Preserving the Pancreas Graft: Outcomes of Surgical Repair of Duodenal Leaks in Enterically Drained Pancreas Allografts

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Background. Duodenal leak remains a major cause of morbidity and graft loss in pancreas transplant recipients. The role and efficacy of surgical and image-guided interventions to salvage enterically drained grafts with a duodenal leak has yet to be defined. **Methods.** We investigated the incidence, treatment, and outcome of duodenal leak in 426 pancreas transplantation recipients from 2000 to 2015. **Results.** Duodenal leak developed in 33 (7.8%) recipients after a median follow-up of 5.3 (range, 0.5-15.2) years. Most leaks occurred during the first year (n = 22; 67%), and most were located near the proximal and distal duodenal staple line. Graft pancreatectomy was performed in 8 patients as primary therapy because of unfavorable local and/or systemic conditions. Salvage was attempted in 25 patients using percutaneous drainage (n = 4), surgical drainage (n = 4), or surgical repair (n = 17). Percutaneous or surgical drainage failed to control the leak in 7 of these 8 patients, and all 7 ultimately required graft pancreatectomy for persistent leak and sepsis. Surgical repair salvaged 14 grafts, and 13 grafts continue to function after a median follow-up of 2.9 (range, 1.1-6.3) years after repair. **Conclusions.** Our study shows that in selected patients a duodenal leak can be repaired successfully and safely in enterically drained grafts.

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Pancreas transplantation is an established treatment for patients with insulin-dependent diabetes mellitus that not only offers improved quality of life[1-4] but also improves long-term patient survival over renal transplantation alone

in those with end-stage nephropathy.[1,5,6] Advances in donor and recipient selection criteria, organ procurement and preservation, immunosuppressive therapy, and surgical techniques have steadily increased pancreas graft survival rates; 5- and 10-year survival rates now exceed 80% and 70%, respectively, in many centers.[7,8] During the evolution of pancreas transplantation, the duodenal segment became the favored conduit for draining pancreatic exocrine secretions into the bladder[9,10] and intestine.[8,11] Since the late 1990s, most centers have adopted intestinal drainage, with or without a Roux-en-Y limb, as their standard.[11] More recently, several centers have explored the utility of anastomosing the graft duodenum to the recipient duodenum, which facilitates endoscopic surveillance biopsies to detect occult rejection and cytomegalovirus (CMV) infection.[12,13]

Duodenal leaks occur in 5% to 20% of recipients and are a significant cause of morbidity.[14-16] We have previously identified reperfusion injury and preoperative cardiovascular interventions as risk factors for the development of a duodenal leak.[16] Duodenal leaks in bladder-drained grafts can be treated successfully in many patients, often with simple measures such as bladder decompression.[17] By contrast, leaks in enterically drained grafts pose more management challenges and carry a greater risk of graft loss and mortality. Graft pancreatectomy provides definitive, and perhaps the safest, treatment, but renders the recipient insulin-dependent with an attendant loss of quality-of-life and the prospect of retransplantation.[18] Case-report studies suggest that surgical

and image-guided interventions can salvage some enterically drained grafts, although their generalizability and long-term effectiveness remain unclear.[19,20] In our previous study, we identified risk factors for the development of a duodenal leak, whereas, in this study, we characterize the clinical presentation, pathology, and treatment of duodenal leaks in enterically drained pancreas grafts, and analyze the impact of salvage procedures on patient and graft outcomes.

MATERIALS AND METHODS

Study Population

We included all synchronous pancreas-kidney (SPK), pancreas-after-kidney (PAK), and pancreas-transplant-alone (PTA) transplants performed at Toronto General Hospital, University Health Network, between January 2000 and October 2015. Duodenal leak was suspected in recipients who presented with fever, hyperamylasemia, or abdominal pain in association with imaging findings of fluid and free air adjacent to the graft duodenum; the diagnosis was confirmed by surgery or percutaneous drainage. Time of the leak was defined as the number of days from transplantation to leak confirmation. Exclusion criteria consisted of patients with leaks from the Roux-en-Y (n = 3) and recipients who experienced a duodenal leak who had less than 6 months follow up after occurrence of the leak (n = 0).

