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Chronic rejection with or without transplant vasculopathy

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Abstract

Background Chronic allograft nephropathy (CAN) is defined and graded in the Banff '97 scheme by the severity of interstitial fibrosis and tubular atrophy. It has been denoted that chronic rejection can be diagnosed if the typical vascular lesions are seen, consisting of fibrointimal thickening. We observed several patients who developed CAN without vascular changes or signs of cyclosporine toxicity. Therefore, we assessed the risk factor profiles of CAN with and without transplant vasculopathy.

Methods A cohort of 654 cadaveric renal transplants performed between 1983 and 1997 that functioned for more than six months was studied. Fifty-four transplants had CAN defined by a significant decline in renal function together with interstitial fibrosis and tubular atrophy without signs of cyclosporine nephrotoxicity or recurrent disease. Using the Banff CV score, 23 of 54 cases (43%) had a chronic vasculopathy score of 0 or 1 whereas 31 cases (57%) had a CV score of 2 or 3. Applying multivariate logistic regression, predictor variables of the two groups were compared with 231 transplants with a stable function for at least five years.

Results Graft histology was obtained at a mean of 2.4 and 2.9 years after transplantation in the group with or without vasculopathy, respectively. Acute rejection episodes (ARE) after three months post-transplantation were the strongest risk factor for both forms of CAN, odds ratio (OR) 14.7 (6.0-36.0). CAN with vasculopathy was also associated with transplants performed in the 1980s, OR 4.95 (1.65-14.9) and with creatinine clearance at 6 months, OR 0.58 (0.44-0.75) per 10 ml/min increase. In contrast, young recipient age, OR 0.69 (0.47-0.99) per 10 years increase, and the presence of panel reactive antibodies at the time of transplantation, OR 1.26 (1.08-1.47) per 10% increase, were independent risk factors for CAN without vasculopathy.

Conclusions After exclusion of cyclosporine toxicity or recurrent disease CAN occurred without moderate or severe transplant vasculopathy in 43% of the cases. The correlation with young recipient age, sensitization and late ARE suggest an immune pathogenesis, consistent with chronic rejection.

Introduction

Chronic allograft nephropathy (CAN) is the term used to describe the fibrosclerotic changes in long-surviving renal transplants. The lesions may involve all anatomic compartments of the kidney and give rise to fibrous intimal thickening of the arteries, transplant glomerulopathy and glomerulosclerosis, interstitial fibrosis and tubular atrophy (1). CAN is considered to result from both immune and non-immune injury to the graft (2). Associated risk factors such as a young recipient age, high panel reactive antibodies (PRA), histoincompatibility and acute rejection episodes (ARE) suggest an immune pathogenesis, consistent with 'rejection' (3). On the other hand, non-immune damage due to old donor age, hyperlipidemia, arterial or glomerular hypertension, smoking or cyclosporine exposure may also contribute to the development of CAN (4).

In the Banff '97 classification, CAN has been graded by the severity of interstitial fibrosis and tubular atrophy, recognizing that these changes are present in almost all biopsies and have the strongest correlation with outcome (5). However, given the lack of specificity of these lesions, it has been suggested that chronic rejection can be diagnosed if typical vascular lesions are observed. This transplant vasculopathy consists of fibrointimal thickening of arteries, breaks in the elastic layer and vessel wall infiltration with inflammatory cells. The vascular narrowing with downstream ischemia is held responsible for the chronic glomerular and tubulointerstitial lesions. However, we observed several patients who developed CAN without obvious vasculopathy or signs of cyclosporine toxicity suggesting that chronic rejection may emerge independent of vascular obliteration.

In the present study CAN was defined in grafts that show a significant decline in renal function together with tubulointerstitial damage without signs of late cyclosporine nephrotoxicity or recurrent disease. To determine the risk profiles of the various forms of CAN, we categorized CAN on the basis of whether significant vasculopathy was present and compared these two groups with a group of patients with long-term stable graft function.

