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Protocol Biopsies of Stable Renal Allografts: Our First Experience

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Abstract

Aims: The aim of the present study was to identify subclinical rejections (SR) and histological markers of chronic allograft nephropathy (CAN) in protocol biopsies at 1 in living related kidney transplantation and the possible implications of these findings on the graft function. Methods: Protocol graft biopsies at the first month after transplantation were obtained in 23 living related allograft recipients using automated biopsy "gun". Slides were prepared according to standard techniques. Biopsies were blindly reviewed by the same pathologist using descriptive morphologic criteria according to the Banff scoring scheme (0-3) for evidence of acute and chronic changes and for arteriolar hyalinosis. The sum of the scores was recorded as the chronicity index (CI). Results: Donors mean age was 58.6±12 y. and the recipients mean age was 34±6.9 y. Normal histological finding or CI 0 was found in 13%, CI 1 in 22% and CI 2 in 65% of the patients. When the groups were compared according to the donors age (<55> years), the serum creatinine (sCr) at first month was significantly higher and creatinine clearance (Crcl) lower in the marginal donor group compared to the younger donor group. There was no significant difference in histopathological finding and CI score, except in arteriolar hialynosis between the marginal and younger donor groups. Also, the biopsies with high (CI ≥5) and low scores (CI < 5) were compared. At first month after transplantation sCr was higher in the group with high CI, and Crcl was respectively lower. Conclusions: One month biopsy may be valuable for determining of subclinical rejection and the possible impact on the outcome of renal allograft function. Protocol biopsies may be helpful to optimize the level of immunosuppression in patients with "subclinical" rejection, perhaps as a step towards more individualized approach in patient follow-up.

Introduction

Rejection remains a significant problem following renal transplantation and although powerful anti-rejection therapy is available, its unguided use is associated with significant morbidity and mortality.

The goal of the Banff classification of renal allograft rejection was a scheme in which a given biopsy grading would imply a prognosis for a therapeutic response or long-term function.

The aim of the study was to identify subclinical rejections (SR) and histological markers of chronic allograft nephropathy (CAN) in protocol biopsies at 1 month in living related kidney transplantation and the possible implication of these findings for the graft function.

Material and methods

Protocol biopsies at the first month after transplantation were obtained in 23 patients using automated biopsy "gun". Biopsies were formalin fixed, embedded in paraffin, serially sectioned at 3-5 μm thickness and stained with hematoxylin-eosin (HE), periodic acid-Schiff (PAS), Masson's trichrome and silver methenamine.

The biopsies were considered sufficient when containing ≥7 glomeruli or at least one artery. Renal lesions were blindly reviewed by the same pathologist using descriptive morphologic criteria according to the Banff scoring schema for evidence of acute and chronic changes and especially arteriolar hyalinosis. Arteriolar hyalinisation is an important finding which may signify chronic changes - rejection, donor disease or cyclosporine toxicity.

Histological features such as glomerulitis, inflammatory infiltration, tubulitis, intimal arteritis, interstitial fibrosis, tubular atrophy, arteriolar hyalinosis, glomerulopathy and vascular fibrosis were scored on a scale of 0-3 according to criteria laid down in the Banff classification. The sum of the scores was recorded as the CI (chronicity index).

A protocol renal allograft biopsy was performed in grafts if they fulfilled the following inclusion criteria: serum creatinine lower than 200 μmol/l at the time of biopsy, proteinuria lower than 1 g/24 hours. Patients who suffered from post-transplant acute tubular necrosis or presented with an episode of acute rejection (delayed graft function - DGF) before performing the protocol biopsy were included if they fulfilled the inclusion criteria.

Immunosuppressive protocol

Induction with Daclizumab 1 mg/kg BW at implantation and thereafter every 2 weeks (5 doses), and methylprednisolone 500 mg at implantation followed by standard triple therapy: cyclosporine A (Neoral) 6-8 mg/kg/day to reach target C2 levels, prednisolone 1 mg/kg/day tapered to 0.1 mg/kg/day after 8 weeks and mycophenolate mofetil (CellCept) 1 g bid.

Patients were classified according to scores in two groups: biopsies with high (CI≥5) and low scores (CI<5), and according to the donor age: younger (<55) and marginal donor group (≥55).

The following variables were evaluated: age of the donor and recipient, donor GFR, RI, CIT, WIT, HLA mismatch,

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serum creatinine, creatinine clearance and CyA levels at 1 and 6 month after transplantation.

Results

Donors' and the recipients' mean age was 58.6±12y and 34±6.9y, respectively. The serum creatinine (sCr) at first month was significantly higher and creatinine clearance (Crcl) lower in the marginal donor group compared to the younger donor group. (Table I). There was no significant difference in histopathological finding and CI score, except in arteriolar hialynosis between the marginal and younger donor groups (Table II). At first month after transplantation sCr was higher in the group with high CI, and Crcl was respectively lower (Table III).

The group with high CI had significantly lower donors GFR and higher RI. There was no patient with DGF in the group with low CI compared to the group with high CI, where DGF was recognized in 4 patients.