Details of the presenting complaint, physical findings, and investigations (blood work, cultures, and imaging) were analyzed retrospectively. We collected donor and recipient demographic data (sex, age, body mass index, and CMV and Epstein-Barr virus status); donor-specific data (cause of death, neurological vs cardiocirculatory arrest donor, pancreas cold ischemic time and warm ischemia time; recipient-specific data (type of transplant (SPK, PAK, or PTA), pancreas retransplantation, panel-reactive antibodies, duration of diabetes and dialysis before transplantation). Duration of follow-up and outcomes of interest such as postoperative complications, infections (bacterial, viral, and fungal), rejection episodes, pancreas graft failure (defined as return to insulin dependency), cause of graft loss, and death were also collected.

Data were entered prospectively into the Organ Transplant Tracking Record (Chronic Care Solutions; Omaha, NE) database and analyzed retrospectively. The University Health Network Research Ethics Board approved the study (REB 13-6912).

Surgical Procedures

Pancreas recovery and transplant procedures were performed as described previously.[16] Briefly, during the back-bench preparation of the graft, the duodenal segment was shortened to 8 to 10 cm in length with a gastrointestinal anastomosis (GIA) stapler, ensuring that a vascular arcade was immediately adjacent to the staple lines. The staple line was not routinely inverted with a Lembert suture. Systemic venous drainage to the vena cava and exocrine drainage to a Roux-en-Y limb of jejunum was used in most recipients. The duodenal-jejunal anastomosis was performed in a 2-layer hand-sewn fashion. The final orientation of the graft was behind the right colon with head up and tail toward the pelvis. Intraoperative systemic anticoagulation was not employed. In SPK recipients, the kidney was revascularized before the pancreas. Antibiotic prophylaxis consisted of cefazolin for

24 hours. The graft duodenum was cultured during surgery, and those recipients with positive cultures were treated with the appropriate antimicrobial agent(s). Postoperative anticoagulation consisted of daily prophylactic unfractionated heparin, 5000 U and acetylsalicylic acid, 81 mg. Protocol graft ultrasound was performed on the first postoperative day.

Immunosuppression

All recipients had a negative antihuman globulin complement-dependent cytotoxic T cell (before 2013) or flow cytometry cross-match (after 2013) at the time of transplantation. The presence of donor-specific antibodies (DSA) did not preclude transplantation provided the crossmatch was negative. Thymoglobulin induction (5-7 mg/kg recipient body weight) was administered routinely. All patients received methylprednisolone 500 mg intraoperatively, followed by a rapid taper from 200 to 20 mg/d on day 5. The oral prednisone dosage began at 20 mg/d, was reduced to 5 mg/d at 6 months, and maintained between 2.5 and 5 mg/d thereafter. Tacrolimus (target level of 10-14 μg/L at day 7 and 5-10 μg/L at 6 months) and mycophenolate mofetil (500 mg twice a day) were initiated on postoperative days 2 to 5. Recipients with DSA also received intravenous immunoglobulin (1 g/kg) perioperatively.

CMV Prophylaxis

CMV-negative recipients of CMV-positive organs received valganciclovir for 6 months and CMV-positive recipients received 3 months of therapy. In high-risk patients (ie, CMV-positive organ to CMV-naive recipients), CMV viremia was monitored by quantitative polymerase chain reaction for 3 months after the cessation of valganciclovir; a 6-week course of valganciclovir was started in those patients who became viremic.

Statistical Analysis

Data are expressed as median (range) and the Kruskal-Wallis test was used to compare groups. Categorical variables were compared with the χ^2 test. P less than 0.05 was considered statistically significant. Follow-up was carried out until October 2015. Statistical calculations were performed using Prism 5 (GraphPad Software, San Diego, CA).