Patients and methods

We studied 654 cadaveric kidney transplants performed in our center between 1983 and 1997 that functioned for more than six months. The standard immunosuppressive regimen consisted of prednisone and once-daily cyclosporine (Sandimmune) or azathioprine. Patients were followed until death, return to dialysis, or until July 1, 1998. CAN, our study end-point, was defined

Table 1. Clinical characteristics of cases with CAN or stable graft function

	CAN (n=54)	Stable function (n=231)	*P*
Year of transplantation (% 1980s)	67	54	0.08
Repeat transplants (%)	20	14	0.27
Recipient age (years)	41 ± 13	45 ± 13	0.03[a]
Cigarettes smoking (%)	59	40	0.01[a]
Current panel reactive antibodies (%)	19 ± 31	9 ± 19	0.01[a]
Donor age (years)	38 ± 16	35 ± 14	0.25
HLA-A,B,DR mismatches (#)	1.9 ± 1.0	1.9 ± 1.1	0.75
HLA-A,B,DR shares (#)	3.4 ± 0.9	3.7 ± 1.0	0.09
CREG mismatches (#)	1.3 ± 0.9	1.1 ± 0.9	0.12
CREG shares (#)	4.2 ± 1.2	4.6 ± 1.1	0.02[a]
Cold ischemia time (hours)	31 ± 7	29 ± 7	0.20
Delayed graft function (%)	23	30	0.36
Interstitial / vascular / clinical ARE (%)	48 / 26 / 6	35 / 13 / 8	<0.01[a]
Last ARE < 3 months / > 3 months (%)	35 / 44	50 / 6	<0.01[a]
Azathioprine / cyclosporine @ 6 months (%)	30 / 70	28 / 72	0.87
Dipstick proteinuria >1+ @ 6 months. (%)	14	3	<0.01[a]
Serum creatinine @ 6 months (µmol/l)	178 ± 77	149 ± 62	<0.01[a]
ECC @ 6 months (ml/min)	50 ± 25	64 ± 23	<0.01[a]
Slope 1000/creatinine > 6 months (l/µmol/yr)	-16.1 ± 9.4	0.4 ± 1.1	<0.01[a]

Data are expressed as mean ± standard deviation. [a]P<0.05. CAN: chronic allograft nephropathy, CREG: crossreactive groups of MHC class I, ARE: acute rejection episode, ECC: endogenous creatinine clearance.

functionally and histologically according to the diagnostic criteria from the fourth Alexis Carrel conference (6). To assess whether there was significant deterioration of renal function, regression lines were constructed of the reciprocal of the serum creatinine levels from 6 months after transplantation until the end of follow-up. To improve the estimate of the regression lines, especially in patients with a variable decline in renal function, a breakpoint analysis was included (7). The curves of the reciprocal creatinine-versus-time were also used to define stable graft function. We examined all biopsies and nephrectomies from beyond 6 months performed in patients with a significant decline in renal function. Blinded for clinical information, graft histology was read according to the Banff ’97 classification (YS, FK, JAB). Biopsies or nephrectomies with unsatisfactory specimen adequacy (less than 7 glomeruli or no arteries) were discarded from evaluation whereas all marginal (8-10 glomeruli and 1 artery) and adequate (>10 glomeruli and more than one artery) biopsies were included in the study (5). CAN was defined as the presence of interstitial fibrosis and/or tubular atrophy with or without histopathologic features of obliterative vascular disease or glomerulopathy. Patients with clinical or histological signs of de novo or recurrent glomerulonephritis or predominant cyclosporine toxicity, i.e. the presence of arteriolar hyalinosis (8), were excluded from analysis. Most biopsies were taken before the conversion from Sandimmune to Neoral, a switch that increased the problem of cyclosporine

