DESCRIPTION OF THE NEPHROLOGY TRAINING PROGRAM UNIVERSITY OF ALABAMA AT BIRMINGHAM SCHOOL OF MEDICINE

The Nephrology Training Program at the University of Alabama at Birmingham (UAB) offers two types of training: an academic track (one clinical year, followed by 3 yr of basic research training) and a clinical track (one clinical year, followed by 1 to 2 yr in clinical or laboratory investigation). Clinical activities take place at three hospitals and in the outpatient nephrology clinics. The trainees receive extensive clinical experience (400 in-center and home dialysis patients, 275 kidney transplants per year, 80 renal ward inpatients per month, and 100 nephrology consults per month). The program accepts four to five trainees per year.

The Nephrology Division also sponsors a special third-year fellowship (one fellow/year) for additional training of transplant physicians. These fellows have usually completed at least 2 yr of traditional nephrology training. This extra year involves 6 months of clinical activity on a large, combined medical-surgical transplant service (both inpatient and outpatient) with heavy direct patient care activity. Nearly 200 outpatient transplant visits per week and an inpatient census of more than 45 patients are typical.

Tissue typing, organ procurement, and exposure to other solid-organ transplants (pancreas, heart, liver) are part of the transplant physician's experience. Laboratory and clinical investigation are featured, and a number of transplantation-related teaching and working conferences are held weekly. There are four full-time transplant surgeons and three full-time transplant physicians. Clinical (patient-oriented) research interests range from posttransplantation hypertension to transplantation bone disease and make extensive use of the General Clinical Research Center. There are ongoing animal and human studies focused on immune tolerance and cytokine activity after transplantation. Of special interest are studies of ESRD and transplantation in blacks. The tissue typing laboratory and the organ procurement agency are among the most active in the Southeast.

Preferential Rejection of the Kidney in a Simultaneous Kidney-Pancreas Transplant

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ABSTRACT

A case of selective kidney allograft rejection with stable pancreas function in a patient who received simultaneous kidney-pancreas allograft from the same donor is reported. Pancreas function was shown to be normal within the first month posttransplant by both a glucose tolerance test (despite a high corticosteroid dose) and stable urinary amylase values during biopsy-proven acute renal allograft rejection. This patient subsequently rejected his kidney allograft as documented by histopathologic evidence of severe chronic vascular rejection and acute tubulointerstitial rejection, yet his pancreas function remained intact. He subsequently received a six-antigen-matched kidney, continues to have
normal fasting glucose and normal glucose tolerance by oral glucose tolerance test, and is without evidence of glucosuria. He has never had a clinical rejection of his pancreas, as evidenced by either a decline in urinary amylase or hyperglycemia, and has not required insulin except in the perioperitive period of his second kidney transplant, at which time he was receiving high doses of both corticosteroids and cyclosporin. It is suggested that preferential rejection and subsequent loss of the kidney, although infrequent, do occur in combined renal-pancreas allografts and that maintenance of immunosuppression is justified until retransplant of kidney is available.

Key Words: Kidney-pancreas transplant, kidney rejection, kidney retransplant

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urgeons use multiple solid-organ transplants for patients with multiple organ failure. Often, these organ transplant operations are simultaneous and the organ source is the same donor. Investigators have noted that liver transplants appear to protect a simultaneous kidney transplant (1), whereas pancreas transplants appear to increase the frequency of kidney allograft rejections (2–5). Others have reported that simultaneous pancreas and kidney (SPK) transplantation results in longer pancreas survival than a pancreas transplant alone and have suggested that the kidney provides a "protective effect" on the transplanted pancreas either by immunologic mechanisms or more likely by allowing earlier detection of pancreas rejection when associated with acute renal rejection (6). Clinically, it appears that one organ may suffer a rejection episode while the other seems unaffected by the immune attack (7,8), although often simultaneous rejection can be documented by biopsies of both kidney and pancreas in combined transplants in animal models (9,10).

