

Case Study

Simultaneous pancreas-kidney transplant: Pancreatic graft failure in the first-year post-transplantMickaela Nixon¹ and Carlo D L Ceresa²¹Medical Sciences Division, University of Oxford, UK²Nuffield Department of Surgical Sciences, University of Oxford, UK

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Key Learning Points**Carlo D L Ceresa**

Simultaneous pancreas and kidney (SPK) transplantation offers patients with diabetes mellitus and end-stage renal failure an opportunity to achieve insulin independence with a reduction in diabetes-associated complications, freedom from dialysis and prolongation of life. It is a successful treatment, with approximately 80% of grafts surviving at 5 years in the UK. However, good outcomes are reliant on several key factors including donor and recipient selection, organ retrieval and preparation, implantation with associated ischaemia/reperfusion injury and post-operative management including immunosuppressive strategies.

This case focuses on the early loss of a pancreas graft in an SPK recipient. It addresses the merits of SPK transplantation in general and explores in detail the potential causes of graft loss. Most pertinent to this case, we appreciate that graft loss could be due to several insults rather than a singular pathology. Despite an optimal donor (young donor after brain-stem death), the recipient suffered graft thrombosis, pancreatitis, full-thickness wound dehiscence and duodenal leak. It is important to consider the complex and sometimes unpredictable nature of pancreas transplantation where complications must be rapidly identified and managed.

Introduction

Approximately 15% of the pancreas grafts transplanted simultaneously with a kidney in insulin-dependent diabetics fail within the first year.¹⁻³ Aside from rendering the recipient insulin-dependent, this failure has the additional disadvantages of decreased patient and renal allograft survival.¹ In this case report, the experiences of a patient with Type 1 diabetes who suffered pancreatic graft failure less than one month after receiving a simultaneous pancreas-kidney transplant are shared. Subsequently, the merits of the simultaneous transplant compared to other therapies are investigated, highlighting the importance of pancreatic graft function one-year post-transplant. Finally, research investigating the causes of early pancreatic graft failure is presented and discussed.

Surgical case

ML is a man in his early thirties who received a simultaneous pancreas-kidney (SPK) transplant from a young (<30 years of age) deceased donor after brainstem death after being on the transplant waiting list for approximately one year. Diagnosed with Type 1 diabetes mellitus (T1DM) at 16 years of age, ML struggled with a number of diabetes-related complications. In his late twenties he was diagnosed with mild diabetic neuropathy and retinopathy. He also suffered from diabetic nephropathy,

with his kidney function declining to an estimated glomerular filtration rate as low as 3mL/min/1.73m² prior to being started on haemodialysis. Additionally, ML struggled from hypoglycaemic unawareness, experiencing frequent hypoglycaemic events, sometimes up to three times a day.

ML was on haemodialysis for 20 months prior to his transplant. Despite thorough monitoring, and cholecalciferol and Sevelamer, ML's calcium and phosphate were erratic throughout dialysis. Also, his inter-dialytic fluid gains (in excess of 4 Litres) and pre-dialysis blood pressures (systolic around 160mmHg) were regular causes for concern, sometimes warranting daily dialysis. Finally, as a qualified painter and decorator, ML struggled to find employment given his thrice weekly dialysis schedule. The freedom, glycaemic control and reduced burden of diabetes-related complications typically afforded by transplantation made application to the transplant waitlist a straightforward decision for ML.