nephrotoxicity in our population (9). Nephrectomies were done in a minority of the patients on the clinical indication of pain, fever or hematuria.
We used the Banff chronic vascular (CV) score to categorize CAN in a form without or with minimal vasculopathy (CV 0-1) and in a form with moderate or severe vasculopathy (CV 2-3) (5). Using uni- and multivariate logistic regression analysis, predictor variables of CAN were compared with those in 231 cases with a stable graft function for at least 5 years post-transplantation. Panel reactive antibodies, age and cigarette smoking at time of transplantation were the recipient variables investigated. Donor age was used as a donor variable. Transplant parameters included: year of transplantation, repeat transplant, cold ischemia time and delayed graft function defined as the need for dialysis in the first week. The influence of HLA mismatches and shares on the occurrence of CAN was evaluated at the level of private antigens and crossreactive groups (CREG), as described previously (10). An acute rejection episode was defined by a rapid decline in renal function; in 94% of the cases this diagnosis was confirmed by histopathology. Interstitial rejection was diagnosed when an interstitial infiltrate and tubulitis were present (Banff grade borderline or I); the diagnosis of acute vascular rejection was made whenever an arteritis was present (Banff grade II or III). We used the time interval between transplantation and the last treated ARE (within or after three months) and the histological type of acute rejection as rejection factors. Dipstick proteinuria, serum creatinine concentration and endogenous creatinine clearance at six months were evaluated as clinical parameters. As a result of the randomized and clinical early conversion from cyclosporine to azathioprine in many patients, maintenance drug regimen at six months posttransplant was studied as variable. Since the reciprocal of the serum creatinine concentration decreases linearly with time in the majority of patients with chronic renal disease, we used the slope of this relationship as a measure of the rate of decline in renal function. Deterioration of renal function may start at any time point after transplantation. To identify a change in the slope of the regression line we included a breakpoint analysis (11). We used the broken line in case of a significantly better fit of the residual sum of squares than the straight line. Patients with a negative slope of the straight or broken line, significantly different from zero, were considered to have a decline in renal function. Stable graft function was defined as having not a significant decline of the regression line for at least five years post-transplantation.
The two samples t test for continuous and dichotomous variables was used to determine the significance of differences of baseline characteristics between the CAN group and the patients with stable function, and of biopsy data of the two forms of CAN. Graft survival of the two groups was compared using

Kaplan-Meier curves, including a log-rank test.
Logistic regression models were used to predict the presence of CAN based on the set of recipient, donor and transplant variables. CAN and its forms with and without vasculopathy were compared with 231 stable transplants. Odds ratios (OR) and 95% confidence intervals were estimated for each of the variables in the model. Significant predictors (P value < 0.05) were fitted in a multivariate model. Forward selection techniques were used to choose independent risk factors.

Results

In 604 transplants (92%) sufficient data points were available to construct the regression line of 1/Cr. The mean number of creatinine readings per transplant was 53, range 7-468. Breakpoint analysis revealed a better fit of the broken line in 129/604 cases (21%). In 266 cases (41%) there was a negative slope of the straight (n=170) or broken (n=96) line of 1/Cr, which was significantly different from zero. Graft loss censored for patient death with a functioning transplant occurred in 99/266 cases (37%). Graft histology was available in 111/266 (42%) cases. After exclusion of recurrent/de novo glomerulonephritis (28), acute rejection (9), cyclosporine toxicity (6) or inadequate specimens (12), CAN was diagnosed in 54 cases; in 45 patients based on biopsies and in 9 cases on nephrectomy specimens. Specimen adequacy was scored marginal

Table 2. Clinical characteristics of CAN with or without vasculopathy

	No vasculopathy (n=23)	Vasculopathy (n=31)	*P*
Year of transplantation (% 1980s)	57	74	0.18
Repeat transplants (%)	22	19	0.83
Recipient age (years)	40 ± 13	42 ± 14	0.55
Cigarettes smoking (%)	61	58	0.84
Current panel reactive antibodies (%)	22 ± 34	16 ± 29	0.42
Donor age (years)	31 ± 14	43 ± 16	<0.01[a]
HLA-A,B,DR mismatches (#)	2.0 ± 1.0	1.9 ± 1.0	0.76
HLA-A,B,DR shares (#)	3.5 ± 1.1	3.4 ± 0.7	0.56
CREG mismatches (#)	1.4 ± 1.0	1.3 ± 0.9	0.62
CREG shares (#)	3.9 ± 1.4	4.4 ± 1.1	0.20
Cold ischemia time (hours)	29 ± 7	32 ± 7	0.08
Delayed graft function (%)	16	29	0.35
Interstitial / vascular ARE (%)	52 / 17	45 /32	0.56
Last ARE < 3 months / > 3 months (%)	26 / 48	42 / 42	0.57
Azathioprine / cyclosporine @ 6 months (%)	22 / 78	35 / 65	0.37
Dipstick proteinuria >1+ @ 6 months (%)	10	17	0.52
Serum creatinine @ 6 months (μmol/l)	148 ± 45	201 ± 87	0.01[a]
ECC @ 6 months (ml/min)	60 ± 30	42 ± 17	0.01[a]
Slope 1000/creatinine > 6 months (l/μmol/yr)	-14.9 ± 9.3	-13.7 ± 7.7	0.60

Data are expressed as mean ± standard deviation. [a]P<0.05. Abbreviations as in table 1.