RESULTS

Study Group

Between January 2000 and October 2015, 426 pancreas transplantations were performed (299 SPK and 127 PAK/PTA). A duodenal leak developed in 33 (7.8%) recipients (17 SPK and 16 PAK) after a median follow-up of 5.3 (0.5-15.2) years. The median time interval between transplantation and diagnosis of the leak was 69 (4-4326) days (Table 1). Most leaks occurred during the first year (n = 22; 67%), and the remainder presented sporadically beyond the first year (Figure 1). Among the entire cohort, 44 grafts (10.6%) failed in the first posttransplant year; duodenal leak accounted for most failures (30%; Table 2).

Clinical Presentation

Most patients (85%) presented with right lower quadrant abdominal pain that began at a median of 6 days before assessment; they were usually afebrile and exhibited tenderness and signs of focal peritonitis in the right lower quadrant. The

TABLE 1.

Recipient, donor, graft, and leak characteristics

	Drainage (n = 8[a])	Duodenal repair (n = 17)	Graft pancreatectomy (n = 8)	P
Recipient characteristics				
Median age (range), y	47 (27-57)	42 (31-56)	47 (35-55)	0.32
Median body weight (range), kg	81 (64-98)	75 (51-103)	69 (56-84)	0.12
Median BMI (range), kg/m^2	27 (20-34)	24 (19-33)	24 (20-30)	0.18
Male sex, n (%)	7 (88)	10 (59)	5 (63)	0.35
Median duration of diabetes (range), y	29 (16-51)	26 (18-45)	34 (21-39)	0.38
Median time on dialysis (range), y	2 (0-3)	4 (0-7)	2.4 (1-4)	0.06
SPK transplant, n (%)	3 (38)	12 (71)	5 (63)	0.29
DSA present, n (%)	2 (25)	3 (18)	1 (13)	0.81
Repeat transplant, n (%)	1 (13)	4 (24)	0 (0)	—
Donor characteristics				
Median age (range), y	22 (13-44)	30 (14-43)	26 (17-43)	0.74
Median body weight (range), kg	72 (57-99)	65 (45-97)	76 (54-94)	0.34
Median BMI (range), kg/m^2	24 (21-32)	22 (18-37)	24 (19-26)	0.54
Male sex, n (%)	3 (43)	10 (71)	5 (71)	0.39
NDD donor, n (%)	8 (100)	17 (100)	8 (100)	—
Graft characteristics				
Median warm ischemia time (range), min	34 (25-40)	32 (25-37)	30 (25-30)	0.49
Median cold ischemia time (range), min	439 (388-744)	540 (406-811)	478 (417-664)	0.67
Leak characteristics				
Leak within 3 mo—n (%)	4 (50)	11 (65)	4 (50)	0.69
Median time from transplant to leak (range), d	111 (11-4326)	61 (4-2459)	92 (12-1637)	0.81

[a]Leaks that were treated with IR and surgical drainage were grouped together.
BMI, Body mass index; NDD, neurological determination of death.

rest presented with more diffuse abdominal pain and tenderness, often accompanied by signs of septic shock (hypotension and tachycardia). Blood tests revealed leukocytosis in 15 (45%), leukopenia in 4 (12%), and hyperamylasemia in 18 (55%). CT imaging in 31 of 32 patients supported the suspected diagnosis of a duodenal leak: intra-abdominal fluid collections and/or free air adjacent to the graft duodenum were the most common findings. One patient who presented in septic shock and abdominal pain was taken directly to surgery without preoperative imaging.

We searched the patient's history for potential duodenal leak risk factors. Two patients received treatment for biopsy-proven acute pancreas rejection less than 3 months prior

presentation. Another patient, who had undergone hip replacement surgery 5 days before presentation, was found to have a critical stenosis in the right common iliac artery proximal to the iliac artery Y-graft. In retrospect, hypotension during the hip surgery may have accentuated graft ischemia. No vessel thromboses were identified in the protocol ultrasound.

