ORIGINAL ARTICLE

Concurrent biopsies of both grafts in recipients of simultaneous pancreas and kidney demonstrate high rates of discordance for rejection as well as discordance in type of rejection – a retrospective study

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SUMMARY

It is commonly assumed that in simultaneous pancreas and kidney (SPK) recipients, rejection of the two organs is concordant. As a result, concurrent biopsies of both organs are rarely performed and there are limited histological data on how often rejection is in fact discordant. We reviewed all SPK recipients transplanted at the University of Wisconsin between January 01, 2001, and December 31, 2016, that underwent biopsy of both organs. We included all patients whose biopsies were within 30 days. If patients were treated for rejection between biopsies, they were excluded if the biopsies were more than 4 days apart. Ninety-one simultaneous biopsies were performed within 30 days of each other, and 40 met our inclusion criteria. A total of 25 (62.5%) patients had concordance of biopsy findings: 11 had rejection of both organs, and 14 had no rejection of either organ. The other 15 (37.5%) were discordant for rejection, with 10 having pancreas-only rejection and five kidney-only rejection. It was striking to find that four of the 11 patients with concordance for rejection (36%) had different types (AMR, ACR, or mixed) of rejection in the two organs. This large series of simultaneous pancreas and kidney biopsies demonstrates the continued utility of performing biopsies of both organs.

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Key words
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Introduction

Over 75% of pancreas transplants are performed at the same time as a kidney transplant, in the form of a simultaneous pancreas and kidney transplant (SPK) [1,2]. In the United States, more than 28 000 pancreas transplants have been reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR) [3]. Pancreas allograft survival continues to improve. Among all pancreas

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recipients, including pancreas transplant alone or pancreas after kidney (PAK) transplant recipients, those with an SPK experienced the best pancreas allograft survival rates with 86% at 1 year and 54% at 10 years [4].

Kidney or pancreas rejection can occur any time after SPK and is a major obstacle to prolonged graft survival [5]. In SPK recipients, serum amylase, lipase, glucose, and creatinine, as well as proteinuria, are routinely monitored to detect rejection. In clinical practice, abnormalities of either pancreas or kidney function, or both, may be observed, raising the question of which organ(s) to biopsy. Many have assumed that rejection is usually concordant; that is, rejection is either found in both organs or neither organ. The argument is therefore that if pancreas enzymes and kidney function parameters are both abnormal, or if kidney function is abnormal in the absence of pancreas enzyme elevations, a kidney biopsy is sufficient to diagnose rejection, and an additional biopsy of the pancreas will not affect clinical management. However, this approach has never been validated, and the assumption that concordance is universal has been questioned [6]. Here, we assess the utility of performing biopsies of both the kidney and pancreas allografts by reporting not only the rates of rejection concordance, but also the frequency of rejection in the two organs being of sufficiently different rejection type or severity to merit different treatments.

Methods

Study population and design

This was a single-center, retrospective study of SPK recipients from the same donor transplanted at the University of Wisconsin between January 01, 2001, and December 31, 2016, who underwent biopsy of both functional organs. We included all patients whose biopsies were within 30 days of each other. If patients were treated for rejection between biopsies, they were excluded if the biopsies were more than 4 days apart, due to a concern that the treatment would reduce the ability to detect rejection or skew the severity in the opposite organ. Biopsies of explanted organs and postreperfusion biopsies also were excluded. Patients were divided into a concordant group for rejection and a discordant group for rejection. We categorized biopsies as concordant if they had rejection in both allografts or no rejection in both allografts, otherwise they were considered discordant. This study was approved by the Health Sciences Institutional Review Board at the University of Wisconsin.

Data collection

Data collection included basic demographic information, date of SPK transplantation, age, race and gender, induction immunosuppression, wait time for transplant, and type of deceased donor. We collected the histology of pancreas and kidney biopsies as well as graft survival.

Kidney rejection treatment

Treatment of acute cellular rejection (ACR) was based on Banff criteria. Borderline or Banff I rejection was treated with steroid pulse, while Banff II and III ACR was treated with steroid pulse plus thymoglobulin, 6–10.5 mg/kg in 4–7 divided doses.