During the transplant itself, the donor pancreas was transplanted to ML's right iliac fossa and the kidney to the contralateral fossa, with both organs placed intraperitoneally through a lower midline incision. An alternative to this approach is the ipsilateral placement of the organs, which does not benefit from the organ isolation of a contralateral approach but does localise vascular dissection unilaterally, preserving the other side for future

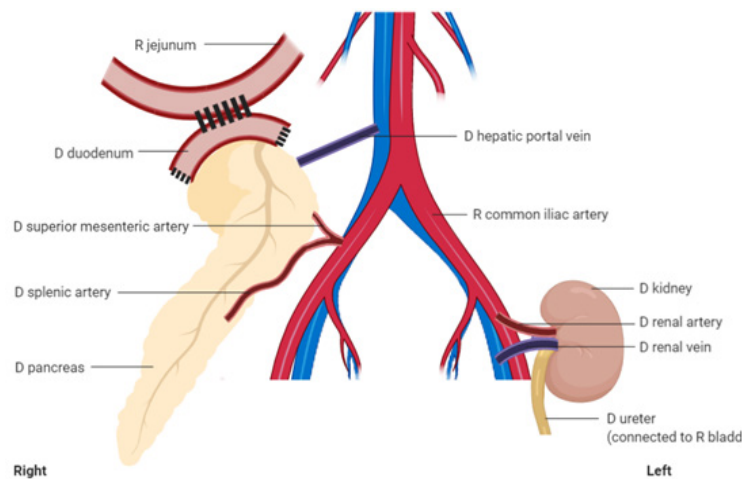


Figure 1: Simultaneous pancreas kidney transplant as in ML. Features contralateral placement of grafted organs, intestinal exocrine drainage (via the duodenal-jejunal anastomosis) and endocrine drainage into the systemic circulation (via the donor hepatic portal vein). Vascular supply of the pancreatic graft via a Y-graft connecting the donor superior mesenteric artery and splenic artery to the recipient right common iliac artery. R: recipient; D: Donor.

transplants.⁴ As is standard, ML's pancreas was not excised in order to preserve its native exocrine function which is typically spared in T1DM. The donor pancreas was connected such that its exocrine secretions drained enterically via anastomotic joining of the donor duodenum to ML's small intestine (Figure 1).^{5,6} An alternative, reserved for when a pancreas is transplanted independently of a kidney, is to anastomose the donor duodenum to the recipient bladder however, this has been associated with an increased incidence of metabolic and urological complications compared to enteric drainage.^{7,8} Vascular supply of the pancreatic graft was provided via a Y-graft of the donor superior mesenteric and splenic arteries connected to ML's right common iliac artery. The donor hepatic portal vein was connected to ML's inferior vena cava, directing venous and endocrine drainage into the systemic circulation. An alternative, now lesser used, approach is to connect the donor hepatic vein to the recipient superior mesenteric vein, directing initial drainage into the portal circulation. Morbidity and graft survival as well as metabolic and immunologic markers have been found to be comparable between the approaches.^{2,5,6}

After the transplant, ML's stay in hospital was prolonged by complications. Computed Tomography (CT) imaging three days post-transplant showed an arterial thrombus in the donor Y-graft. However, the pancreas enhanced homogeneously. Four days post-transplant, ML returned to theatre for a saline washout due to a full thickness infra-umbilical dehiscence such that small bowel and free serosanguinous fluid were visible. Pancreatitis was identified in the grafted pancreas however, there were no other abnormalities found including in the surrounding vessels and the transplanted kidney. Nine days post-transplant, ongoing fevers and unsettling tachycardia warranted an abdominal CT which showed small amounts of free fluid in the abdomen and diffuse swelling of the grafted pancreas. This prompted a return to theatre where a further washout and drain insertions were performed. 12 days post-transplant, ML returned to theatre for the third time due to the presence of bile in the post-operative drains and continually rising inflammatory markers. The suspicion of ongoing graft pancreatitis and a duodenal leak was confirmed, with the graft described as 'oedematous' and 'undergoing generalised saponification.' Also found

was evidence of a hole in the superior staple line of the graft duodenum. 18 days post-transplant, ML once again returned to theatre, and his pancreatic graft was explanted.