Management

All patients received broad-spectrum antimicrobial agents at presentation, which were tailored once culture results became available. The cultures grew typical intestinal flora, most commonly *Escherichia coli*, enterococcus, and bacteroidies species.

We separated the patients into 2 main groups based on whether the leak was managed initially by interventional radiology (IR; n = 4) or surgery (n = 29). Within the surgery group, the patients were further subdivided per their treatment: drainage (n = 4), repair (n = 17), or pancreatectomy (n = 8). Recipient, donor, and graft characteristics in these groups were similar (Table 1). Thirty-two patients ultimately

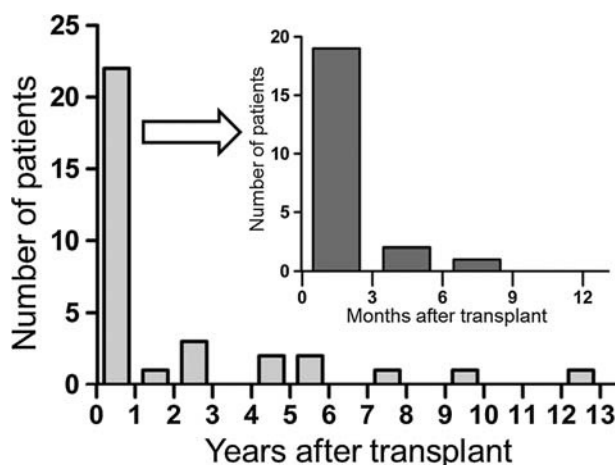**FIGURE 1.** Time from transplant to diagnosis of duodenal leak. Insert—leaks within the first year.

TABLE 2.

Causes of pancreas graft loss in first year

Cause of graft loss	n = 44 (%)
Duodenal leak	13 (30)
Rejection	9 (21)
Acute pancreatitis	8 (18)
Thrombosis	6 (14)
Death with a functioning graft	4 (9)
Infection	2 (5)
Medication nonadherence	2 (5)

underwent surgery for the duodenal leak. Most leaks occurred near the distal or proximal staple line (45% and 27%, respectively); 15% were in the body of the duodenum or at the anastomosis; and in 12%, the site was not identified precisely. The location of the duodenal leak did not correlate with presenting symptoms, physical findings, or initial management.

(A) IR Drainage

IR inserted a percutaneous drain into peripancreatic fluid collections in 4 patients (12%): 3 underwent graft pancreatectomy 8, 35, and 56 days later for persistent drainage and/or uncontrolled sepsis. One leak resolved uneventfully with IR drainage alone.

(B) Surgery

(i) Drainage

Four patients (12%) underwent surgical exploration at presentation to hospital; however, a leak was not identified and drains were placed adjacent to the graft duodenum as a precautionary measure. A persistent leak developed in all 4 patients, and all required graft pancreatectomy 2, 4, 8, and 20 days later for sepsis.

(ii) Duodenal Repair

Seventeen patients (52%) underwent immediate surgical repair of the duodenal leak. Eleven leaks were located at, or near, the distal staple line; 6 were located near the proximal staple line. Most were small punctate holes measuring 2 to 3 mm in diameter; the surrounding duodenum was typically well-vascularized, and viable, and the pancreas parenchyma appeared normal. After the leak was identified, 2 to 4 cm of duodenum was mobilized from the head of the pancreas to enable a tension-free resection with a GIA stapling device (n = 14) or closure with sutures (n = 3). One patient who underwent surgical repair of the distal staple line required surgery 8 days later to repair a new leak in the proximal staple line (only the first leak is included in analysis). Two patients underwent drainage procedures of a peripancreatic collection (1 surgically and 1 by IR) 96 and 833 days after the initial duodenal repair; a controlled fistula to the graft duodenum ensued in both patients, which eventually resolved. Three patients required graft pancreatectomy at 6, 6, 21 days for a persistent leak. Patients undergoing duodenal repair had a median hospital length of stay of 14 (6-86) days.

