Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Kidney retransplantation following graft loss to polyoma virus-associated nephropathy: an effective treatment option in simultaneous pancreas and kidney transplant recipients

Martina Mindlova,[1] Petr Boucek,[1] Frantisek Saudek,[1] Teodora Jedinakova,[1] Ludek Voska,[2] Eva Honsova,[2] Kvetoslav Lipar,[3] Milos Adamec[3] and Hans H. Hirsch[4]

1 Diabetes Centre, Institute for Clinical and Experimental Medicine, Prague, Czech Republic
2 Department of Pathology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic
3 Transplant Centre, Institute for Clinical and Experimental Medicine, Prague, Czech Republic
4 Transplantation Virology, Institute for Medical Microbiology, Basel, Switzerland

Keywords
kidney retransplantation, polyomavirus-associated nephropathy, simultaneous pancreas and kidney transplantation.

Correspondence
Petr Boucek MD, Diabetes Centre, Institute for Clinical and Experimental Medicine, Videnska 9, Prague 4, 14021, Czech Republic. Tel.: +420 261366024; fax: +420 261362820; e-mail: petr.boucek@ikem.cz

Received: 9 October 2007
Revision requested: 10 November 2007
Accepted: 28 November 2007

doi:10.1111/j.1432-2277.2007.00620.x

Summary

Polyomavirus-associated nephropathy (PVAN) has emerged as an important cause of graft loss following kidney transplantation. Experience with kidney retransplantation (reKT) in PVAN is very limited, especially in the setting of uninterrupted immunosuppression protecting the still functioning pancreatic graft after simultaneous pancreas/kidney transplantation (SPK). We present a review of five cases of reKT in four SPK recipients with Type 1 diabetes mellitus from a single centre (a second reKT was performed in one patient following first reKT failure due PVAN recurrence). Pre-emptive nephrectomy of the failed graft was performed in three of the cases and all kidney grafts for reKT were harvested from cadaveric donors. All patients are dialysis- and insulin-independent at 30 (9–55), median (range), months following last reKT with maintenance immunosuppression consisting of tacrolimus/sirolimus in three and cyclosporine A/mycophenolate mofetil in one patient. In conclusion, reKT represents an effective treatment option in SPK patients with kidney failure on account of PVAN. Use of interventions designed to reduce active viral replication, including pre-emptive nephrectomy of the failed graft, should be considered before reKT.

Introduction

Polyomavirus-associated nephropathy (PVAN) has become an important problem in renal transplantation affecting 1–10% of patients [1]. Since no specific treatment of proven efficacy is available, the primary mode of intervention consists of modification and/or reduction of immunosuppressive therapy. Still, many cases of PVAN are diagnosed in an advanced stage with allograft dysfunction (PVAN B, diffuse interstitial nephritis). Such cases are associated with an almost 50% rate of graft loss which increases to over 90% in stage PVAN C (tubular atrophy and interstitial fibrosis) [2].

Kidney retransplantation (reKT) represents a possible treatment option following graft failure but limited experience published so far consists of descriptions of individual cases with several questions related to this procedure remaining unsettled [3,4]. These include the need for pre-emptive graft nephrectomy and the role of temporary discontinuation of immunosuppression to reduce viral loads and to eliminate a possible re-infection source as well as the switch to a different immunosuppressive regimen following retransplantation.

These questions may be even more relevant in the cases of PVAN in the setting of combined kidney/pancreas transplants (SPK) where the unaffected function

of the pancreatic graft mandates the continuation of some form of immunosuppressive treatment even after kidney graft failure. However, only very limited information on PVAN in SPK is available [5–7]. In a single-centre report, PVAN was the leading cause of kidney graft loss in the first 2 years after SPK [5]. This notion was however challenged in another retrospective analysis [6]. In this report we describe our experience with reKT in four SPK patients with kidney allograft loss on account of PVAN.

Methods

A retrospective review of five reKT in four Type 1 diabetic patients [M/F 2/2, aged median (range) 36 (27–52) years, with duration of diabetes 22 (17–26) years] after a successful SPK at the Institute for Clinical and Experimental Medicine (1999–2002).

The demographic and clinical characteristics of the first transplants and retransplants are presented in Tables 1 and 2, respectively.

Results

Polyomavirus-associated nephropathy was biopsy-proven at 20 (8–22) months after SPK and was classified in most cases as stage B [1]. Despite modifications of immunosuppression in all patients (dose reduction, switchover from mycophenolate mofetil to sirolimus in one case and switchover from cyclosporine A to azathioprine in another patient) and cidofovir treatment in one (40–0.54 mg/kg BW – every 2 weeks), graft failure occurred in all patients at 29 (23–39) months after SPK and 13 (1–23) months after diagnosis of PVAN. No changes in the function of the pancreatic grafts were noticed and all patients remained insulin-independent.