The graft loss was attributed to the failure of the donor duodenal staple line, resulting in a continuing bile leak from the duodenum, and concurrent acute graft pancreatitis, resulting in gross inflammation of the allograft. Histopathological analysis of the explanted pancreas identified haemorrhagic areas with some exudate macroscopically, and evidence of fat necrosis of the peripancreatic adipose tissue in addition to auto-digestion of the parenchyma microscopically. The donor duodenum, although poorly preserved, had features consistent with ischaemia. The associated vasculature showed no evidence of thrombosis or vasculitis and there was no visible evidence of acute rejection, dysplasia or malignancy.

Throughout the 18 days post-transplant, ML was insulin independent. His random blood glucose levels remained below 9.0mmol/L, far lower than the levels of >20mmol/L prior to transplantation, indicating pancreatic graft function. Similarly, ML's serum creatinine levels, the primary measure of kidney graft function, systematically decreased from 1,000 $\mu\text{mol/L}$ post-transplant to settle at 120-130 $\mu\text{mol/L}$. His urine output also significantly increased relative to his native output, indicative of good kidney allograft function.

ML had been in hospital in excess of three weeks at the time of writing. Speaking with him between his subsequent operations he often voiced regret for undergoing the SPK transplant. ML's transplant and broader in-hospital experience prompted further investigation into the overall merits of, and causes of early pancreatic graft failure in, SPK transplants.

Overview of pancreas transplantation

T1DM is a condition driven by the autoimmune-mediated destruction of pancreatic beta-cells, leading to insulin insufficiency. Unmanaged, it can lead to a range of complications including nephropathy and end-stage renal disease (ESRD) which necessitates renal replacement therapy. In 1966, William Kelly and Richard Lillehei performed the first pancreas and renal transplantations into patients with T1DM with renal failure.⁹ T1DM with advanced chronic kidney disease or ESRD has remained

the primary indication for simultaneous pancreas and kidney transplants (SPK) ever since.¹⁰ Additionally, SPK is indicated in select Type 2 diabetes mellitus (T2DM) patients who are insulin-dependent and typically satisfy additional criteria.¹¹⁻¹³ The overarching objectives of an SPK are to gain insulin independence, alleviate the need for dialysis, and prevent diabetes-associated complications. Most SPK procedures involve grafts from a single deceased donor after brainstem death, with approximately 3% procured from a deceased donor after cardiac death.¹⁴

SPK compared to maintenance therapy

SPK results in better patient outcomes than maintenance therapy consisting of insulin and dialysis. A study of Korean diabetic patients with ESRD showed that 7-year mortality was significantly reduced in SPK transplant recipients compared to those who remained on dialysis.¹⁵ Isla Pera et al., using the 36-Item Short Form Health Survey, showed that post-SPK transplant patients had a higher quality of life compared to the patients who remained on maintenance therapy, with significance seen across all dimensions.¹⁶

Insulin independence is achieved after one year in the majority of SPK patients, exemplified by 96% of the 25 SPK patients followed by Gerber et al. reaching independence and subsequently suffering no episodes of severe hypoglycaemia in the 3 years post-transplant.¹⁷ Their Haemoglobin A1c, a marker of glycaemic control, also significantly improved (8.7% pre-transplant to 5.8% 3-years post-SPK).¹⁷ The broader benefits of pancreas transplantation-mediated normoglycemia include improved:

- neuropathic measures – motor and sensory nerve conduction indices were found to significantly improve starting 1-year and continuing 10-years post pancreas transplant, whilst function declined in non-transplanted, insulin-dependent controls¹⁸
- renal function – SPK transplantation was found to prevent new-onset diabetic nephropathy and reverse existing lesions after 5 years of normoglycemia^{19,20}
- markers of cardiovascular disease – abnormal lipid profiles of insulin-dependent diabetics were found to significantly improve 2 months post-SPK with triglycerides significantly lower and high-density lipoprotein cholesterol higher²¹

- retinopathy - although an area of debate, some research has found significantly more transplanted patients experience stabilization or even regression of existing retinopathy compared to non-transplanted T1DM patients, as measured by retinal lesions^{3,22,23}

Although difficult to control for inherent differences in transplant-appropriate versus non-transplanted populations, these studies support the long-term benefits of SPK transplantation in insulin-dependent diabetics with renal failure.