Patients who underwent an episode of acute rejection had significantly higher score and "borderline" changes (mild tubulitis and inflammation) vs. patients without acute rejection (Table V). Normal histological finding or CI 0 was found in 13%, CI 1 in 22% and CI 2 in 65% of the patients (Table VI).

The most prominent histological findings for chronicity (interstitial fibrosis, tubular atrophy and vascular fibrous intimal thickening) at 1 month biopsy being grade 1 were summed to 37. Banff scores for acute lesions (inflammatory infiltration, intimal arteritis, tubulitis and glomerulitis) at 1 month biopsy being grade 1 were summed to 32.

Table I: Biochemical and clinical data at baseline, 1 and 6 months post transplantation in marginal (≥55) and younger donor group (≤55)

	Donor age				
	< 55, N°=8		≥ 55, N°=15		
	Mean	SD	Mean	SD	P value
1 month sCr	99.25	22.66	127.40	30.10	*0.016*
6 month sCr	123.75	37.01	142.73	40.16	0.140
1 month Crcl	82.84	15.89	65.65	14.74	*0.008*
6 month Crcl	70.21	27.00	60.84	14.57	0.144
Donor GFR	56.65	16.74	49.07	12.69	0.117
Donor RI	0.65	0.06	0.68	0.03	*0.050*

Table II: Histopathological findings in marginal and younger donor group

	Donor age < 55, N°=8		≥ 55, N°=15		
	Mean	SD	Mean	SD	P value
glomerulitis	0.13	0.35	0.47	0.74	0.118
mononuc. cell inf.	1.13	0.65	1.27	0.88	0.347
tubulitis	1.00	0.64	1.27	0.88	0.223
intimal arteritis	0.38	0.74	0.40	0.63	0.467
arteriolar hyalinosis	0.00	0.00	0.33	0.49	*0.035*
glomerulopathy	0.13	0.35	0.20	0.41	0.334
interstitial fibrosis	0.75	0.46	0.60	0.51	0.247
tubular atrophy	0.63	0.74	0.53	0.52	0.366
vascular fibrosis	0.38	0.52	0.53	0.52	0.246
CI score	4.50	2.67	5.60	2.90	0.192

Table III: Biochemical and clinical data at baseline, 1 and 6 months post transplantation according to the patohistological scores

	Chronicity index CI < 5, N°=8		CI ≥ 5, N°=15		
	Mean	SD	Mean	SD	P value
1 month sCr	104.00	20.72	124.87	32.88	0.060
6 month sCr	131.88	35.39	138.40	42.31	0.357
1 month Crcl	82.90	21.20	65.62	10.85	*0.008*
6 month Crcl	68.41	28.94	61.80	13.21	0.228
Donor age	56.38	15.34	62.00	11.77	0.168
Donor GFR	61.13	12.82	46.68	12.75	*0.009*
Donor RI	0.64	0.05	0.68	0.03	*0.025*
DGF	0.00	0.00	0.40	0.51	*0.019*
score	2.13	1.81	6.87	1.55	*0.000*

Table IV: Biochemical and clinical data at baseline, 1 and 6 months post transplantation and patohistological scores in patients with and without acute rejection episode

	Acute rejection YES		NO		
	Mean	SD	Mean	SD	P value
1 month sCr	123.57	35.92	115.000	28.65	0.274
6 month sCr	135.14	40.38	136.56	40.21	0.469
1 month Crcl	74.63	18.08	70.32	16.93	0.294
6 month Crcl	68.46	24.65	62.19	17.70	0.248
Donor age	58.14	14.30	60.88	12.88	0.328
Donor GFR	46.74	10.83	53.88	15.41	0.141
score	6.57	1.90	4.63	2.99	0.060
mononuc. cell inf.	1.71	0.49	1.00	0.82	*0.022*
tubulitis	1.71	0.49	0.94	0.77	*0.012*

Table V: Light microscopic findings and scores at 1 month protocol biopsy

	Score (N° of patients)			
	1	2	3	4
glomerulitis (g)	17	4	2	0
mononuclear cell infiltration (i)	4	11	7	1
tubulitis (t)	4	12	6	1
intimal arteritis (v)	16	5	2	0
arteriolar hyalinosis (ah)	18	5	0	0
glomerulopathy (cg)	19	4	0	0
interstitial fibrosis (ci)	8	15	0	0
tubular atrophy (ct)	11	11	1	0
vascular fibrosis (cv)	12	11	0	0
chronicity index (CI) φ	3	5	15	0

φ = Scoring chronicity index (CI). CI 0=0, CI 1=1-4 (25%-50%), CI 2=5-12 (>50%)

Conclusions

We conclude that the presence of CTN in protocol biopsies performed early after transplantation in patients with well functioning grafts provides relevant information to detect patients at risk for accelerated graft deterioration due to chronic transplant nephropathy. The predictive value of protocol biopsies is independent of renal functional impairment (DGF). One month biopsy may be valuable for determining of subclinical rejection and the possible impact on the outcome of renal allograft function. Protocol biopsies may be helpful to optimize the level of immunosuppression in patients with "subclinical" rejection, perhaps as a step towards more individualized approach in patient follow-up.

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