Antibody-mediated rejection (AMR) treatment protocols were based on both the severity of rejection and the time of diagnosis of AMR after transplant. For early rejection (within 3 months post-transplant), treatment included dexamethasone 100 mg pulse, plasmapheresis (PP) 4–6 sessions, and IVIG 100 mg/kg after each PP. Late rejection (>3 months post-transplant) was treated with dexamethasone 100 mg pulse and IVIG 200 mg/kg every 2 weeks × 3. Baseline immunosuppression was also increased by approximately 25%. Rituximab 375 mg/m^2 was added to the treatment of either early or late rejection based on clinical characteristics such as younger age, better kidney function, higher DSA, greater microcirculation inflammation, and lower chronicity score. In mixed rejection, steroid pulse, IVIG, thymoglobulin 10.5 mg/kg ± rituximab ± bortezomib were used.

Pancreas allograft biopsy

Elevated pancreatic enzymes were the most common indication for pancreatic allograft biopsy. Our approach to the patient with elevated enzymes included history and physical, fasting C-peptide, HbA1C, donor-specific antibodies (DSA), and an imaging study, preferably CT scan of the abdomen and pelvis with IV and oral contrast [7]. In our practice, we performed ultrasound-guided biopsy with an 18-gauge automatic biopsy device. Our trajectory for biopsy is ideally toward the tail, avoiding the splenic artery and vein. If we are unsuccessful, or there is no suitable safe window free of overlying bowel, then we proceed with CT-guided biopsy using a posterior approach, or alternatively an open or laparoscopic biopsy, but this is rarely required. In our experience with pancreas biopsies of 422

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recipients, only 22 (6%) were nondiagnostic, mainly due to sampling error [8].

All pancreas transplants in the study were enteric drained, since after July 1996, bladder drainage was almost never used.

Pancreas rejection treatment

Treatment of pancreas rejection was based on the type and severity of rejection and was graded by the Banff criteria [9]. ACR was treated with IV steroid pulse with or without thymoglobulin 6–12 mg/kg in 4–10 divided doses, while mixed rejection was treated with steroids, thymoglobulin, IVIG, and PP. AMR was treated with steroids, IVIG, and PP [7].

Statistical analysis

Continuous data were compared using Student's *t*-test or the Wilcoxon rank-sum test, as appropriate, while categorical data were analyzed using Fisher's exact test or chi-square test. P values < 0.05 were considered statistically significant.

Results

Baseline characteristics

There were 91 cases of pancreas and kidney biopsies performed within 30 days of each other in SPK recipients. Of those, 40 met our inclusion criteria of two functional allografts with no treatment for rejection between the biopsies, or if rejection was treated, the biopsies were within 4 days of each other. Biopsies were excluded because either the pancreas (15), kidney (6), or both organs had been explanted (7), because the kidney was biopsied at the time of transplant reperfusion (6), because treatment was given more than 4 days before the kidney (8) or pancreas (6) biopsy, or because the kidney and pancreas were from different donors (3) (Fig. 1). Of the 40 pairs of biopsies studied, 25 had biopsy findings that were concordant for rejection, while 15 were discordant, so that rejection was present in one allograft but not the other. All kidney and pancreas biopsies were performed by the real ultrasound-guided approach except for one patient who underwent open pancreas biopsy at the time of open cholecystectomy.

The mean age at time of transplant was 43.7 ± 8.87 years, and 50% of patients were female. The mean interval between the two-allograft biopsies was 4 ± 7 days, and other baseline characteristics are detailed in Table 1.

Table 1. Baseline characteristics.