SPK compared to kidney transplant

SPK has been shown to result in better patient and kidney allograft survival when compared to a kidney transplant alone (KTA) plus insulin. In a study of 29 patients eligible for a SPK, those who had a SPK with the pancreas graft surviving for at least two years had significantly lower 6, 8 and 10-year mortalities than those who had a functioning kidney graft alone (20% 10-year mortality post-SPK versus 80%).²⁴ Refining this further, an analysis of 18,549 T1DM patients with renal failure reported equivalent 72% 8-year recipient survival rates post-SPK and living-donor KTA, significantly greater than the 55% reported in deceased kidney donor recipients.²⁵ Stratifying further still, using records of 8,000+ SPK-eligible patients, Weiss et al. found that the 7-year mortality in those with a functional pancreatic graft one year post-SPK was significantly lower than in living-donor KTA, SPK with a non-functioning graft at one year, and deceased-donor KTA recipients (11%, 20%, 26% and 35%, respectively).¹

Pancreatic graft function one-year post-transplant appears to also be a predictor of kidney allograft survival. Weiss et al. found that 72% of SPK recipients with a functioning pancreas graft after one year had a surviving kidney allograft after 7 years.¹ This was significantly higher than the 64% 7-year kidney allograft survival rate in living-donor KTA, 60% in SPK with pancreatic failure within one year and 50% in deceased-donor KTA.¹ Overall, these results highlight the importance of early pancreatic graft function in both recipient and renal graft survival.

Pancreatic allograft survival and function in SPK

Despite higher failure rates during the first-year post-transplant, pancreas grafts show comparable failure

Study	Description of study population	First 90 days post-transplant	First year post-transplant
Alhamad et al. 2019 ¹³	669 T2DM patients with kidney disease who received SPK transplants between 2000 and 2016 and who survived and had a functioning kidney 3 months post-transplant	6%	-
Kandaswamy et al., 2018 ³⁰	Aggregate SPK transplant data of procedures conducted across the USA in 2017-2018; Includes all-cause graft failure in first 90 days post-transplant	5.1%^ (5.9%)	-
Kandaswamy et al., 2018 ³⁰	Aggregate SPK transplant data of procedures conducted across the USA in 2015-2016; Includes all-cause graft failure in first 90 days post-transplant	8.5%^ (8.7%)	-
Kandaswamy et al., 2013 ³⁶	Aggregate SPK transplant data of procedures conducted across the USA in 2012-2013; Includes all-cause graft failure in first 90 days post-transplant (note: data from transplant centres is not audited)	4.9%^ (7.6%)	14.2%**
Gruessner and Gruessner, 2016 ²	3,797 SPK transplants between 2010 to 2014 reported in the International Pancreas Transplant Registry and the United Network for Organ Sharing	7.7%*	10.9%
Gruessner and Gruessner, 2016 ²	4,266 SPK transplants between 2005 to 2009 reported in the International Pancreas Transplant Registry and the United Network for Organ Sharing	10.5%*	14.6%
Wolfe et al., 2009 ²⁷ + McCullough et al., 2009 ²⁶	848 SPK transplants conducted across the USA in 2007; Graft survival rates unadjusted for recipient death	-	14%

Table 1. Rates of pancreatic graft failure in the first 90 days and first year post SPK transplant. Studies ordered with those based on the most recent transplant data at the top.