We report a case of a patient with end-stage kidney failure from Type I (juvenile-onset) diabetes mellitus. He received a simultaneous kidney and pancreas transplant from the same cadaveric donor. The kidney allograft subsequently had classic clinical and histologic rejection and had to be removed; the pancreas allograft continued to function well, and therefore, immunosuppressive therapy was continued. Three months after the removal of the original severely rejected kidney allograft, the patient received a second (six-antigen-matched) kidney allograft. This patient has had excellent function of both the original poorly matched pancreas allograft and the second well-matched kidney allograft for more than 2.5 yr since he was retransplanted with a second cadaveric kidney to replace his original irreversibly rejected kidney allograft.

CASE REPORT

The patient is a 31-year-old white man who developed diabetes mellitus at age 15 and began insulin therapy. He developed diabetic retinopathy and was legally blind by age 28. He also had neuropathy, gastroparesis, and hypertension, which his physicians attributed to his diabetes. He required 70 U of intermediate-acting insulin daily.

Three years before transplantation, he was noted to have an elevated serum creatinine and proteinuria. He was monitored by his local physician, who noted progressive renal insufficiency with proteinuria, symptoms of congestive heart failure, and a creatinine of 972 μmol/L (11 mg/dL). He began hemodialysis therapy and was evaluated for a transplant in January 1989. Coronary arteriography, done during his transplant evaluation, did not reveal evidence of coronary artery disease. The patient was blood type O and had the following human major histocompatibility complex (HLA) antigens identified: A1;3; B8;34 and DR 1.3. In March 1989, he received a kidney and a pancreas from a blood group O cadaveric donor in whom these HLA antigens were identified: A3; B7;35 and DR 2.7. Quadruple induction chemotherapy was begun at the time of transplant and consisted of Minnesota antilymphoblastic globulin (20 mg/kg per day), methylprednisolone (30 mg/day), and azathioprine (25 mg/day). Cyclosporin therapy was initiated on Day 2 after serum creatinine fell below 3.0 mg/dL. Minnesota antilymphoblastic globulin was discontinued on Day 5 after therapeutic cyclosporin levels were achieved. There was immediate function of the kidney and the pancreas. Hemoglobin A1C was 9.0% on the day of his transplant. By the fourth postoperative day, the patient’s glucose was in the 3.9 to 5.6 mmol/L (70 to 100 mg/dL) range without the use of insulin and his serum creatinine was 115 μmol/L (1.3 mg/dL).

On Day 9 after transplantation, however, the patient had an increase in serum creatinine to 212 μmol/L (2.4 mg/dL) and a fall in urine output. His serum glucose was 6.2 mmol/L (112 mg/dL), and his serum amylase remained normal. Urine amylase, an indicator of exocrine pancreatic transplant function in bladder-drained pancreas allografts (11), did not change significantly from baseline values of 35,000 to 55,000 IU/L. He was treated for acute rejection with 3 g of IV methylprednisolone on Days 9 to 11 without any improvement in serum creatinine. The patient did respond to an 8-day course of therapy with monoclonal antibody treatment (OKT3, 5 mg/day), with the creatinine falling back to 159 μmol/L (1.8 mg/dL). A subsequent rejection episode 3 days after the completion of OKT3 therapy prompted an open renal biopsy, which showed moderate acute tubulointerstitial rejection (Figure 1). His serum creatinine continued to increase to a peak of 796 μmol/L.
L (9.0 mg/dL), but with a repeat course of OKT3 monoclonal antibody therapy over 11 days, his creatinine stabilized at 256 to 265 \( \mu \)mol/L (2.9 to 3.0 mg/dL). CD3\(^+\) T cell counts were not measured, but lymphocytes were consistently below 5% of the peripheral leukocytes during OKT3 therapy. Triple therapy was continued throughout his clinical course (azathioprine, prednisone, and cyclosporin). The patient remained free of insulin, and glucose levels continued to be within normal limits during all episodes of acute rejection. Six months later, the patient was again admitted for acute rejection, at which time, an allograft nephrectomy revealed severe vascular and mild tubulointerstitial rejection (Figure 2). His blood glucose remained in the normal range, and his pancreas allograft was not removed.

Figure 1. Biopsy of kidney 1 month posttransplantation. Acute cell-mediated rejection of the renal allograft at a time when blood glucose was normal and the pancreas allograft appeared to function normally (original magnification, \( \times 400 \)).

