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Brief Communication

Immediate re-transplantation following early kidney transplant thrombosis

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ABSTRACT:

Allograft thrombosis is a devastating early complication of renal transplantation that ultimately leads to allograft loss. We report here on our experience of nine cases of immediate re-transplantation following early kidney transplant thrombosis at a single centre between January 1990 and June 2009. The mean age was 42.9 years at time of transplant. For seven patients, the allograft thrombosis was their first kidney transplant and seven of the nine cases had a deceased donor transplant. The initial transplants functioned for a mean of 1.67 days and the patients received a second allograft at a mean of 3.1 days after graft failure. All of the re-transplants worked immediately. Four allografts failed after a mean of 52.5 months (2–155 months). Two of these died with a functioning allograft, one failed owing to chronic allograft nephropathy and one owing to persistent acute cellular rejection. The remaining five patients still have a functioning allograft after a mean of 101.8 months (7–187 months). One year allograft and patient survival after re-transplantation were 87.5% and 100% respectively (after 5 years, both were 57%). Immediate re-transplantation following early kidney transplant thrombosis can be a success. It may be considered in selected cases after allograft thrombosis.

The causes of very early allograft failure are usually technical in nature with allograft thrombosis (arterial, venous or both) being the most common. Renal allograft thrombosis is a devastating complication that ultimately leads to allograft loss. It generally occurs in the first two postoperative weeks and is reported in up to 6% of kidney transplants.[1] In patients with end-stage liver disease, re-transplantation after early primary allograft failure is frequently undertaken owing to the dismal prognosis associated with not re-transplanting the patient.[2,3] Good outcomes can be expected, at least after the first re-transplant.[2] In renal transplantation, there is often not the same degree of urgency in finding another allograft after primary transplant failure owing to the availability of other renal replacement therapies. The median time to re-transplantation at our centre after an early allograft failure (within 30 days) is 3 years (Phelan PJ, O'Kelly P, Tarazi M, Tarazi N, Salehmohamed MR, Little DM, Magee C, Conlon PJ. Renal allograft loss in the first postoperative month: causes and consequences. unpubl. data, 2011). We report here on our experience of immediate re-transplantation following early kidney transplant thrombosis at a single centre. To our knowledge, this is the first report of its kind in the literature.

PATIENTS AND METHODS

Patients

Our institution is the only kidney transplantation centre in the Republic of Ireland, performing 140–170 transplants per

year. We conducted a retrospective analysis of all deceased and living donor kidney-only recipients in Ireland between the 1 January 1990 and 30 June 2009 who experienced an early (<14 day) allograft thrombosis. We then individually examined the patients who received a rapid re-transplant. Patient demographic and outcome data were collected from our prospectively updated transplant database. Kaplan–Meier methods were used to estimate allograft and patient survival.

Patients with an early allograft failure may be prioritized at our centre for another organ depending on the clinical circumstances. If deemed medically and psychologically suitable, patients can be immediately re-listed and may be offered an ABO-compatible (non-identical) allograft if one becomes available.

Transplant operations

Transplants were performed in the setting of a negative complement-dependent cytotoxicity (CDC) cross-match and a negative CDC plus flow cytometry cross-match from 2002 onwards. Similar criteria were applied for the re-transplant. Operations were performed using a standard surgical technique with end to side anastomosis to recipient external or common iliac vessels using a Carrel patch. Multiple renal arteries were dealt with using a neo-Carrel patch or side-to-side anastomosis for similar sized arteries. Vena caval extension was routinely used for all right-sided kidneys to obtain additional length for the right renal vein, as described by Chopin *et al*.[4] Four of the repeat allografts were transplanted onto the contralateral side of the initial allograft with the remaining five being transplanted onto the ipsilateral side at the time of allograft nephrectomy. Panel reactive antibodies (PRA) were determined by use of the CDC assay, NIH Basic technique.

