRP levels; fasting blood glucose levels and C-peptide levels were within the normal range. At ultrasound and/or CT scan, peripancreatic fluid collections rich in protein indicative for abscess formation were detected in all cases. In two patients IAI was associated with bacteremia. Routine intraoperative swabs of donor tissue (perfusion solution, ureter, duodenum), abdominal drain, and PD catheter ($n = 45$) revealed bacterial growth in nine instances

(20%). We were not able, however, to demonstrate any correlation between intraoperative bacterial and/or yeast contamination and the development of IAI.

Outcome in patients with IAI

In the majority of cases ($n = 10, 91\%$) a single ($n = 6$) or multiple ($n = 4$) relaparotomies were necessary to control the severe local process by drainage of peripancreatic fluid collections together with extensive abdominal lavage. In one patient percutaneous drainage alone was sufficient to control local inflammation. Overall, transplant pancreatectomy had to be performed in five cases (45% of IAI). A duodenal leak due to ischemic injury was identified as a possible source for infection in only one patient. A mixed microbial flora was encountered in nine cases (median 5 different organisms) and a single organism was found in two cases. A total of 50 organisms were cultured: CNS 8, SA 2, streptococci 4, enterococci 6, Gram + rods 3, *E. coli* 4, *Klebsiella* 5, *Enterobacter/Serratia*/other Gram– rods 7, *Pseudomonas aeruginosa* 1, *Acinetobacter* 1, *B. fragilis* 3, *Prevotella* sp. 1, *Candida* 5. A substantial amount of these isolates showed altered sensitivity with resistance to many antibiotics. Due to shifts in the spectrum of isolated pathogens, the antibiotic treatment had to be frequently changed. At present, all patients are alive with well-functioning renal grafts. Fifty-five percent of pancreatic grafts were saved despite severe IAI.

A comparison of patients with or without IAI (Table 1) showed no statistical difference with regard to gender, age, time on dialysis, type of dialysis, donor BMI, treatment for acute rejection, and recipient body weight. However, significant differences were noticed for pancreas CIT (13.3 vs 11.2 h) and donor age (36.7 vs 28.3 years).

Histology of removed pancreatic grafts

Histologic examination of pancreatic transplants removed for IAI basically revealed two distinct patterns of histologic appearance. The first pattern was peripancreatitis with intact exocrine and endocrine tissue (Fig. 1). The inflammatory process was restricted to the peripancreatic tissue without involvement of the exocrine compartment or the islets. Of note, pericapsular vicryl ligatures presented as inflammatory foci reflected by a dense cellular infiltrate surrounding the suture material. The second pattern showed pancreatitis and vascular damage similar to acute rejection (Fig. 2). In the majority of specimens a dense mononuclear infiltrate within the exocrine compartment was seen. In addition, a pronounced vascular involvement with myointimal hyperplasia and clot formation was detected.