Table 3. Univariate analysis of risk factors of CAN and its forms with or without vasculopathy

	CAN (n=54)	No vasculopathy (n=23)	Vasculopathy (n=31)
Year of transplantation (83-89 vs. 90-97)	1.73 (0.93-3.21)	1.12 (0.47-2.66)	2.48 (1.07-5.77)[a]
Recipient age (10 years increase)	0.78 (0.62-0.98)[a]	0.72 (0.52-1.00)[a]	0.83 (0.61-1.10)
Smoking cigarettes	2.14 (1.17-3.92)[a]	2.29 (0.95-5.51)	2.04 (0.95-4.36)
Panel reactive antibodies (10% increase)	1.16 (1.04-1.31)[a]	1.22 (1.05-1.41)[a]	1.12 (0.97-1.31)
Donor age (10 years increase)	1.13 (0.92-1.37)	0.81 (0.32-2.08)	1.41 (1.08-1.82)[a]
HLA-A,B,DR mismatches (antigen)	1.04 (0.80-1.37)	1.07 (0.73-1.57)	1.02 (0.73-1.44)
HLA-A,B,DR shares (antigen)	0.77 (0.55-1.08)	0.84 (0.54-1.30)	0.71 (0.48-1.07)
CREG mismatches (group)	1.22 (0.92-1.63)	1.29 (0.87-1.91)	1.16 (0.81-1.67)
CREG shares (group)	0.73 (0.56-0.98)[a]	0.59 (0.40-0.88)[a]	0.85 (0.60-1.20)
Cold ischemia time (hour)	1.03 (0.99-1.08)	0.99 (0.92-1.05)	1.06 (1.01-1.13)[a]
Delayed graft function	0.71 (0.34-1.47)	0.45 (0.13-1.58)	0.95 (0.38-2.15)
Interstitial vs. no ARE	2.98 (1.31-6.40)[a]	2.25 (0.91-7.02)	3.54 (1.22-10.2)[a]
Vascular vs. no ARE	4.29 (1.76-10.4)[a]	2.24 (0.59-8.48)	6.73 (2.14-21.2)[a]
Last ARE < 3 months vs. no ARE	1.52 (0.69-3.34)	0.88 (0.27-2.81)	2.28 (0.79-6.23)
Last ARE > 3 months vs. no ARE	14.7 (6.00-36.0)[a]	12.3 (3.98-38.3)[a]	17.5 (5.46-56.1)[a]
Azathioprine vs. cyclosporine @ 6 months	1.08 (0.56-2.06)	0.71 (0.25-1.99)	1.41 (0.64-3.09)
Dipstick proteinuria >1+ @ 6 months (%)	5.21 (1.74-15.6)[a]	3.55 (0.69-18.4)	6.40 (1.89-21.7)[a]
Serum creatinine @ 6 months (10 µmol/l increase)	1.06 (1.02-1.20)[a]	1.00 (0.93-1.07)	1.08 (1.03-1.14)[a]
ECC @ 6 months (10 ml/min increase)	0.73 (0.62-0.85)[a]	0.92 (0.76-1.02)	0.56 (0.44-0.71)[a]

Data are expressed as odds ratio (95% confidence interval). [a]$p<0.05$. Abbreviations as in table 1.

in 12 and adequate in 42 transplants. Table 1 compares the characteristics of these 54 patients with 231 cases with a stable transplant function for at least five years. Recipient age was lower in the CAN group, pre-transplant sensitization and percentage of smokers were higher. While the number of HLA mismatches was not different, CAN patients had a significantly lower number of shared CREG. CAN patients had more ARE, especially those of a vascular type and those that occurred after three months. Furthermore, they had more proteinuria and a lower renal function at 6 months. Maintenance drug regimen was not different between those with CAN or those with stable function.