All patients underwent reKT at 36 (27–63) months after SPK. Patients 1 and 4 were retransplanted before losing their graft function with graft nephrectomy performed at the time of reKT. In patients 2 and 3, a pre-emptive nephrectomy was done during dialysis treatment at 9 and 18 months before reKT.

In patient 1, PVAN recurred at 6 months and graft failure occurred at 1 year after first reKT despite changes in immunosuppression (tacrolimus reduced, MMF switched to sirolimus, prednisone discontinued). Following a period of dialysis and a pre-emptive nephrectomy of the second kidney graft, a second reKT was performed (Table 1).

All patients are currently dialysis- and insulin-independent (30/09/2007). Clinical and laboratory features of reKT are presented in Table 2. The follow-up duration is 30 (9–55) months from the last reKT. Maintenance immunosuppression consists in most cases of the combination of tacrolimus/sirolimus; patient 1 is being treated by cyclosporine A/mycophenolate mofetil. Patient 4 has low-level plasma and high-level urine BK virus (BKV) replication; other patients are BKV DNA negative.

Discussion

Kidney retransplantation following previous allograft failure on account of PVAN is primarily confronted with the potential risk of its recurrence. However, recurrence was not frequent in reports published so far (affecting just two of 15 patients) although it may be higher than the occurrence of PVAN in primary transplants [4].

As suggested recently in the recommendations of an international expert panel [1], absence of polyomavirus replication should be confirmed prior to reKT. Reduction or discontinuation of immunosuppression, administration of antiviral drugs or pre-emptive allograft ureteronephrectomy may be tried in this respect. The latter should be certainly considered in SPK cases, where neither major reduction nor termination of immunosuppressive therapy after kidney graft failure on account of PVAN is possible. The risks of an additional surgical procedure may be offset by the rapid disappearance of viral plasma loads following graft nephrectomy with fast or moderately fast clearance rates independent of continued immunosuppressive regimes [8]. Although a decrease of plasma viral loads is achievable by the reduction of immunosuppression alone, active long-term surveillance of the level of viraemia is probably indispensable in such cases.

On the other hand Womer *et al.* [9] recently reported on two patients (with SPK as the primary transplant procedure in one case) who underwent a successful pre-emptive living-donor reKT despite active viraemia.Absence of PVAN recurrence and continuation of stable graft function were observed after 21 and 12 months of follow-up. In the opinion of the authors, this approach was justified to prevent the detrimental effects of time on dialysis on patient and graft survival. Living donor transplantation with less peri-operative damage of the graft, lower rates of acute rejection and generally better HLA-matching was also considered to carry a lower risk of PVAN recurrence than cadaveric donor transplants. Screening of living kidney donors for BKV infection before retransplantation could be also performed.

Though duration of follow-up in one case is probably insufficient to exclude reliably a PVAN relapse, data from our centre represent the most extensive experience in SPK recipients from a single centre published so far. In our

Journal compilation © 2007 European Society for Organ Transplantation **21** (2008) 353–356

Table 1. Demographic and clinical characteristics of SPK patients with PVAN.

Patient No.	Gender	Duration of diabetes (years)	Age at the time of SPK(years)	Initial IS	Rejection treatment	Time from SPK to PVAN diagnosis (months)	Stage of PVAN at the time of diagnosis	PVAN treatment	Time from PVAN diagnosis to graft failure or reKT (months)	Time on dialysis (months)	Pre-emptive NE (months before reKT)	Time to reKT (months)
1 (SPK)	M	21	35	Tac, MMF	3.75 g MP	21	B	Red of IS	6	0	0	27
1 (1st reKT)	–	–	–	Tac, MMF, prednisone	1.5 g MP	6	B	Switch MMF/Siro, Red Tac, Disc, prednisone	6	25	15	37
2	F	23	52	Tac, Siro	0	22	A	Red of IS	1	17	9	40
3	M	26	37	CsA, MMF	0.5 g MP, 1.8 g ATG	20	B	Switch MMF/Siro, CsA/Aza, Aza/prednisone, cidofovir	19	24	18	63
4	F	17	27	Tac, MMF	0	8	B	Red of IS	23	0	0	31
Median (range)		22 (17–26)	36 (27–52)			21 (8–22)*			13 (1–23)*			36 (27–63)*

SPK, simultaneous pancreas/kidney transplantation; PVAN, polyomavirus-associated nephropathy; MP, methylprednisolone; ATG, antithymocyte globulin; Tac, tacrolimus; MMF, mycophenolate mofetil; CsA, cyclosporine A; Aza, azathioprine; Siro, sirolimus; IS, immunosuppression; Red, reduction; Disc, discontinuation; NE, nephrectomy; reKT, kidney retransplantation.
*Time periods following first reKT in patient 1 not included.