The patient returned to chronic hemodialysis and did not require insulin therapy for his diabetes. In January 1990 (9 months after his initial kidney and pancreas transplant), he received another cadaveric kidney transplant. This kidney was from a six-antigen HLA-matched donor (A 1,3; B 8,34; and DR 1,3). Initially there was no function because of ATN, but after 9 days, renal function began. The patient’s creatinine was lowered to 133 \( \mu \)mol/L (1.5 mg/dL) and has remained stable ever since. Insulin therapy was briefly required during high-dose methylprednisolone and cyclosporin therapy in the perioperative period but was no longer required to maintain euglycemia within 1 month posttransplant. He underwent two oral glucose tolerance tests, the first during his initial acute rejection (March 1989) and the second 7.5 months after his second (six antigen match) renal allograft. Both have shown normal fasting blood glucose and a normal glucose tolerance test.

Figure 2. Nephrectomy specimen 7 months after transplantation showing ongoing cellular rejection along with marked vascular disease and scarring. Pancreas function continued to be normal (original magnification, \( \times 250 \)).

**DISCUSSION**

This case report provides histologic documentation of a patient’s ability to reject a renal allograft such that it no longer functions and yet maintain normal function of a simultaneously placed pancreas allograft from the same donor. Histologically and clinically, the rejection episode was classic in the kidney allograft. The patient continued to have normoglycemia despite rejection of his kidney, and immunosuppression for the pancreas allograft was continued. A subsequent cadaveric kidney transplant during maintenance of immunosuppression for the original pancreas allograft has resulted in both normal creatinine and normoglycemia 3 yr after immunologic destruction of the first kidney allograft.

There is substantial evidence that patients with SPK transplants have an increased incidence of rejections (2–5), postoperative complications (5,12), and hospitalizations (13) over those with kidney transplants alone. The unfavorable incidence of rejections in the SPK group compared with that in diabetic recipients who receive primary kidney transplant alone occurs despite the use of more immunosuppressive therapy in the SPK group (2,4,5). These clinical results mirror the findings in animal studies that immunosuppression protocols that uniformly prevent rejection of heart and kidney allografts do not prevent rejection of pancreas allografts (14,15). The doubling of the incidence of rejection in the SPK recipients (compared with the kidney transplant alone patients) may reflect the greater number of HLA mismatches in the SPK group (4,13), because previous reports do suggest that HLA class II (DR) matching improves pancreas (16) and kidney (17) graft survival. Thus, the increased incidence of rejection in SPK patients may be due, in part, to the
TABLE 1. Literature review of kidney and pancreas transplants