The 54 cases with CAN were analyzed according the Banff CV score. Twenty-three grafts (43%) had a CV score 0 (n=9) or 1 (n=14), while 31 (57%) had a CV score of 2 (n=11) or 3 (n=20) and were categorized as CAN without or with vasculopathy, respectively. Mean time between transplantation and the diagnosis of CAN with or without vasculopathy was 2.4 and 2.9 years, respectively. Subsequent graft loss, censored for other causes than chronic rejection, occurred in 77 and 61% respectively, almost significantly different (figure 1). In the 45 biopsy-confirmed cases there were no significant differences in mean number of arteries (2.0 versus 2.2) and number of glomeruli (15 versus 13). Immunosuppressive agents, renal function, blood pressure and proteinuria at time of the biopsy were not different between the two groups. Transplant

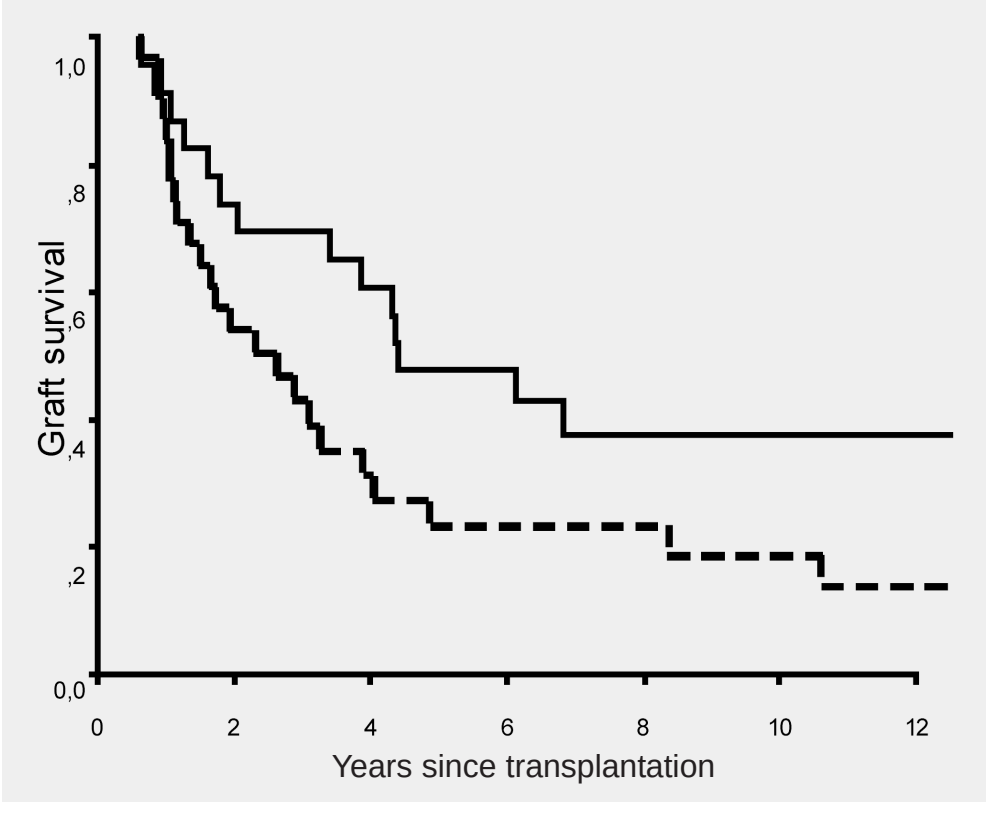

Figure 1 Kaplan-Meier graft survival for CAN without (solid line) or with (dashed line) vasculopathy. Log-rank test: P = 0.06

glomerulopathy (CG score 1-3) was present in 8/23 cases without vasculopathy and in 3/31 transplants with vasculopathy. The extent of tubulointerstitial changes was comparable. Of note, all nephrectomies showed diffuse and concentric thickening of the arterial intima (CV score of 3) and signs of ischemia such as bleeding and edema. Table 2 compares the clinical characteristics of both forms of CAN. Mean donor age was 12 years higher and renal function was worse at six months in the group with vasculopathy compared to the group without vasculopathy.