Initial medications

Before 2005, antibody induction in the form of anti-thymocyte globulin (ATG) was reserved for high immunological risk patients (highly sensitized, repeat transplants). From 2005, basiliximab induction was routinely administered to all recipients. Repeat induction was not given for the re-transplant after allograft thrombosis. Initial immunosuppression consisted of a calcineurin inhibitor (ciclosporin (4 mg/kg twice daily; before 2001) or tacrolimus (0.1 mg/kg twice daily; 2001 onwards)), an anti-metabolite (azathioprine (2 mg/kg daily; before 2002) or mycophenolate mofetil (500 mg twice daily; 2002 onwards)) and steroids. Ciclosporine doses were adjusted to achieve troughs of 200–250 ng/mL in the early post-transplant period with maintenance concentrations of 120–180 ng/mL after 6 months. Tacrolimus doses were titrated to troughs of 10–12 ng/mL in the early post-transplant period, gradually decreasing to maintenance concentrations of 6–8 ng/mL at one year. Prednisolone was weaned gradually to 5 mg per day by 3 months post transplantation. A decision was then made whether to continue corticosteroids. This decision was made based on perceived immunological risk (prior transplantation, degree of human leucocyte antigen (HLA) mismatch, peak PRA level) on an individual patient basis. Perioperative heparin prophylaxis against venous thromboembolism was not routinely used. Patients at risk for CMV disease (recipient, donor or both CMV positive) received CMV prophylaxis from 1992 onwards. This consisted of acyclovir up until 1998, valaciclovir from 1998 until 2004 and valganciclovir used since then (dosage adjusted for renal function). All patients received co-trimoxazole for pneumocystosis prevention. Both prophylactic agents were used for the first four post-transplant months.

RESULTS

Initial allograft

From the beginning of January 1990 to the end of June 2009, 2509 kidney transplants were performed at our centre (2466 deceased donor, reflecting the traditional low rate of living donation in Ireland in this time period). Overall, 73 (2.9%) patients experienced an early (<14 days) allograft thrombosis. There were 48 patients (65.7%) who were eventually re-transplanted. Of these, nine patients (five male) experienced an early primary graft thrombosis without evidence of acute rejection or history of venous thromboembolism and were subsequently re-transplanted within 2 weeks (0–12 days) of the previous transplant. In these cases, the transplanting surgeon deemed the thrombosis to be technical in nature and did not consider the presence of an inherited thrombophilia to be likely. The fact none of the patients had experienced a prior thrombotic event bolstered this viewpoint. The vessel thrombosed was the renal vein in six cases, both artery and vein in one case and unknown/insufficient data in two cases. All nine patients had undergone transplant nephrectomy and there was no evidence of acute rejection on explant histology. The mean age was 42.9 years (23–67 years) at time of transplant (see Table 1) and the mean follow up of the nine cases was 85 months (7–187 months). The first transplant was from a deceased donor in seven cases with two cases from a living donor. Of note, two cases were from very young donors (aged 5 and 8 years), which is a known risk factor for allograft thrombosis.[5] For seven patients, the allograft thrombosis was their first kidney transplant. The initial transplants functioned for a mean of 1.67 days (0–7 days) and the patients received a second allograft at a mean of 3.1 days (1–8 days) after the initial allograft failure.

Antibody sensitization

Mean peak PRA for the nine patients was 14.4%. All seven first-time transplant patients had an initial PRA $\leq$ 10%

Table 1 Baseline patient demographic and transplant data for initial allograft

No.	Sex	Age	Cause ESRD	Year of transplant	Transplant No.	Peak PRA %	Transplant type	Donor age	Time to failure (days)	Time from failure to re-transplant (days)
1	M	64	HTN	1992	1	0	DD	39	<1	3
2	M	67	CIN	1993	1	0	DD	5	1	3
3	F	23	Calculi	1994	1	10	DD	41	7	12
4	F	37	VUR	1994	3	60	DD	40	<1	2
5	M	32	GN	1996	1	0	DD	45	7	8
6	F	29	GN	1998	2	60	LRD	41	<1	7
7	F	55	APKD	1999	1	0	DD	8	<1	1
8	M	51	IgAN	2007	1	0	DD	46	<1	3
9	M	24	GN	2009	1	0	LRD	53	<1	3

APKD, adult polycystic kidney disease; CIN, chronic interstitial nephritis; DD, deceased donor; ESRD, end-stage renal disease; GN, glomeulonephritis (unspecified); HTN, hypertension; IgAN, IgA nephropathy; LRD, living related donor; VUR, vesicoureteric reflux.

