Chronic Allograft Dysfunction—Is There a Treatment?

A.C. Ferreira, H. Viana, F. Carvalho, J.R. Pinto, M.J. Galvão, F. Nolasco, and J.R. Santos

---

ABSTRACT

Background. The major causes of renal transplant loss are death and chronic allograft dysfunction (CAD). The aims of this study were to determine the incidence of CAD in our population and the relation between allograft survival and immunosuppressive regimens.

Methods. We studied retrospectively 473 patients who received deceased donor kidney transplants with at least 1 allograft biopsy between January 1990 and May 2007. Clinical data included age, gender, biopsy data, and immunosuppression before and after kidney biopsy. Mean age was 45.4 ± 12.7 years including 65% males with a mean follow-up of 6.7 ± 4.5 years. CAD was observed in 177 of 473 biopsies: 48 patients showed interstitial fibrosis (IF); 101 chronic rejection (CR); 16 transplant glomerulopathy (TG); and 12, CR and TG. Mean follow-up since the discovery of the histologic feature was 60.5 ± 50.5 months for IF; 38.3 ± 40.8 for CR, and 18.2 ± 19.2 for TG.

Results. CAD, which was more common in younger patients ($P = .03$), correlated upon univariate and multivariate analysis with CKD stage 5d development ($P < .001$). Deposition of C4d in peritubular capillaries was more frequent among CAD patients ($P = .004$), an association with particular relevance to recipients with CR ($P = .02$) and TG ($P < .001$). When we analyzed CAD subpopulation, we observed a positive correlation between allograft survival and immunosuppression modification after biopsy. Substitution of sirolimus (40/177) was shown in univariate, multivariate and Cox regression analyses to be a renal protector ($P < .002$). Allograft survival was also correlated with initial mycophenolate mofetil versus azathioprine, (62/177) immunosuppression ($P < .001$).

Conclusion. CAD, a frequent histologic feature, may benefit from sirolimus conversion.

RENAL TRANSPLANTATION has become the treatment of choice for CKD stage 5d. The major causes of renal transplant loss are death and chronic allograft dysfunction (CAD).^{1–3} CAD is a generic term for renal allograft dysfunction in the absence of active acute rejection, drug toxicity, or other diseases. It is characterised by pathologic changes that involve all parts of renal parenchyma including the presence of interstitial fibrosis (IF) or tubular atrophy (TA).² The Banff 2005 group included in this category the terms chronic rejection (CR) and transplant glomerulopathy (TG).¹ Currently, there is no effective treatment for CAD, beside control of blood pressure. Various immunosuppressive regimens have been evaluated to limit the risk of CAD development or to limit its effects.^{2,3} The aims of this study were to determine the incidence of CAD in our population and its relationship to allograft survival and immunosuppressive regimens.

PATIENTS AND METHODS

This retrospective study included 473 patients who received deceased donor kidney transplantation with at least 1 allograft biopsy between January 1990 and May 2007. All biopsies were performed based on clinical features; there were no protocol biopsies. Clinical data included age, gender, biopsy data, and immunosuppression before and after the kidney biopsy. According to histologic features, the patients were divided into 2 groups: the CAD group and a control group.

Univariate analysis (Spearman correlation) and multivariate analysis (linear regression, 95% confidence interval [CI], using a

---

From the Nephrology Department, Hospital de Curry Cabral, Lisbon, Portugal.

Address reprint requests to Ana Carina da Costa Ferreira, Rua da Beneficência n°8, 1069 Lisbon, Portugal. E-mail: karinadacostafer@hotmail.com

forward method) were performed with the SPSS system 15.0 (SPSS Inc., Chicago, IL); a $P < .05$ was considered significant.

RESULTS

Data for the variables recorded during the study are summarized in Table 1. CAD was present in 177 of 473 recipients (37.4%). We subdivided these patients into 3 categories: patients with nonspecific IF/TA; patients with CR, which was defined by IF/TA and pathologic changes in blood vessels; and patients with TG, defined by duplication of glomerular basement membrane. Using these histologic criteria, 48 patients had IF/AT; 101 CR; 16 TG; and 12 both CR and TG. Mean follow-up since histologic feature was 60.5 ± 50.5 months for IF; 38.3 ± 40.8 for CR; and 18.2 ± 19.2 for TG. Since January 2005, PTC C4d deposition was performed on all kidney biopsies. Overall, 17 patients showed C4d deposition in PTC: 12 with CAD and 5 without.

Upon univariate analysis, CAD was more frequent among younger patients ($r = -0.98$; $P = .03$) and correlated with PTC C4d deposition ($r = 0.1$; $P = .004$) and with allograft loss ($r = .2$; $P < .0001$), particularly with CKD phase 5d development ($r = 0.27$; $P < .001$). Upon multivariate analysis, there was a positive correlation between CAD and PTC C4d deposition ($P = .008$; 95% CI, 0.08–0.53) and CKD phase 5d development ($P < .001$; 95% CI, 0.2–0.4). Deposition of C4d in PTC was more frequent among CAD patients, an association with particular relevance to recipients with CR ($r = 0.1$; $P = .02$) and TG ($r = 0.2$; $P < .001$). Using linear regression, a correlation was only achieved in TG patients ($P < .001$; 95% CI, 0.1–0.3).