Tables 3 and 4 compares the risk profiles of the two forms of CAN after uni- and multivariate analysis, respectively. CAN with vasculopathy was associated with transplantation in the 1980s, older donor age, cold ischemia time, vascular and late ARE and graft dysfunction at 6 months. Stepwise selection of these significant factors revealed the following risk factors in a multivariate model: year of transplantation, 1983-1989 versus 1990-1997, OR 4.95 (1.65-14.9), ARE after 3 months, OR 15.0 (4.08-50.0) and creatinine clearance at 6 months,

OR 0.58 (0.44-0.75) per 10 ml/min increase. CAN without vasculopathy was predicted by younger recipient age, sensitization at time of transplantation, sharing less CREG and late ARE in univariate analysis. Independent risk factors were recipient age, OR 0.69 (0.49-0.99) per 10 years increase, panel reactive antibodies, OR 1.26 (1.08-1.47) per 10% increase and also ARE after 3 months, OR 10.4 (3.13-34.5).

Discussion

This study shows that chronic renal graft rejection can occur in the absence of apparent transplant vasculopathy. In our cohort of renal transplants we defined CAN by a significant decline in renal function, interstitial fibrosis and tubular atrophy without signs of cyclosporine nephrotoxicity or recurrent disease (6). Based on the semiquantitative CV score of the Banff schema, we divided CAN in a form with moderate or severe vasculopathy and a form with no or minimal vasculopathy. It was found that 43% of the cases did not have significant fibrointimal thickening of arteries and therefore had parenchymal deterioration from a mechanism other than ischemia. Although the biopsy specimens fulfilled the adequacy criteria of the Banff classification (5) and comparable numbers of arteries were assigned in the two groups, we cannot exclude that sampling variation has led to an underestimation of the CV score. However, we found remarkable differences in the risk profiles of the two forms of CAN; in the absence of moderate or severe thickening of arteries, CAN was independently associated with young recipient age, sensitization at the time of transplantation and late ARE, three markers of presumed immunological reactivity. Young age has been associated with a state of relatively high immune responsiveness to alloantigens (12) as well as medication non-compliance (13). Pretransplant sensitization increases the risk of chronic rejection (14) and late graft loss (15). This study confirms our previous report showing a beneficial effect of sharing CREG on long-term graft survival (10). From our multivariate analysis we conclude that histoincompatibility of MHC class I is associated with late ARE, the major risk factor of CAN. In accordance with a recently published study, we found that transplant glomerulopathy occurred preferentially in the group without vasculopathy (16). As transplant glomerulopathy is considered to result from rejection, this is another argument that chronic rejection may emerge without vasculopathy. Despite the lack of obliterative vasculopathy, sixty percent of these transplants were lost during the observation period, which is compatible with the poor prognosis of chronic tubulointerstitial changes (1,17). Thus, chronic tubulointerstitial lesions in graft biopsies may develop independent of chronic vascular obliteration in association with a risk factor

profile consistent with an immunological pathogenesis.
CAN with vasculopathy was found mainly in transplants done in the 1980s. The strong association with acute vascular rejection suggests a transition from acute to chronic vascular rejection, a correlation reported in subsequent protocol biopsies at 3 and 12 months (18). The detrimental effect of acute vascular rejection on later outcome and its relation with HLA-DR mismatches, cold ischemia time and immunosuppression has been observed previously (19). The Eurotransplant matching policy, aiming for no more than 2 HLA mismatches and, preferably, no DR mismatches may have resulted in a relatively low frequency of severe vascular rejection in our cohort. However, the association of the vascular lesions with older donor age questions the specificity of the extensive vascular lesions for the diagnosis of chronic rejection. Differentiation between donor-derived atherosclerosis and non-immune driven vascular damage by recipient factors such as hypertension, hyperlipidemia, smoking, and chronic rejection associated vasculopathy is difficult, especially when these entities coexist. Donor-derived fibrointimal thickening might already be present at implantation of kidneys of older donors (20) and constitutes the main determinant of outcome at 1-2 years (21). Furthermore, arteriosclerotic wall thickening in baseline biopsies correlates with its presence in late biopsies (17). Others demonstrated that the presence of vascular lesions in protocol biopsies at 3 months post-transplantation has strong prognostic implications, as cases with CAN and transplant vasculopathy had a 10 year graft survival of 41% compared to 82% among those with CAN but without vasculopathy (22).