Mean interval between biopsies (days)	4 ± 7
Mean age at time of transplant	43.7 ± 8.87
Female	20 (50%)
Non-Caucasian	5 (13%)
Nondiabetes type I	4 (10%)
Mean wait time for transplants (days)	158 ± 143
Donation after cardiac death	4 (10%)
Expanded criteria donor	4 (10%)
Induction immunosuppressive	
Antithymocyte globulin	6 (15%)
Alemtuzumab	13 (33%)
Basiliximab	21 (53%)

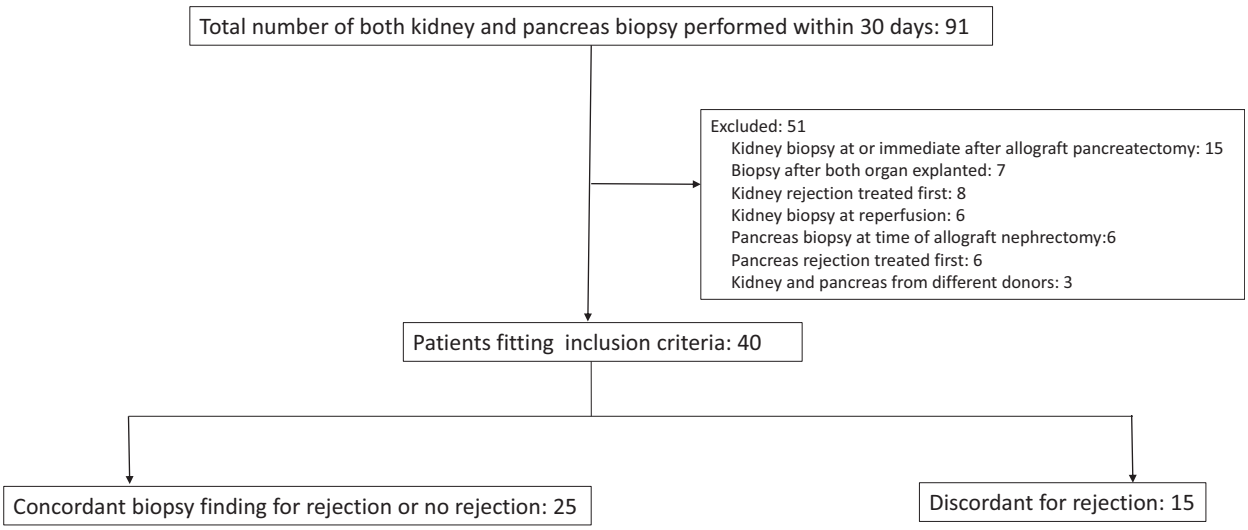

Figure 1 Simultaneous pancreas and kidney transplant recipients with biopsies of both allografts.

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Concordance and discordance

Of the 25 patients with concordant biopsy findings, 11 had rejection in both organs and 14 did not have any rejection (Table 2). Of 11 recipients with rejection in both organs, seven had the same type of rejection: Six showed ACR in both organs, and one showed mixed rejection in both biopsies. Most striking, four of the 11 recipients with rejection in both organs exhibited a different type of rejection in each allograft. One recipient had ACR in the kidney but AMR in the pancreas, one had AMR in the kidney but ACR in the pancreas, one had AMR in the kidney and mixed rejection in the pancreas, and one had ACR in pancreas and mixed rejection in kidney. These differences in pathology between the two organs had a significant impact on the choice of treatment for these four patients. Ten of 11 patients in this group had ACR or mixed rejection of the pancreas: Seven had grade II ACR, two had grade I ACR, and one had grade III ACR. Three patients had mixed or AMR of the pancreas, with diffuse c4d positivity and diffuse capillaritis. The pathology on kidney biopsies ranged from borderline rejection to Banff IIA. All patients with AMR or mixed rejection of kidney were positive for c4d.

We also found some differences in the pathology of organs that were concordant for lack of rejection. In one, evidence of adenovirus infection was found on the kidney biopsy, but not the pancreas; two had BK nephropathy and no rejection in pancreas; one had features of membranoproliferative on the kidney biopsy and no rejection in pancreas. Of 15 patients with discordance for the presence of rejection, 10 had pancreas rejection only, while five had kidney rejection only. Among eight patients with pancreas-only rejection showing ACR or mixed rejection, four had grade I ACR, three had grade II ACR, and one had grade III ACR. Three had mixed or AMR, of which two had c4d-negative AMR. There was no case of the borderline rejection.