Table 2 Outcome data for the repeat transplant

No.	Immunosuppression	Delayed graft function	Acute rejection	Time to acute rejection (days)	Allograft survival (months)	Cause of allograft loss
1	C/A/P	–	No	–	155	Death
2	C/A/P	–	Banff I‡	28	2	AR
3	C/A/P	–	No	–	29	Death
4	C/A/P/ATG	–	No	–	187†	–
5	C/A/P	–	Banff II	26	24	CAN
6	T/M/P/ATG	–	No	–	160†	–
7	T/M/P	–	No	–	126†	–
8	T/M/P/B	–	B/L	10	29†	–
9	T/M/P/B	–	No	–	7†	–

†Still functioning. ‡Biopsy performed after empirical treatment for rejection. A, azathioprine; AR, acute rejection; ATG, anti-thymocyte globulin; B, basiliximab; B/L, borderline; C, cyclosporine; CAN, chronic allograft nephropathy; M, mycophenolic acid; P, prednisone; T, tacrolimus.

before the episode of allograft thrombosis. The remaining two patients, who had previously been transplanted, had a peak PRA of 60%. The initial cross-match was repeated, and was negative, in the two patients who had an allograft thrombosis diagnosed at 7 days post-transplant.

We measured peak PRA pre-transplant for patients eventually re-transplanted at a later date ($n = 43$). Median PRA was 5% (interquartile range (IQR) 0–15%) before the initial failed allograft and increased to 27.5% (IQR 0–75%) before their second transplant ($P = 0.0375$).

Re-transplantation

All re-transplants were of deceased donor origin. Five patients with an ABO blood group of A or B received a group O kidney. The remaining four patients (two group O, one group A and one group AB) received ABO identical re-transplants. Immediate graft function was achieved in eight cases with the remaining allograft beginning to function on the first postoperative day (see Table 2 for full outcome data). No patients experienced antibody-mediated rejection but three developed acute cellular rejection in the first month post-transplantation (one borderline, one each of Banff grade I and II). Four grafts failed after a median of 26.5 months (2–155 months). Two of these died with a functioning allograft, one failed owing to chronic allograft nephropathy (exactly 2 years after re-transplantation) and one owing to persistent acute cellular rejection (2 months post transplant). This patient had empirical treatment, including an intravenous corticosteroid boost, for acute rejection. By the time a biopsy was performed (20 days after treatment was initiated) the acute rejection was graded as mild. However, his renal function continued to deteriorate and the allograft was lost 2 weeks later. The remaining five patients still have a functioning allograft (as of December 2009) after a median of 124 months (7–187 months). One year graft and patient survival after re-transplantation were 87.5% and 100% respectively. After 5 years, graft and patient survival were both 57% (Figs 1, 2).

DISCUSSION

We have reported on nine cases from our institution of immediate re-transplantation following early kidney trans-

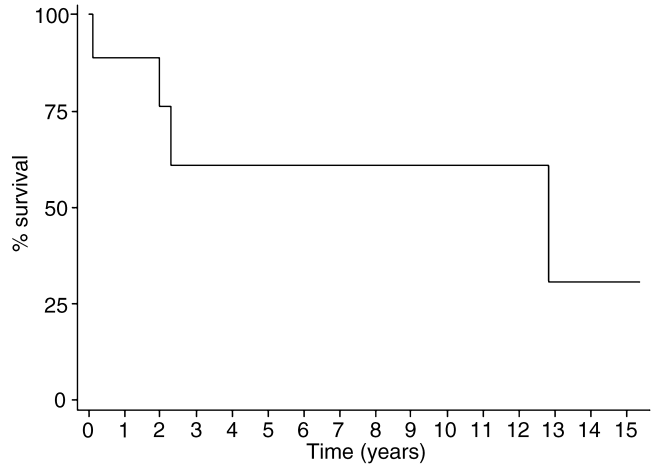

Fig. 1 Kaplan–Meier curve showing allograft survival.

