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RENAL ALLOGRAFT REJECTION WITH NORMAL RENAL FUNCTION IN SIMULTANEOUS KIDNEY/PANCREAS RECIPIENTS:
Does Dissynchronous Rejection Really Exist?

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Abstract

Background. Between July 1, 1994 and December 1, 1998, 147 simultaneous kidney/pancreas transplantations were performed at our center. Of 95 patients who experienced at least one acute renal allograft rejection episode after transplantation, 7 (7.4%) developed rejection in the presence of stable and normal or near-normal renal function.

Methods. The indication for renal allograft biopsy was a rising serum lipase, i.e., suspected pancreatic rejection. All seven patients were treated with steroids and augmentation of the

tacrolimus dose, with a fall in the serum lipase and no change in the serum creatinine.

Results. The serum creatinine levels just before, at the time of, 1 week after the biopsy, and at most recent follow-up were 1.4 ± 0.4 , 1.3 ± 0.3 , 1.2 ± 0.2 , and 1.2 ± 0.2 mg/dl. The serum lipase levels just before, at the time of, 1 week after the biopsy, and at most recent follow-up were 1022 ± 1157 mg/dl, 874 ± 996 mg/dl, 243 ± 260 mg/dl, and 94 ± 75 mg/dl. The tacrolimus dosages and levels at the time of the biopsy and 1 week later were 14.9 ± 5.0 mg/day and 15.0 ± 4.0 ng/ml, and 16.4 ± 6.3 mg/day and 15.1 ± 6.8 ng/ml.

Conclusions. These findings suggest that, in patients undergoing simultaneous kidney/pancreas transplantation, the entity of dissynchronous pancreatic allograft rejection without renal allograft rejection may not really exist. These data also make an additional fundamental point that acute rejection may occur in patients with normal and stable renal function.

*Abbreviation: SPK, simultaneous pancreas-kidney transplantation.

An important advantage of simultaneous pancreas-kidney transplantation (SPK*) is that the immunologic state of the pancreas can be monitored by following the kidney. The latter organ is easily monitored by the serum creatinine and is relatively straightforward to biopsy. Most of the time, pancreatic allograft rejection is diagnosed and treated concomitantly with the kidney because of kidney-related events. However, the phenomenon of dissynchronous rejection (or even loss) (1) of the pancreas without renal allograft rejection has been described, and is said to occur as often as 27% of the time (2). In addition, in experimental models, discordant grades of rejection were seen in as many as 75% of cases (3).

We have previously described a strong association between an elevation in the serum lipase and pancreatic rejection (4, 5). In this paper, we describe a small number of SPK recipients who underwent renal allograft biopsy, because of a rising serum lipase, despite having normal and stable renal function. We noted unequivocal histologic evidence of rejection in the renal allografts and saw a fall in the serum lipase after treating the patients for rejection, without a change in renal function. This observation raises the question of whether dissynchronous

pancreatic allograft rejection really exists, and further makes the point that renal allograft rejection can occur despite normal and stable renal function. In addition, uncontrolled renal allograft rejection in patients with stable renal function may lead to scarring and be a harbinger of chronic rejection.

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PATIENTS AND METHODS

Between July 1, 1994, and December 1, 1998, 147 SPKs were performed at our center, all under tacrolimus-based immunosuppression. The details of the immunosuppressive protocols, technical aspects of the transplant procedure, and outcomes have been reported previously ([6-9](#)). Ninety-five (64.4%) patients experienced at least one episode of renal allograft rejection, diagnosed either by percutaneous core biopsy or fine needle aspiration. In 88 (92.6%) of these patients, the indication for biopsy was a rise in the serum creatinine (including even a subtle rise, e.g., from 1.1 to 1.2 or 1.3 mg/dl). In seven (7.4%), the indication for renal allograft biopsy was a rising serum lipase (six underwent percutaneous renal allograft biopsy, and one patient underwent a fine needle aspiration). The serum creatinine and lipase levels just before, on the date of, 1 week after the biopsy, and at most recent follow-up were recorded, as were the tacrolimus dose and levels on the day of the biopsy and 1 week after the biopsy, and the histology of the renal biopsies.

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RESULTS

The serial mean serum creatinine and lipase levels are shown in [Table 1](#). The serum creatinine levels were relatively stable and did not change appreciably before, at the time of, or after the biopsy. The serum lipase levels were markedly elevated just before and at the time of renal biopsy; by 1 week after the biopsies, they had fallen dramatically, and at most recent follow-up were completely normal.



Table 1

All seven patients undergoing renal biopsy had histologic or cytologic evidence of mild acute cellular rejection (Banff 1A) ([10](#)). All were treated with steroid boluses and a slight augmentation of the tacrolimus dose ([Table 2](#)). Subsequent renal biopsies were not performed, in view of clinically and biochemically stable renal and pancreatic function.



Table 2

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DISCUSSION

The overwhelming majority of renal allograft rejections were diagnosed by renal allograft biopsies performed because of a rise in the serum creatinine. In seven cases, rejection was seen in the setting of stable and normal or near normal renal function, and the only indication for biopsy was a rise in serum lipase, i.e., a suggestion of pancreatic allograft rejection. Although we have seen a rising lipase in association with normal renal function and a negative biopsy, this has happened only once. Although the number of cases described in this report is small, and they constitute less than 10% of renal allograft rejection episodes in SPK recipients, they illustrate two important points. First, isolated pancreatic allograft rejection in the absence of renal allograft rejection may not really exist. If our observations are correct and generalizable, one can biopsy a clinically stable and normally functioning kidney in the case of suspected pancreatic allograft rejection, with a relatively high likelihood of finding histologic evidence of rejection. Response to treatment can be seen with a falling lipase. The second and potentially more interesting point is that renal allograft rejection can occur in the presence of normal renal function. This observation could argue for the need to perform protocol biopsies at specified times after isolated kidney transplantation, to diagnose clinically occult rejection, a point that has been made by others ([11-13](#)). If this finding occurs with the same or greater frequency in kidney transplant alone patients, chronic rejection could conceivably be at least partially prevented, if it occurs as a consequence of undiagnosed (and therefore untreated) mild acute rejection.

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TABLE 1. Serum creatinine and lipase levels				
	Before biopsy	Date of biopsy	Biopsy +7	Most recent
Serum creatinine (mg/dl)	1.4±0.4	1.3±0.3	1.2±0.2	1.2±0.2
Serum lipase (mg/dl)	1022±1157	874±996	243±160	94±75

TABLE 2. Tacrolimus dose		
Tacrolimus	Date of biopsy	Biopsy +7
Dose (mg/day)	14.9±5	16.4±6.3
Level (ng/ml)	15.0±4.0	15.1±6.8