(^) Data interpreted from published graphs, reported figures in brackets for all types of pancreas transplants(*) Calculated based on figures reported assuming 70% of graft failure in the first 90 days was due to TF, as reported for 2010-2014 data (***) One-year survival figures based on 2008 transplant cohort

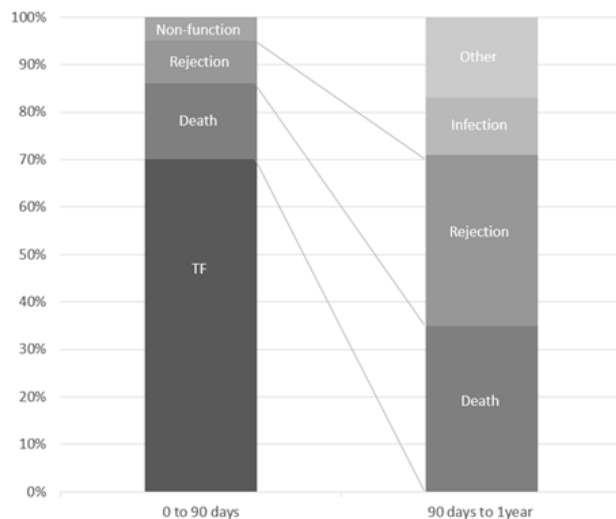


Figure 2. Causes of pancreatic graft failure during the first-year post SPK transplantation. Adapted from Gruessner and Gruessner, 2016 and based on data from the International Pancreas Transplant Registry. Includes SPK transplants conducted between 2010 and 2014. TF: technical failure; death: death of a recipient with a functioning graft; rejection: includes acute rejection in 0 to 90 days, and acute and chronic rejection in 90 days to 1 year; non-function: primary non-functional graft; other includes partially functioning grafts, malignancy and unknown causes of failure.

rates to kidney grafts after the first year. Based on data published in 2008/2009, pancreatic allograft survival rates post-SPK were found to decrease from 86% to 73% to 53% at one, 5 and 10-years post-transplant, a step-change comparable to kidney allograft survival post-SPK of 93-95%, 79% and 60%.^{3,26,27} Pancreatic graft loss over that time is gradual and constant, with limited significant functional loss.²⁸ For example, Mora et al., comparing graft function in SPK patients one versus 10-years post-transplant, observed no differences in either HbA1c nor fasting glycemia levels, with a non-significant decline in insulin levels.²⁹

Pancreatic allograft failure within one year post transplant

Understanding pancreas graft function one-year post-transplant is critical because it is appreciably higher than SPK kidney graft failure rates and significantly correlates with recipient and kidney allograft survival post-SPK.¹³ Although most studies estimate one-year pancreas graft failure to be approximately 15%, exact figures vary, driven by a lack of standard definition of graft failure as well as improvements in the procedure itself (Table 1).¹⁻³ Standardization is expected in future studies, as the United Network for Organ Sharing Pancreas Transplantation Committee formally defined pancreas graft failure in 2018 as the presence of one or more of the following criteria:³⁰

- A recipient's transplanted pancreas is removed
- A recipient re-registers for a pancreas
- A recipient registers for an islet transplant
- A recipient's insulin use is ≥ 0.5 units/kg/day for 90 consecutive days
- A recipient dies

Pancreas allograft failure in the first 90 days is typically analysed separately from the remaining 9 months of the first-year post-transplant given the different rates and aetiologies. Gruessner and Gruessner, using the International Pancreas Transplant Registry, provide the most extensive analysis. Using data from 2010-2014, they determined the pancreatic allograft failure rate to be 7.7% in the first 90 days, accounting for the majority of the 10.9% failure rate one-year post-transplant (Table 1).² The higher rate of early graft failure was driven by technical failure (TF) defined as graft failure in the first 90 days post-transplant due to reasons other than rejection or death of the recipient for reasons unrelated to the transplant. TF includes thrombosis in the graft vasculature, anastomotic leaks, bleeding, and allograft pancreatitis, amongst other

things.³¹

Gruessner and Gruessner reported a TF rate of 5.4%, accounting for ~70% of pancreatic graft loss in the first 90 days, a rate which appears to be falling over time as would be expected with surgical advancements (Table 2).² Graft thrombosis was the leading driver of TF, accounting for approximately 75%, a finding consistent with other studies (Table 2).² The other drivers of failure within 90 days post-transplant were death of a recipient with a functioning graft and acute pancreatic rejection (Figure 2).² In the latter 9 months of the first year post-transplant, death with a functioning graft and rejection were the largest drivers of graft loss followed by infection (Figure 2).²