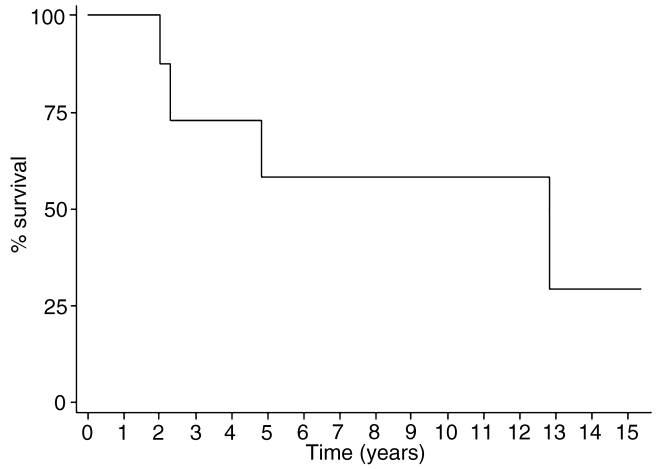

Fig. 2 Kaplan–Meier curve showing patient survival.

plant thrombosis. Primary renal transplant failure is associated with significant mortality particularly when thrombosis is the cause of graft loss (see Kaplan and Meier-Kriesche,[6] and Phelan PJ, O'Kelly P, Tarazi M, Tarazi N, Salehmohamed MR, Little DM, Magee C, Conlon PJ. Renal allograft loss in the first postoperative month: causes and consequences. unpubl. data, 2011). Repeat transplantation, in general, has been associated with large reductions in 5-year mortality for both diabetic and non-diabetic end-stage renal disease patients.[7] Re-transplanting in the early post-nephrectomy period may be preferable because extensive adhesions have not yet formed. Moreover, allograft loss due to thrombosis may be less sensitizing than early loss from severe rejection. This may facilitate finding another suitably matched kidney.

However, there are obstacles to re-transplantation. Before proceeding with re-transplantation, any underlying factors contributing to the graft thrombosis must be addressed. Surgical issues such as problems establishing the vascular anastomosis and positioning of the allograft must be sought. Frequently, there is no obvious surgical cause identified. Ruling out hyperacute rejection and arguably screening for a hyper-coagulable state should be undertaken before attempting re-transplantation. In our series, there were no history of prior thrombotic events and allograft failure was felt to be technical in nature. Therefore, screening for a hyper-coagulable state was not performed as it would have been impractical to obtain a result within the time window for re-transplantation. This allowed patients to be rapidly re-listed. It is prudent to stress that this was a clinical judgement by the transplanting surgeon, which would vary on a case-to-case basis. Another barrier to re-transplantation is the issue of sensitization to donor HLA. This commonly leads to difficulty in finding a compatible match for these patients, especially if re-transplantation is delayed. Most of our patients had a low level of antibody sensitization which facilitated rapid re-transplantation. The two patients who had a high level of sensitization (PRA 60%) would arguably have had a very long wait for another kidney or become 'un-transplantable' if they had not been rapidly re-transplanted after the allograft thrombosis. Moreover, we have shown a significant increase in PRA after allograft thrombosis for patients eventually re-transplanted. Of note, both these re-transplants are still functioning, rejection free, after 160 and 187 months.

Lower survival rates compared with the first kidney transplant have been reported among re-transplants by several authors.[8–10] However, the time between transplants is generally prolonged in these studies, which allows for an immune response to develop to the initial allograft. The higher levels of antibody sensitization in these patients translate into decreased graft survival.[11,12] Humar *et al*. reported equivalent outcomes to primary transplant recipients in a small group of patients ($n = 16$) transplanted after allograft thrombosis.[13] Patients who experience an early allograft failure owing to technical/surgical factors with no evidence of an immunological cause are often eligible for rapid re-listing and immediate re-transplantation. These patients are prioritized at our centre for another organ and may receive an ABO-compatible (non-identical) allograft depending on the clinical circumstances.

There are some limitations to this study. First, we acknowledge the inherent weaknesses of any retrospective, single centre study. However, confining the study to one centre reduces the confounding effects of multiple surgeons and multiple perioperative protocols. Another limitation of the study is the long time lag between the first and last case. Over this period there have been significant changes to immunosuppression regimes and improvements in early allograft survival which makes comparisons difficult.

We have described our experience with immediate re-transplantation following early primary kidney transplant thrombosis. We have shown that emergency re-transplantation in this setting can be a successful remedy to

a devastating complication. The patient with allograft thrombosis should be carefully evaluated for an immunological aetiology, but if not present, we feel that rapid re-transplantation should be considered.

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