There was no difference between the two groups in the time between transplant and biopsy. The mean interval from transplant to pancreas biopsy in the concordance group was 674.9 ± 1051 days and in the discordance group was 582.9 ± 1083 days ($P = 0.79$). Similarly, the mean interval between transplant and kidney biopsy in the concordance group was 675.2 ± 1050 days and in the discordance group was 578.6 ± 1082 days ($P = 0.78$).

There were a total of 22 pancreas allograft failures on last follow-up in February 2017, 16 in the concordant

Table 2. Categorization of patients by concordance or discordance for rejection.

	Concordant ($n = 25$)			Discordant ($n = 15$)		
Variables	Rejection ($n = 11$)	No rejection ($n = 14$)	All	Pancreas Rejection only ($n = 10$)	Kidney rejection only ($n = 5$)	All
Mean interval between biopsies (days)	3 ± 6	6 ± 6.54	4 ± 6.33	6 ± 6.7	1 ± 5.6	5 ± 6.0 ($P = 0.69$ vs. all concordant)
Biopsy findings	6 ACR in both allografts 1 mixed in both allografts 1 AMR in pancreas and ACR in kidney 1 ACR in pancreas and AMR in kidney 1 mixed in pancreas and AMR in kidney 1 ACR in pancreas and mixed in kidney	9 no rejection both allografts 1 pancreatitis in pancreas and ATN in kidney 1 adenovirus in kidney, no pancreas rejection 2 BK nephropathy in kidney, no rejection in pancreas 1 MPGN in kidney, no rejection in pancreas		6 ACR in pancreas, no rejection in kidney 2 AMR in pancreas, no rejection in kidney 1 ACR in pancreas, BK nephropathy in kidney 1 mixed rejection in pancreas, no rejection in kidney	3 no pancreas rejection, AMR in kidney 1 no pancreas rejection, kidney mixed rejection 1 no pancreas rejection, ACR in kidney	

ACR, acute cellular rejection; AMR, antibody-mediated rejection; ATN, acute tubular rejection; MPGN, membranoproliferative glomerulonephritis.

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group, and six in the discordant group. The mean pancreas allograft survival after diagnosis of rejection was 2.82 ± 3.13 years. There were a total of 19 kidney allograft failures, 11 in the concordant group, and eight in the discordant group with a mean kidney allograft survival after diagnosis of rejection of 4.18 ± 3.58 years.

Discussion

In our series of 40 SPK patients with biopsies of both kidney and pancreas, 25 (62.5%) had findings concordant for rejection. Eleven had rejection of both organs, and fourteen had no rejection of either organ. The other 15 (37.5%) were discordant for rejection, with 10 having pancreas-only rejection and five kidney-only rejection. Clearly, the presence of rejection in the pancreas has a critical impact on the treatment plan in a patient with no rejection in the kidney. In addition, it was striking that only seven of 11 patients with concordance for rejection had the same types (AMR, ACR, or mixed) of rejection; that is, 36% had differences in the specific types of rejection, which may warrant different types of treatment. For example, in a patient with ACR in the kidney, the finding of AMR or mixed rejection in the pancreas would suggest the addition of plasmapheresis and/or IVIG to a plan for a steroid pulse.

Pancreas and kidney rejection are not uncommon in SPK. In a large series of pancreas transplant recipients, mainly in the form of SPK, the incidence of biopsy-proven pancreas rejection within the first year of transplant was 21%, with an equal distribution of AMR, ACR, and mixed rejection [10]. In the Euro-SPK 001 study of 205 patients with three-year follow-up, 92 (45%) recipients experienced at least one episode of rejection. Rejections were either biopsy-proven or clinical, and more commonly reported in the kidney allograft than the pancreas allograft [11]. In another study, comparing SPK and kidney alone recipients with a median follow-up of 55 months, kidney alone recipients had a significantly higher rate of kidney rejection, at 30% compared to 10% in SPK ($P = 0.037$). The authors suggested this difference might be due to the stronger immunosuppression used in SPK recipients [12].