Collectively, 14 (82%) leaks were repaired successfully; the success rate was similar for leaks that presented during or after the first year (10 of 12 vs 4 of 6, respectively). Thirteen grafts continue to function well after a median follow-up of 2.9 (1.1-6.3) years; 1 graft failed at 477 days from a new duodenal leak.

(iii) Graft Pancreatectomy

Eight patients (24%) underwent graft pancreatectomy at the initial operation. Factors that contributed to the intraoperative decision to remove the graft included severe generalized peritonitis (n = 8), septic shock (n = 2), dusky appearance of the duodenum (n = 1), and concurrent severe pancreatitis (n = 1). Graft pancreatectomy was planned before the operation in 1 patient whose graft had failed from chronic rejection 2 to 3 months earlier. The leaks in this group occurred at the distal staple line (n = 2), proximal staple line (n = 2), or central portion of the duodenum (n = 4). The patients undergoing graft pancreatectomy as initial treatment had a median length of stay of 12 (7-19) days.

Pathology

Histopathologic evaluation of the 19 graft explants revealed various features of immune-mediated injury in the pancreas portion of 7 grafts (chronic cell-mediated rejection (n = 1), C4d-positive staining (n = 3), mild acute rejection (n = 2), and indeterminate acute rejection (n = 1)) that were accompanied by focal mucosal ulcerations in the duodenum and transplant arteriopathy. All but 1 of these grafts were removed during the first 6 months after transplantation. One explant showed ischemic necrosis of the duodenum without rejection. The remaining 11 graft explants showed nonspecific mixed inflammatory infiltrates. None of the resected duodenal specimens in the duodenal repair group showed evidence of rejection or CMV infection. Notably, there were no pathologic differences in the specimens between those that underwent successful or unsuccessful repair. None of the patients had DSA at the time of the leak; however, DSA developed in 3 patients 2, 4, and 12 months after successful repair.

Mortality

Two (6.1%) patients with duodenal leak died. In both patients, confounding factors contributed to their death. One patient had an undefined systemic inflammatory process that caused extensive skin necrosis in the right lower extremity before the leak developed. The duodenal leak was treated initially with surgical drainage followed by graft pancreatectomy. The other death occurred in a nonadherent patient who presented with acute graft rejection, depressive psychosis, and muscle wasting. A duodenal leak developed during treatment of the rejection, which was treated initially with surgical drainage followed by graft pancreatectomy. The patient's family requested withdrawal of medical support.

Retransplantation

Seven of the 17 patients who lost their graft from a duodenal leak received a second pancreas transplant 3.4 (0.8-5.8) years later. The initial management of their leak was graft pancreatectomy (n = 3), drainage (n = 3), and repair (n = 1). Five retransplants continue to function well with a median follow-up of 2.0 (1.2-5.7) years. Two retransplants failed, 1 at 11 days from pancreatitis and 1 at 921 days from acute rejection related to medication nonadherence. Ten patients were not listed for retransplantation (5 for medical reasons, 1 for medication nonadherence, 1 for malignancy, and 3 due to patient preference).

DISCUSSION

Duodenal leak is devastating for enterically drained pancreas transplants: graft loss ensued in 58% (19/33) of the patients with this complication in our study. As the risk of graft loss from acute rejection and other technical complications such as thrombosis have declined, duodenal leak has emerged as a leading threat to pancreas graft survival, especially during the first year after transplantation.[15,21,22] Reducing the incidence of duodenal leak presents a daunting challenge, because most patients do not have an obvious cause or precipitating event. Our study confirms that in selected patients a duodenal leak can be repaired successfully and safely in enterically drained grafts.