Table 4. Multivariate analysis of risk factors of CAN and its forms with or without vasculopathy

	OR (95% CI)	*P*
CAN (n=54)		
Recipient age (10 years increase)	0.71 (0.53-0.96)	0.025
Smoking cigarettes	2.14 (1.17-3.92)	0.006
Panel reactive antibodies (10% increase)	1.28 (1.09-1.48)	0.002
Last ARE > 3 months vs no ARE	12.6 (4.36.-36.7)	<0.001
Dipstick proteinuria >1+ @ 6 months (%)	4.77 (1.12-20.3)	0.034
ECC @ 6 months (10 ml/min increase)	0.78 (0.64-0.93)	0.006
CAN without vasculopathy (n=23)		
Recipient age (10 years increase)	0.69 (0.47-0.99)	0.044
Panel reactive antibodies (10% increase)	1.26 (1.08-1.47)	0.006
Last ARE > 3 months vs no ARE	10.4 (3.13-34.5)	<0.001
CAN with vasculopathy (n=31)		
Year of transplantation (83-89 vs. 90-97)	4.95 (1.65-14.9)	0.004
Last ARE > 3 months vs no ARE	15.0 (4.08-50.0)	<0.001
ECC @ 6 months (10 ml/min increase)	0.58 (0.44-0.75)	<0.001

Abbreviations as in table 1.

In another study graft loss was independently predicted by either fibrointimal thickening or interstitial fibrosis at three months (18). In contrast to tubulointerstitial damage, arterial wall thickening at time of late dysfunction lacks prognostic impact (17,23). In transplant nephrectomies, performed because of pain or hematuria in a selected group of patients, we observed the most severe form of vasculopathy consisting of concentric thickening of the arterial intima with infiltration of mononuclear cells, features that are considered more specific of true chronic rejection (5). The larger number of arteries in the nephrectomies allowed us to appreciate the diffuse nature of chronic vascular rejection. Old donor age and acute vascular rejection episodes obviously contributed to graft dysfunction at 6 months and subsequent lower graft survival in this group.

In our multivariate analysis however, the timing of ARE was more predictive of CAN than the histological type. ARE after three months were the strongest risk factor for both forms of CAN whereas acute rejection within three months did not have a long-term adverse effect. This strong association of late ARE and subsequent CAN has consistently been reported in the literature (24-26). The notion that acute interstitial cellular rejection can lead to interstitial fibrosis without chronic vasculopathy or glomerulopathy has earlier been reported (27). Novel immunosuppressive regimens might be less capable to prevent late rejection activity compared to early ARE which explains the relatively lack of improvement of long-term graft survival (28) and the increased impact of acute rejection on chronic transplant failure in recent era (29).

The data presented in this paper suggests the existence of a pure interstitial and a more generalized interstitial and vascular type of chronic rejection. Such a distinction is well accepted for acute rejection because it is easily recognized and has prognostic implications (5,19). Since the introduction of cyclosporine in the 1980s the incidence of vascular rejection has diminished which suggests that vascular rejection results from the most vigorous immune response (19). Rather than intensity of the response, the specificity of graft infiltrating T cells is also important (30). An immune response against endothelial antigens would result in vascular rejection whereas interstitial rejection would emerge from a reaction against antigens on tubular epithelium. Induced expression of class II MHC antigens and interactions between adhesion molecules on T lymphocytes and endothelial cells has been shown to play a role in graft vasculitis (31). Although little information is available regarding the antigenic profile of tubular epithelial cells, specific cytotoxic T cells have been isolated from rejecting kidneys that lyse tubular cells (30,32). The capacity of T cells, expressing upregulated integrin (CD103), to bind E-cadherin on tubular epithelial cells is an additional factor in the pathogenesis of specific tissue damage in allograft

rejection (33). Disruption of the tubular basement membrane and proliferation of myofibroblasts as consequence of tubulitis has recently been shown to correlate with CAN in the absence of arterial injury (34).
In our well-match cohort of renal transplants, chronic allograft nephropathy occurred without moderate or severe transplant vasculopathy in 43% of the cases. The association with young recipient age, sensitization and late ARE suggests immune-mediated graft destruction. Fibrous intimal thickening of arteries, related with donor age, is not a condition sine qua non for chronic rejection in clinical transplantation.

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