The most common indication for pancreas allograft biopsy is a rise in the pancreatic enzymes [10]. Although the incidence of subclinical pancreatic rejection is unknown, we previously reported three cases of rejection on explant samples among 11 pancreatectomies performed at the time of a repeat pancreas transplant. All three patients were on full-dose immunosuppressive medications and had normal pancreatic enzymes [13]. Similarly, subclinical rejection of the kidney, in the absence of a rise in serum creatinine or proteinuria, is well described. Kraus *et al.* [14] reported an incidence of ACR or AMR of over 20% in the first year after kidney transplantation with a positive cross-match. Even in patients with a negative cross-match, the incidence of subclinical rejection is estimated to be approximately 10% [15].

All allograft biopsies are invasive procedures, so have associated risk. One of the rationales for performing kidney biopsies and not necessarily pancreas biopsies in SPK recipients is that pancreas biopsies are often perceived to be associated with greater risk. However, in a large series of 232 pancreas allograft biopsies, complications were only found in 6 (2.6%). Most of the complications were minor: Three had intra-abdominal hemorrhage, one each had gross hematuria, allograft pancreatitis, and severe pain requiring overnight hospitalization [16]. In our experience at the University of Wisconsin, we have performed more than 400 percutaneous pancreas biopsies since 1992, with a very low complication rate and no graft losses. Two patients required reoperation: one for bleeding and one for evacuation of pancreatic ascites, which ultimately resolved, and both patients still retain excellent graft function [8]. In a series of 3738 kidney allograft biopsies, the rate of complications was 1.8%. While most complications were mild or moderate, 0.21% had severe complications and 0.19% had life-threatening complications, although no deaths occurred [17].

Our findings are consistent with the smaller study of Troxell *et al.* [6], who found a 38% rate of discordance for rejection in a series of 21 patients. While they included all biopsies done within 7 days of each other, they do not mention whether or not their patients received treatment for rejection between biopsies [6]. Similar results were found in an animal model, in which a 27% rate of discordant rejection was found among 23 SPK recipient dogs [18]. We extend these findings by showing that even among patients with rejection in both organs, the type of rejection is often significantly different and requires different treatments.

Some have suggested that in SPK recipients, kidney rejection precedes or parallels pancreas rejection and that kidney rejection is 2–3 times more common than pancreas rejection [19]. However, it may be that many, or even most, of the pancreas rejections were previously missed due to infrequent biopsies being performed, on the assumption that kidney biopsies can serve as a surrogate for the pancreas biopsy. Pancreas rejection remains the single most significant cause of

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graft loss, and it cannot be reliably diagnosed noninvasively [20]. Our findings suggest that performing a pancreas biopsy in addition to a kidney biopsy often provides critical information that will alter patient management.

Limitations of this study include its being limited to a single center, which may have a different population and clinical approach from other centers. Our study also has a limited sample size due to the strict selection criteria. However, ours is the largest reported series of its kind. In summary, there is substantial incidence of discordant rejections in SPK recipients. Even among those with concordance for the presence of rejection, there is a clinically meaningful rate of finding different types of rejection in the two organs. In the hands of experienced biopsy providers, pancreas and kidney biopsies can usually be performed safely and strong consideration should be given to performing both biopsies.

Authorship

SP: involved in concept, design, data collection, analysis, manuscript preparation, and editing. EA, BCA, AD, RRR, HWS and DK: involved in design, analysis, manuscript preparation, and editing. FA: involved in data collection and editing. JO and DM involved in concept, design, analysis, manuscript preparation, and editing.

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Conflict of interest

The authors have no financial disclosures.