When we analyzed the CAD subpopulation, and at the end of follow-up, 47.5% ($n = 84$) had developed CKD stage 5d: 37% of IF/TA patients, 53.1% of CR patients, and 39.3% of TG patients. We observed a positive correlation between allograft loss and PTC C4d deposition upon both univariate and multivariate analyses ($r = 0.4$; $P = .008$; 95% CI, 0.2–0.9). Allograft survival positively correlated with immunosuppressive therapy modification after kidney biopsy, which occurred in 50 of 177 patients ($r = 0.2$; $P = .002$). It was positively correlated with initial therapy using mycophenolate mofetil (MMF) versus azathioprine on both

univariate and multivariate analyses (62/177; $r = 0.3$; $P < .001$; 95% CI, 0.1–0.4). Introduction of sirolimus (40/177) in univariate, multivariate, and Cox regression analyses correlated with allograft survival ($r = 0.3$; $P < .001$; 95% CI, -0.1 to -0.5 ; $P < .002$, respectively), namely a 20% better graft survival at 2 years after the index biopsy. The graft survival was 80% among those who received sirolimus versus 60% among those never treated with this drug ($P = .00029$, log-rank test).

DISCUSSION

The histologic diagnosis of CAD represents the final pathway of renal allograft damage.³ In this population, it represented a common histologic feature associated with loss of allograft function. Deposition of C4d in PTC was a risk factor for this outcome, as it was already described in other reports.^{4,5} During humoral rejection, antibody deposition in PTC resulted in activation of the classical pathway of complement generating C4d, which binds covalently to PTC. This observation suggests that antibody-mediated rejection is a contributor to some forms of the chronic renal allograft lesion, formerly known as TG, which is a pathologic condition associated with poor allograft survival.⁶ Our study demonstrated that C4d deposition was frequent among the TG subgroup.

To reduce the incidence of CAD and allograft loss, it is necessary to find preventive and therapeutic measures. Therapeutic strategies have centred on avoidance of calcineurin inhibitors, but this strategy is associated with higher rates of acute rejection episodes, which are a known risk factor for development of CAD.³ MMF has been used to reduce incidence of CAD or its effects. Both de novo use and conversion therapy are superior to the use of azathioprine.^{3,7} Sirolimus, an antiproliferative, non-nephrotoxic drug has been shown to be effective in several studies.^{2,3,8,9} In our study we did not observe any difference whether the initial immunosuppressive agent was cyclosporine or tacrolimus maybe because both are nephrotoxins; both agents lead to vasoconstriction, which is reversible, and both produce transforming growth factor- β , leading to interstitial fibrosis, which is progressive and irreversible. Use of

Table 1. Clinical Data

Variable	Patients ($n = 473$)	CAD Group ($n = 177$)	Control Group ($n = 296$)	P
Age (yrs)	45.4 ± 12.7	43.5 ± 13.2	46.5 ± 12.3	.03
Gender				
Male	69%	61%	67.6%	NS
Female	31%	39%	32.4%	NS
Mean follow-up (yrs)	6.7 ± 4.5	6.6 ± 3.9	6.8 ± 4.9	NS
Induction therapeutic (%)	15.4% ($n = 73$)	15.8% ($n = 28$)	15.2% ($n = 45$)	NS
Acute rejection episodes (%)	48.2% ($n = 228$)	51.4% ($n = 92$)	45.6% ($n = 136$)	NS
Cellular vs vascular	191; 81	79; 31	112; 50	
Allograft loss (%)	44.2% ($n = 209$)	55.9% ($n = 99$)	37.2% ($n = 110$)	<.001
CKD stage 5d (%)	31.1% ($n = 147$)	47.5% ($n = 84$)	21.3% ($n = 63$)	<.001
Death (%)	13.1% ($n = 62$)	8.5% ($n = 15$)	15.9% ($n = 47$)	NS

Abbreviation: NS, not significant.

MMF seemed to allow better allograft survival, and sirolimus was found to be a renal protector. Introduction of sirolimus proved to be effective in this population. We believe that this is due to its antiproliferative properties, leading to a reduced proliferation of fibroblasts and vascular smooth muscle cells and because the introduction of this drug allowed us to reduce or even withdrawn calcineurin inhibitors, sparing their effects.

REFERENCES

1. Solez K, Colvin RB, Racusen LC, et al: Banff '05 meeting report: differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy. *Am J Transplant* 7:518, 2007
2. Afzali B, Taylor AL, Goldsmith JA: What can we do about chronic allograft nephropathy: role of immunosuppressive modulations. *Kidney Int* 1:145, 2005
3. Chapman JR, O'Connell PJ, Nankivell BJ: Chronic renal allograft dysfunction. *J Am Soc Nephrol* 16:3015, 2005
4. Haas M, Rahman MH, Racusen LC, et al: C4d and C3d staining in biopsies of ABO and HLA incompatible allografts: correlation with histologic findings. *Am J Transplant* 6:1829, 2006
5. Neto ED, Prado E, Beutel A, et al: C4d positive chronic rejection: a frequent entity with a poor outcome. *Transplantation* 84:1391, 2007
6. Cosio FG, Gloor JM, Sethi S, et al: Transplant glomerulopathy. *Am J Transplant* 8:492, 2008
7. Merville P, Berge F, Deminiere C, et al: Lower incidence of chronic allograft nephropathy at 1 year post-transplantation in patients treated with mycophenolate mofetil. *Am J Transplant* 4:1769, 2004
8. Johnson RW, Kreis H, Oberbauer R, et al: Sirolimus allows early cyclosporine withdrawal in renal transplantation resulting in improved renal function and lower blood pressure. *Transplantation* 72:777, 2001
9. Kruger B, Fischereder M, Jauch KW, et al: Five year follow up after late conversion from calcineurin inhibitors to sirolimus in patients with chronic renal allograft dysfunction. *Transplant Proc* 39:518, 2007