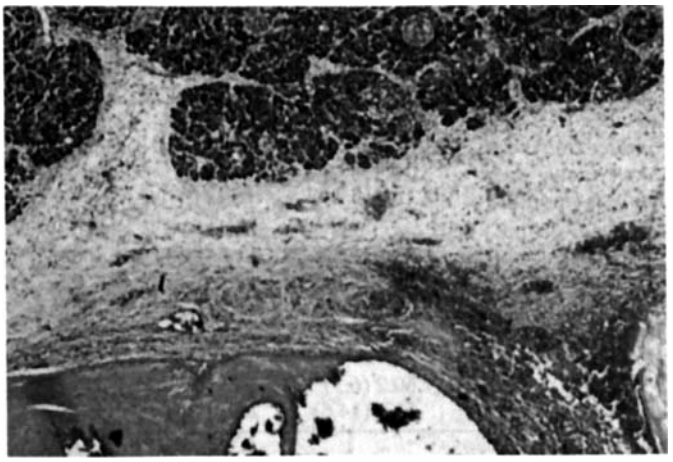

Fig. 1 Peripancreatitis without cellular infiltration of acini and islets

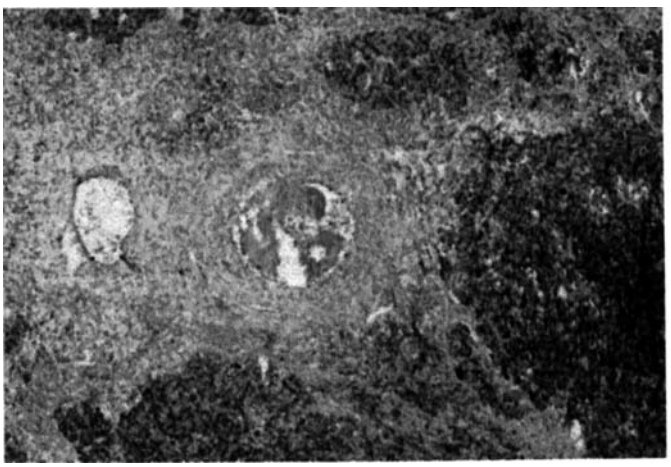

Fig. 2 Intense mononuclear infiltrate of acini with myointimal proliferation

Discussion

The introduction of new immunosuppressive agents made pancreas transplantation the therapy of choice for patients with long standing type I diabetes mellitus and secondary complications. According to the latest IPTR report [1], for the first time in the era of pancreas transplantation, the technical failure rates have exceeded the immunological failure rates. Currently, an increasing proportion of transplant centers are reutilizing the enteric exocrine drainage as primary diversion after SPK transplantation. Hence, a shift from complications in the long term resulting from bladder drainage (i.e., metabolic acidosis, urinary tract infection, duodenal ulcer, and leaks) to immediate postoperative complications after ED (i.e., IAI, gastrointestinal bleeding from the site of anastomosis, pancreatitis) has been noticed [2].

Table 2 Potential risk factors for intraabdominal infection *(IAI)*. Patients with IAI were compared to patients without IAI

	IAI	No IAI	*P*-value
Number	11	29	
Gender (m/f)	8/3	14/15	NS
Age (years)	39.5 (7.3)	39.0 (8.1)	NS
Dialysis (months)	19.7 (15.7)	14.3 (15.0)	NS
PD	3	5	NS
CIT kidney	13.9 (2.3)	11.6 (2.9)	0.0223
CIT pancreas	13.3 (2.6)	11.2 (2.6)	0.0205
Donor age (years)	36.7 (6.5)	28.3 (9.7)	0.0157
Donor BMI	23.7 (1.9)	22.6 (1.8)	NS
Treatment for AR	5	7	NS
BW (kg)	60.2 (6.3)	58.5 (7.9)	NS
Hospital stay (days)	51.5 (14.6)	29.9 (7.3)	≤ 0.0001

In a consecutive series of 40 enteric-drained pancreas transplants performed at our institution, IAI was observed in 27.5% of patients with a mean onset on p.o.d. 12. Patients presented with severe localized to diffuse abdominal pain, fever and elevated CRP levels together with peripancreatic fluid and/or abscess at CT scan. In 2 cases IAI was associated with bacteremia as evidenced by positive blood cultures. In a cohort of 132 patients with 78% enteric-drained cases at the University of Pittsburgh, an overall postoperative infection rate of 38.6% was reported with 25.8% serious infections [3]. It was concluded that bacterial and fungal infections were highly associated with surgical complications. As we observed a duodenal leak in only 1 patient out of 11 without detection of other obvious bowel fistulae in the remaining patients, a primary contamination of the peritoneal cavity during completion of the duodeno-jejunostomy seems possible. This is also consistent with results from a large series of 445 pancreas transplants reported from the University of Minnesota [4]. In their series IAI occurred in 38% of enteric-drained vs 18% of bladder-drained recipients. On the other hand, we were not able to define any correlation between intraoperative bacterial and/or fungal contamination of donor tissue and the development of IAI. Other risk factors contributing to the development of peripancreatitis and IAI are either donor related (hemodynamic instability, usage of catecholamines, donor age), procurement and perfusion injury (amount of flush solution), or preservation and reperfusion injury [4, 5]. Statistically significant differences were evident in our series of 11 patients with IAI compared to the 29 patients with an uneventful postoperative course with regard to CIT of the pancreas and donor age (Table 2).

To our knowledge, an exact histologic characterization of the inflammatory response within the pancreatic graft tissue during peripancreatitis and IAI has not been described in the literature so far. In the five removed pancreas grafts that were available for histologic evaluation, two distinct patterns of inflammation were seen. The first pattern was peripancreatitis without cellular destruction of the exocrine and endocrine compartments of the gland (Fig. 1). The macrophage/granulocyte-dominated infiltrate was mainly found within the peripancreatic fatty tissue adjacent to vicryl suture material. The second pattern showed a mononuclear infiltrate of acini and vascular myointimal proliferation associated with microthrombosis, resembling the typical features of graft rejection with chronic vasculopathy. In the first scenario of peripancreatitis a non-specific immune response, possibly secondary to bacterial or fungal infection, seems to be causal whereas an alloantigen-driven immune reaction resistant to Tac/MMF-based immunosuppression might be the main pathogenetic factor in the latter type of inflammation.

In summary, there remains considerable surgical morbidity after pancreas transplantation despite significantly improved results in the Tac/MMF era with a 12.5% graft loss rate during a mean observation period of 14.6 months at our institution. Severe early posttransplant IAI was the predominant risk factor for graft loss. An early and invasive diagnostic approach is recommended to maximize the chance of graft rescue.

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