The duodenal leak rate in our study (7.8% overall, 2.8% during the first 3 months) matches the 5% to 10% rate reported by others.[15,21,22] In one of the largest single-centre series, Sollinger et al, described a leak rate of 5.7% in 610 enterically drained transplants, of which almost half led to pancreas graft loss.[5] Early leaks (<3 months) are often attributed to technical problems with procurement, preservation, and back-table preparation of the graft, whereas later leaks have been linked to CMV infection and rejection.[23-25] In a previous study, we found that early leaks in SPK recipients correlated with higher peak serum amylase values and previous cardiovascular interventions.[16] None of the patients in our study had CMV infection, which may reflect our CMV prophylaxis protocol as well as monitoring of CMV viremia in high-risk recipients. Only 2 patients received treatment for acute rejection before presentation of the leak; however, 7 of 19 explants showed evidence of occult acute and chronic rejection. Interestingly, of the 12 grafts removed during the first year, 6 showed features of rejection in the pancreas portion of the graft accompanied by focal duodenal mucosal ulcerations, suggesting that optimization of immunosuppression might reduce the risk of duodenal leak.

An attempt to repair a duodenal leak merits consideration provided the patient is hemodynamically stable, abdominal contamination is limited, the duodenum and pancreas appear viable, and the leak has been localized. Excellent long-term graft function and low perioperative morbidity justifies this view. Most of the leaks repaired in our study were adjacent to a staple line, and are amenable to repair by performing a limited duodenal resection with a GIA stapler. Debridement and suture closure with or without a serosal patch may be simpler alternative for small diameter perforations. We favor resection because of the concern of underlying pathology in the duodenum that might compromise healing. Despite this concern, however, none of the resected duodenal specimens revealed a pathologic explanation for the perforation. This finding also suggests that gross evaluation of the duodenum is sufficient to determine whether to proceed with the repair. We construct routinely a roux-en-Y limb to drain pancreatic exocrine secretions during the transplant procedure, which may provide additional safety. Other groups have converted pancreatic exocrine drainage to a roux limb after repairing the duodenal leak for this reason.[20,26]

Percutaneous or operative drainage of the duodenal leak failed to salvage 7 of 8 grafts. Only 1 patient who underwent percutaneous drainage had long-term graft survival. The circumstances that led to a favorable outcome in this patient remain unclear, as their clinical presentation was like the other 7 patients. The inability to localize the leak in 4 patients who underwent surgery highlights one of the pitfalls of this intervention. Every effort should be made to identify the leak during exploration, recognizing that dissection of the pancreas and duodenum in an inflamed operative field is difficult and potentially hinders the development of a controlled fistula. In the absence of an obvious duodenal leak, a leak from the bile duct stump should also be considered and excluded. We have used octreotide in some patients who were drained to promote fistula closure, but apart from reducing the volume of the effluent, there was no appreciable benefit, consistent with other reports.[27-29] Others have resolved chronic fistula by injecting fibrin glue into fistula tract.[30]

Total duodenectomy offers another management approach for duodenal leaks. Orsenigo et al[19] treated 4 duodenal leaks (2 bladder- and 2 enteric-drained) by duodenectomy and pancreatic duct occlusion with Neoprene, which allowed long-term graft function in 3 patients; the other graft failed from rejection. Total duodenectomy with anastomosis of the pancreatic duct to the jejunum was performed successfully by Uva et al[20] in 1 patient with a duodenal leak and by Boggi et al[26] in 2 patients (1 for duodenal leak and 1 for duodenal bleeding). In instances where the duodenum and head of the pancreas are ischemic, pancreaticoduodenectomy has salvaged some grafts.[31] These case reports clearly demonstrate the feasibility and success of aggressive resection. As emphasized by Boggi et al,[26] however, these procedures are generally reserved for stable patients who have limited abdominal contamination.

In summary, we present one of the largest cohort-series of duodenal leak in enterically drained pancreas transplants. The initial management decisions in our patients were dictated largely by patient and graft factors. Operative intervention has been the cornerstone of our approach, reserving IR drainage for hemodynamically stable patients with well-localized drainable collections. Drainage alone, however, resulted in a high rate of graft loss. The high success rate of operative repair was unanticipated and has encouraged us to consider this option more carefully and raise the threshold for graft pancreatectomy.

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