REFERENCES

1. Han DJ, Sutherland DE. Pancreas transplantation. *Gut Liv* 2010; **4**: 450.
2. Gruessner AC. 2011 update on pancreas transplantation: comprehensive trend analysis of 25,000 cases followed up over the course of twenty-four years at the International Pancreas Transplant Registry (IPTR). *Rev Diabet Stud* 2011; **8**: 6.
3. Gruessner RW, Gruessner AC. The current state of pancreas transplantation. *Nat Rev Endocrinol* 2013; **9**: 555.
4. Leichtman AB, Cohen D, Keith D, *et al.* Kidney and pancreas transplantation in the United States, 1997–2006: the HRSA Breakthrough Collaboratives and the 58 DSA Challenge. *Am J Transplant* 2008; **8**: 946.
5. Nankivell BJ, Alexander SI. Rejection of the kidney allograft. *N Engl J Med* 2010; **363**: 1451.
6. Troxell ML, Koslin DB, Norman D, Rayhill S, Mittalhenkle A. Pancreas allograft rejection: analysis of concurrent renal allograft biopsies and posttherapy follow-up biopsies. *Transplantation* 2010; **90**: 75.
7. Redfield RR, Scalea JR, Odorico JS. Simultaneous pancreas and kidney transplantation: current trends and future directions. *Curr Opin Organ Transplant* 2015; **20**: 94.
8. Redfield RR, Kaufman DB, Odorico JS. Diagnosis and treatment of pancreas rejection. *Curr Transplant Rep* 2015; **2**: 169.
9. Drachenberg CB, Odorico J, Demetris AJ, *et al.* Banff schema for grading pancreas allograft rejection: working proposal by a multi-disciplinary international consensus panel. *Am J Transplant* 2008; **8**: 1237.
10. Niederhaus SV, Leverson GE, Lorentzen DF, *et al.* Acute cellular and antibody-mediated rejection of the pancreas allograft: incidence, risk factors and outcomes. *Am J Transplant* 2013; **13**: 2945.
11. Arbogast H, Malaise J, Illner WD, *et al.* Rejection after simultaneous pancreas-kidney transplantation. *Nephrol Dial Transplant* 2005; **20** (Suppl. 2): ii11-7, ii62.
12. Dinckan A, Aliosmanoglu I, Kocak H, Mesci A, Altunbas H, Gurkan A. The impact of method on kidney graft and patient survival in kidney-pancreas transplantations for type I diabetes mellitus. *Int Surg* 2015; **100**: 137.
13. Parajuli S, Odorico J, Astor BC, Djamali A, Sollinger H, Redfield R, et al. Incidence and Indications for Late Allograft Pancreatectomy while on Continued Immunosuppression. *Transplantation* 2016; doi: 10.1097/TP.0000000000001556 [Epub ahead of print]
14. Kraus ES, Parekh RS, Oberai P, *et al.* Subclinical rejection in stable positive crossmatch kidney transplant patients: incidence and correlations. *Am J Transplant* 2009; **9**: 1826.
15. Heilman RL, Nijim S, Chakkera HA, *et al.* Impact of acute rejection on kidney allograft outcomes in recipients on rapid steroid withdrawal. *J Transplant* 2011; **2011**: 583981.
16. Atwell TD, Gorman B, Larson TS, Charboneau JW, Ingalls Hanson BM, Stegall MD. Pancreas transplants: experience with 232 percutaneous US-guided biopsy procedures in 88 patients. *Radiology* 2004; **231**: 845.
17. Redfield RR, McCune KR, Rao A, *et al.* Nature, timing, and severity of complications from ultrasound-guided percutaneous renal transplant biopsy. *Transpl Int* 2016; **29**: 167.
18. Hawthorne WJ, Allen RD, Greenberg ML, *et al.* Simultaneous pancreas and kidney transplant rejection: separate or synchronous events? *Transplantation* 1997; **63**: 352.
19. Becker BN, Odorico JS, Becker YT, *et al.* Simultaneous pancreas-kidney and pancreas transplantation. *J Am Soc Nephrol* 2001; **12**: 2517.
20. Walker JA, Klassen DK, Hooper FJ, *et al.* Late pancreas allograft rejection. Preliminary experience with factors predisposing to rejection. *Transplantation* 1996; **62**: 539.

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