Table 2. Clinical and laboratory features of kidney retransplantation.

Patient No.	IS after reKT	P-Cr (μmol/l) at FU	BK viraemia (copies/ml)	BK viruria (copies/ml)	FU from reKT (months)
1 (2nd reKT)	CsA, MMF	140	<1000	9070	39
2	Tac, Siro	128	<1000	<1000	20
3	Tac, Siro	211*	<1000	<1000	9
4	Tac, Siro	195	7603	130 000 000	55
Median (range)					30 (9–55)

IS, immunosuppression; reKT, kidney retransplantation; CsA, cyclosporine A; MMF, mycophenolate mofetil; Siro, sirolimus; Tac, tacrolimus; FU, follow-up.
Graft function in patient 3 recovering after early acute tubular necrosis.

opinion, they do not seem to offer much support for pre-emptive retransplantation in the setting of active infection. Such an approach had failed in the case of patient 1 described previously [10], in whom PVAN recurred 6 months after a pre-emptive reKT. In the other pre-emptive retransplantation case (patient 4), low-level plasma and high-level urine BKV replication and an impaired graft function were present at follow-up (Table 2), although no PVAN was found in graft biopsies performed 6 and 30 months after retransplantation. Of note, all kidneys used in our series were harvested from deceased donors. Thus, although living donor transplantation may offer certain advantages, both types of transplants should be considered for the purpose of retransplantation.

In conclusion, reKT represents an effective treatment modality in SPK patients with kidney failure on account of PVAN. While evidence from randomized trials is lacking and kidney susceptibility to BK infection may vary, our experience seems to suggest, that it should be done preferably after attaining a significant reduction of BK viral loads through modification of immunosuppression and/or ureteronephrectomy of the primary graft [7]. Systematic monitoring with the use of reliable plasma and urine quantitative assays is indicated for this purpose. Active surveillance is also mandatory following retransplantation to ensure an early detection of recurrence and timely intervention.

Authorship

PB, FS, KL, MA and HHH: designed and performed research; MM, TJ, LV, EH and HHH: collected and analyzed data; MM and PB: wrote the paper; HHH: reviewed the paper.

Funding sources

Supported by the NR8894-3 grant, Internal Grant Agency, Czech Ministry of Health.

References

1. Hirsch HH, Brennan DC, Drachenberg CB, *et al.* Polyomavirus-associated nephropathy in renal transplantation: interdisciplinary analyses and recommendations. *Transplantation* 2005; **79**: 1277.
2. Drachenberg CB, Papadimitriou JC, Hirsch HH, *et al.* Histological patterns of polyomavirus nephropathy: correlation with graft outcome and viral load. *Am J Transplant* 2004; **4**: 2082.
3. Ramos E, Vincenti F, Lu WX, *et al.* Retransplantation in patients with graft loss caused by polyoma virus nephropathy. *Transplantation* 2004; **77**: 131.
4. Hirsch HH, Ramos E. Retransplantation after polyomavirus-associated nephropathy: just do it? *Am J Transplant* 2006; **6**: 7.
5. Lipshutz GS, Mahanty H, Feng S, *et al.* BKV in simultaneous pancreas-kidney transplant recipients: a leading cause of renal graft loss in first 2 years post-transplant. *Am J Transplant* 2004; **5**: 366.
6. Gupta G, Shapiro R, Thai N, Randhawa PS, Vats A. Low incidence of BK virus nephropathy after simultaneous kidney pancreas transplantation. *Transplantation* 2006; **82**: 382.
7. Al Jedai AH, Honaker MR, Trofe J, *et al.* Renal allograft loss as the result of polyomavirus interstitial nephritis after simultaneous kidney-pancreas transplantation: results with kidney retransplantation. *Transplantation* 2003; **75**: 490.
8. Funk GA, Steiger J, Hirsch HH. Rapid dynamics of polyomavirus type BK in renal transplant recipients. *J Infect Dis* 2006; **193**: 80.
9. Womer KL, Meier-Kriesche HU, Patton PR, *et al.* Preemptive retransplantation for BK virus nephropathy: successful outcome despite active viremia. *Am J Transplant* 2006; **6**: 209.
10. Boucek P, Voska L, Saudek F. Successful retransplantation after renal allograft loss to polyoma virus interstitial nephritis. *Transplantation* 2002; **74**: 1478.