<table>
<thead>
<tr>
<th>Author (Ref. No.)</th>
<th>Year</th>
<th>Patient Profile</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hedman et al. (2)</td>
<td>1987</td>
<td>DM, 15 KTA, 19 SPK</td>
<td>Poor kidney allograft survival in combined kidney and pancreas transplantation compared with kidney transplant only, although improved results with quadruple drug therapy.</td>
</tr>
<tr>
<td>Sollinger et al. (12)</td>
<td>1988</td>
<td>DM, 30 SPK, 73 CAD</td>
<td>Combined engraftment does not jeopardize renal allograft functional survival, although 50% more kidney rejections in SPK than primary CAD.</td>
</tr>
<tr>
<td>Klima et al. (7)</td>
<td>1988</td>
<td>35 SPK, 11 PAK</td>
<td>Simultaneous kidney and pancreas rejection most common. Eight patients (10 episodes) with only kidney rejection without evidence of pancreatic rejection (as defined by external pancreatic juice cytology).</td>
</tr>
<tr>
<td>Frisk et al. (3)</td>
<td>1989</td>
<td>DM, All 25 SPK</td>
<td>Kidney more prone to rejection in cases of combined kidney and pancreas transplantation than in kidney transplant alone.</td>
</tr>
<tr>
<td>Grussner et al. (6)</td>
<td>1990</td>
<td>39 SPK, 48 KTA</td>
<td>SPK transplants do not jeopardize the transplanted kidney.</td>
</tr>
<tr>
<td>Nakache et al. (23)</td>
<td>1990</td>
<td>DM, 37 KTA, 66 SPK</td>
<td>Simultaneous transplantation of a pancreas appeared to carry no additional risk to the kidney graft nor to patient survival.</td>
</tr>
<tr>
<td>Rosen et al. (4)</td>
<td>1991</td>
<td>Type I DM, 18 SPK, 18 KTA</td>
<td>No difference in patient survival or &quot;satisfactory&quot; renal allograft function in SPK vs. KTA 18 months posttransplant. Twice the rejection episodes and more infectious complications in SPK recipients.</td>
</tr>
<tr>
<td>Cheung et al. (5)</td>
<td>1992</td>
<td>Type I DM, 69 SPK, 59 KTA</td>
<td>Kidney allograft survival is not deleteriously affected by the addition of a pancreas if recipients &lt;45 yr, but renal allograft survival higher in KTA if &gt;45 yr. Higher incidence of rejection episodes (2x) for SPK vs. KTA.</td>
</tr>
<tr>
<td>Schuij et al. (24)</td>
<td>1992</td>
<td>Type I DM &lt;50 yr, 32 SPK, 28 KTA</td>
<td>No difference in patient or kidney allograft survival in KTA vs. SPK despite greater number of rejections and more surgical complications in SPK group.</td>
</tr>
<tr>
<td>USRDS 1992 Annual Data (13)</td>
<td>1992</td>
<td>First CAD DM, 18–45 yr, 2,788 KTA, 380 SPK</td>
<td>Kidney graft survival significantly higher for SPK than KTA (despite greater number of A, B, and DR mismatches in the SPK group). No difference in patient survival.</td>
</tr>
</tbody>
</table>

*DM, diabetes mellitus; KTA, kidney transplant alone; SPK, simultaneous pancreas and kidney transplant; PAK, pancreas after kidney transplant alone; CAD, cadaveric renal transplant.

Increased exposure to exocrine pancreas donor antigen(s), because immunohistologic staining pancreatic tissue reveals that the exocrine pancreas is potentially more immunogenic than the endocrine pancreas as defined by parenchymal HLA-Class I expression (18) and the lack of Class II antigen expression on endocrine but not exocrine parenchymal cells during rejection (19). This potential immuno-negativity of exocrine pancreas may explain why isolated rat islets transplanted across either Class I or Class II major histocompatibility complex (in humans, the major histocompatibility complex is the HLA gene cluster on chromosome 6. It is referred to as H-2 in mouse and RT1 in rat) antigen barrier have prolonged survival, whereas vascularized whole-pancreas allografts are uniformly rejected (20), despite the use of immunosuppression regimens that uniformly result in prolonged kidney allograft survival (14,15). Further, biopsies of combined allografts in nonimmunosuppressed canines at the onset of creatinine elevation show diffuse mononuclear infiltration in both the kidney and pancreas, but in the pancreas, only the exocrine cells, and not the islets of Langerhans, are involved in the rejection process.
A review of the recent literature (Table 1) suggests that, despite the increased incidence of rejection in the SPK transplant patients, kidney allograft survival is not adversely affected by the simultaneous addition of a pancreas (4,6,16). In fact, for diabetic patients younger than 45 yr old, kidney allograft survival is no different (5,21) or higher (13), despite significantly more HLA-A, HLA-B, and HLA-DR mismatches in SPK patients than in kidney transplant alone.