Technical failure and rejection

Acute rejection is consistently a distant second driver of early death-censored pancreatic graft loss with Gruessner and Gruessner finding rejection to account for <10% of graft loss in the first 90 days (Figure 2).⁷ Overall, rejection was found to drive a 1.2% rate of loss in the first-year post-transplant, a figure supported by Reddy et al.^{2,32} Weiss et al. also found no difference in rejection incidence between pancreas grafts that were functioning versus non-functioning one-year post-transplant.¹ However, the notion of acute pancreatic rejection (APR) accounting for such a small portion of failures has been called into question, given that APR "can be overlooked if [clinical or biochemical] factors alone are relied upon for its diagnosis," and supported by the fact that thorough histological analysis of excised grafts is often not conducted.⁵¹

Acute rejection occurs when the recipient develops an immune response targeting the foreign Human Leukocyte Antigens (HLA) expressed on a transplanted tissue. This recognition can trigger the development of T-cells or antibodies with sensitivity for the transplant HLA, resulting in rejection of the transplanted tissue. The primary mechanism of rejection determines whether it is considered cellular (i.e., T-cell mediated) or antibody-mediated rejection (AMR), with each mechanism driving comparable proportions of APR post-transplant.³⁵ This differs from hyperacute rejection which is mediated by pre-existing antibodies that lead to immediate graft loss, or chronic rejection which is typically a longer-term process characterised by immune-mediated fibrosis and dysfunction of the transplanted tissue.

A number of studies point towards a higher incidence of APR during early pancreatic graft failure than

initially characterized. Kort et al., retrospectively analysing 33 SPKs rejected less than one-year post-transplant, found that AMR was present in grafts that had previously been reported as lost due to TF.³⁴ Using the Banff schema for rejection, AMR was diagnosed in specimens with specific histological parameters, C4d-positive inter-acinar capillaries and circulating donor-specific antibodies, whilst ‘suspicious for AMR’ was identified in specimens with any two of these parameters. 21% of the grafts were diagnosed with AMR and 24% of cases were deemed suspicious of AMR.³⁴ Interestingly, thrombosis occurred with equal frequency across the three groups.

Wallace et al., again leveraging the Banff criteria, investigated APR mediated by both antibodies and T-cells. 23 pancreatic grafts that were explanted less than 3 months post-transplant were re-examined histologically. APR was identified in 9 of the 15 recipients whose grafts were lost “due to duodenal leaks or recurrent peripancreatic collections” however, in contrast to Kort et al., APR was not identified in any of the grafts lost due to thrombosis or ischemia.³⁴

An underappreciation of APR incidence could have important patient implications. Niederhaus et al. found that 20% of pancreatic grafts with an episode of rejection failed within one-year post-transplant, regardless of rejection treatment.³⁵ Also, Kort et al. found APR to be predictive of renal graft survival, with all 7 patients diagnosed with AMR losing their renal grafts within one year.³⁴ Given these critical patient implications, Wallace et al. sensibly call for the re-defining of TF to be death-censored graft failure in the first 90 days post-transplant

in the absence of rejection of the pancreas or duodenum, as confirmed through histological analysis.³¹ Current clinical practice to histologically assess for rejection in SPK recipients is to perform a kidney biopsy, as the kidney is considered a surrogate marker for rejection of the pancreas from the same donor.⁴ However, because there exists a 40% discordance between renal and pancreas biopsies, to truly appreciate the incidence of APR and characterize the underlying aetiology, a pancreas allograft biopsy is needed.³⁵ This pancreatic biopsy should then be assessed and stained, and the presence of circulating donor-specific antibodies ascertained, as per the Banff schema.³⁴

ML’s experience, and those referenced in the studies above, suggests that attributing graft failure to a singular cause is potentially an oversimplification. However, co-existence makes it difficult to identify potential causality. For example, ML’s graft featured thrombosis, acute pancreatitis, duodenal leak and duodenal ischaemia, with no visible histopathological evidence of acute rejection. However, it is important to note that the Banff schema was not leveraged for the assessment of acute rejection. Mindful of the results of Kort et al., and Wallace et al., in cases like that of ML’s, enteric leak could have caused pancreatic inflammation resulting in the upregulation of HLA expression and subsequently APR. Alternatively, APR could have been the primary driver of inflammation that contributed to pancreatic saponification and anastomotic leak. Another potential mechanism could have been that early thrombosis caused subsequent ischaemia and persistent allograft inflammation, leading to failure. Critically, each scenario would require a different

	Gruessner and Gruessner, 2016²	Gruessner and Gruessner, 2016²	Finger et al., 2013³⁷	Humar et al., 2004³⁸
Description of study population	3,797 SPK transplants between 2010 to 2014 reported in the International Pancreas Transplant Registry and the United Network for Organ Sharing	4,266 SPK transplants between 2005 to 2009 reported in the International Pancreas Transplant Registry and the United Network for Organ Sharing	306 SPK transplants between 1998 and 2011 conducted at the University of Minnesota	123 pancreas transplants between 1994 and 2003, which failed due to reasons of TF (of which 50 or 40% of the 123 were SPK)
Overall rate of TF	5.4%	7.4%	13.4%	15.3% (SPK specific)
Thrombosis	4.1% (76%)	5.5% (74%)	6.5% (49%)	8.0% (52.0%)
Infection	0.5% (9%)	0.6% (8%)	1.6% (12%)	2.9% (18.7%)
Graft pancreatitis	0.2% (4%)	0.5% (7%)	4.2% (31%)	3.1% (20.3%)
Anastomotic leak	0.4% (7%)	0.5% (7%)	1.0% (8%)	1.0% (6.5%)
Bleeding	0.2% (4%)	0.2% (3%)	0.0% (0%)	0.4% (2.4%)
Procurement injury	0.1% (2%)	0.1% (1%)	-	-

Table 2. Rate and cause of pancreatic graft Technical Failure (TF) as recorded across various studies. Studies ordered with those based on the most recent transplant data on the left.

management approach. One is left to speculate whether taking a biopsy of the inflamed pancreatic allograft visualised during the initial laparotomy four days post-transplant and assessing it based on the Banff criteria would have clarified a singular root cause for ML's unfolding graft failure and help guide subsequent management.

Conclusions

SPK transplantations are indicated for insulin-dependent diabetes patients with ESRD. Not only have they been shown to improve patient outcomes relative to a maintenance therapy of dialysis and insulin, they have been shown to afford superior patient and kidney allograft survival relative to KTA, especially when the pancreas allograft is functioning one-year post-transplant. Unfortunately, one-year pancreatic allograft failure rates are high at approximately 15%, significantly higher than the 5% failure rate seen with kidney grafts.^{1,2} TF has consistently been found to be the major driver of this high failure rate, accounting for approximately 70% of graft failure within 90 days of transplant, compared to the 10% by immunological-mediated rejection.² However, recent studies suggest this is potentially an artificial distinction that underrepresents the incidence of rejection, to the potential detriment of allograft survival and patient management.

Case studies like that of ML, which featured thrombosis, anastomosis leakage and pancreatitis, shed light on the potentially multi-factorial nature of allograft loss in SPK. It is key that future investigations appreciate this complexity and look to characterise the cause(s) of failure, mindful to identify acute rejection in particular. A more robust understanding will then be able to better inform patient investigation and management if, and when, post-transplant complications arise.

Conflicts of interest

None.

Funding

None.

Consent

The patient has consented to the publication of this case study.

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