The reason for the apparent preferential rejection of the kidney compared with the pancreas in SPK patients is unclear, although most reports agree that combined pancreas and kidney rejection is the most common rejection pattern, followed by an equal or lesser number of kidney-only rejections and, rarely, pancreas-only rejection (4,7,12). This pattern is consistent with our experience at the University of Alabama at Birmingham in 34 SPK patients with 45 episodes of clinical or biopsy-proven rejection, in which 33 (73%) have involved both kidney and pancreas, 10 (22%) have involved the kidney only, and 2 (<5%) have involved only the pancreas (Table 2). Percutaneous biopsies of the pancreas during histologically proven kidney allograft rejection reveal that simultaneous rejection occurs in only 69% of patients (21), and further, pancreas rejection is rarely seen in the absence of kidney rejection (12,21). These clinical results are consistent with experimental models of SPK transplants, in which pancreas rejection can be confirmed by biopsy almost as often as kidney rejection, because cellular infiltration occurs simultaneously in both grafts, but the severity of rejection is more vigorous in the kidney than in the pancreas (22). We cannot determine in our patient whether there was histologic evidence of pancreas allograft rejection at the time of biopsy-proven kidney rejection without a simultaneous biopsy of the pancreas allograft; however, the stable urinary amylase, normal serum glucose, and normal glucose tolerance test during rejection suggest that only the kidney was involved. Others groups have also shown that simultaneously transplanted pancreas and kidneys may be rejected independently of each other with up to 10% of patients losing kidney function yet maintaining pancreas function (7,23). It is interesting to note that, despite the infrequent rejections of the pancreas, the actuarial pancreas allograft survival is less at 1 yr than the kidney allograft survival in combined kidney-pancreas transplants (5,24). The reason for this discrepancy between the incidence of pancreas rejection and pancreas graft survival may be the result of the significant number of technical complications involving the pancreas transplant (24), as well as the different methods used in detecting and defining pancreas versus kidney allograft rejection (25).

TABLE 2. Rejection patterns in SPK transplant patients at The University of Alabama–Birmingham

| No. of Patients with an SPK Transplant | 34*
| No. of Rejections (Kidney and/or Pancreas) | 45
| Organ(s) Involved During Rejection | 33 (73%)
| Rejection of both kidney and pancreas | 10 (22%)
| Rejection of kidney only | 2 (<5%)
| No. of Rejections per Patient | 0
| 0 Rejection episodes | 2
| 1 Rejection episode | 17
| 2 Rejection episodes | 11
| 3 Rejection episodes | 2

* Two patients have incomplete data because of recent transplants.
Diagnosis of acute rejection in pancreas patients based on significant decline in urinary amylase.

Clearly, pancreas graft survival is significantly greater in SPK patients than in patients who receive a pancreas allograft alone (6,25). This suggests that the simultaneous transplantation of a kidney may provide a protective effect on the pancreas graft by allowing earlier detection of pancreas rejection when associated with simultaneous acute renal allograft rejection (6,12). Although many argue that there is no immunologic advantage conferred on a pancreas graft by a concomitant kidney transplant (9), in animal models, survival of both endocrine and exocrine components of the pancreas graft are significantly longer when simultaneously placed with a kidney graft than when the pancreas is transplanted alone, both with and without immunosuppression (14,22).

Our patient's original poor HLA-matched pancreas transplant is now 3 yr beyond the date of transplantation and keeps the patient free of exogenously administered insulin. The original kidney was lost to rejection less than 8 months after transplantation, although it initially had good function. The second kidney now functions well 2.5 yr after transplantation. Since the second transplant, the patient has had an oral glucose tolerance test and glycosylated hemoglobin and serum glucose measurements on numerous occasions, which have all been normal. This patient has not required insulin except in the perioperative period with his second kidney transplant.

This case suggests that one can retransplant a kidney in a patient who has satisfactory pancreatic allograft function despite the prior loss of a kidney. Because isolated renal allograft rejection can occur in SPK transplant patients, we should not give up on immunosuppression for the pancreas unless one can simultaneously document a loss of glycemic control. This is a key issue because one can be confused about the pancreatic function during the course of antire-
rejection therapy, because adequate glucose control can be obscured when large doses of pulse corticosteroids are given. Also, we feel that rapid retransplantation of kidneys in patients with renal allograft failure and a functioning pancreas allograft is indicated because it may facilitate the clinical management of immunosuppression and may improve the impaired host defenses of uremia (26). Furthermore, because recent results suggest that kidney allografts have equal or possibly greater survival when combined with a pancreas allograft and because pancreas grafts clearly survive longer in a combined transplant than pancreas allograft alone, replacement of a failed kidney allograft could possibly result in prolonged graft survival of both the kidney and pancreas.

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REFERENCES