Nephrotic Range Proteinuria in Renal Transplantation: Clinical and Histologic Correlates in a 10-year Retrospective Study

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ABSTRACT

Introduction. There is a high incidence of nephrotic proteinuria in renal transplant recipients, which is an accurate predictor of graft loss. Despite this, its histologic correlates and prognostic implications are still not well characterized. We assessed the clinical and histological correlates of kidney transplantation patients with nephrotic range proteinuria.

Methods. We have retrospectively analyzed clinical and histological data from 50 kidney transplantation biopsy specimens from 44 renal transplant recipients with nephrotic range proteinuria between 2006 and 2015. The median follow-up time was 93 months (range, 14 months to 190 months).

Results. The mean age of the patients was 45.2 ± 13.7 years and our cohort included 86% recipients of deceased-donor grafts. The maintenance immunosuppressive regimen included calcineurin inhibitors in 68% and mammalian target of rapamycin inhibitors in 32% of patients. The average proteinuria was 6.9 ± 3.8 g/d and 52% of patients presented with nephrotic syndrome. The main histological findings were transplant glomerulopathy (22%), de novo glomerular disease (22%), and recurrence of primary disease (22%). Tubular atrophy and interstitial fibrosis was present in 78% of the biopsy specimens. Thirty-one patients (62%) lost the graft at follow-up. There was no statistically significant difference between the histologic diagnosis nor the proteinuria levels and the outcome of the graft.

Conclusions. The main causes of nephrotic range proteinuria in patients undergoing biopsy were transplant glomerulopathy, recurrence of the underlying disease, and de novo glomerulonephritis. Nephrotic range proteinuria was related to a high rate of graft loss.

NEPHROTIC proteinuria in kidney transplant (KT) patients is one of the most accurate predictors of graft loss and patients with nephrotic syndrome have a 5-year graft survival rate significantly lower than patients without proteinuria [1,2]. The 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines on KT suggest frequent measuring of urine protein excretion and renal allograft biopsy for new-onset proteinuria or unexplained nephrotic-range proteinuria [3]. Unfortunately, histologic correlates and prognostic implications of post-transplantation proteinuria are still not well characterized and evidence-based therapies are limited [4].

Our goal was to assess the clinical and histological correlates of KT patients with nephrotic range proteinuria in our center.

PATIENTS AND METHODS

An observational retrospective single-center study was performed from January 1, 2006, to December 31, 2016. Among the 450 KT biopsies performed during that period in our center, we selected all

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the biopsy specimens of patients who presented 24-hour proteinuria ≥3.5 g at the time of the biopsy. A total of 50 biopsy specimens from 44 recipients were selected. The 2011 Banff classification for renal transplant biopsy was used for diagnostic categorization.

Patient records were reviewed for clinical features, response to treatment, and graft outcome. The median follow-up time was 93 months (range, 14 months to 190 months).

Remission was defined as protein excretion of less than 0.5 g/d for 2 consecutive assays.

Data was analyzed using SPSS statistics software (IBM SPSS Statistics for Windows, version 21, IBM Corp., Armonk, NY, USA). Comparisons used the χ^2 test for categorical variables and Student *t* test or the Mann-Whitney U test for continuous variables, as appropriate. Results were considered statistically significant at $P < .05$.

RESULTS

Clinical Characteristics

The 44 recipients evaluated included 64% (N = 32) males with a mean age of 45.2 ± 13.7 years. It was the first transplant for 84% of the patients (N = 42), and 86% (N = 43) received a cadaveric graft, of which 46% fulfilled marginal donor criteria. Regarding immunosuppression, induction with basiliximab was performed in 54% of the recipients (N = 27). The maintenance immunosuppressive included calcineurin inhibitors in 68% and mammalian target of rapamycin (mTOR) inhibitors in 32% of patients (Table 1).

Table 1. Demographic Characteristics, Immunosuppression and Post-transplantation Events of the General Population

Demographic Features	
Age (y) (mean ± SD)	45.2 ± 13.7
Male gender	N = 32, 64%
Cadaveric donor	N = 43, 86%
Expanded criteria donor	N = 23, 46%
BMI (kg/m^2) (mean ± SD)	25.3 ± 3.8
Diabetes mellitus	N = 8, 16%
Hypertension	N = 30, 60%
Primary Kidney Disease	
Undetermined	N = 15, 30%
Chronic glomerulonephritis (unspecified)	N = 14, 28%
Diabetic nephropathy	N = 4, 8%
IgA nephropathy	N = 4, 8%
Nephroangiosclerosis	N = 3, 6%
Focal segmental glomerulosclerosis	N = 3, 6%
Polycystic Kidney Disease	N = 3, 6%
Membranous nephropathy	N = 2, 4%
Type 1 primary hyperoxaluria	N = 2, 4%
HLA mismatches (mean ± SD)	3.0 ± 1.2
Maintenance Immunosuppression	
Regimen including steroids	N = 40, 80%
Calcineurin inhibitors	N = 34, 68%
mTOR inhibitors	N = 15, 30%
Post-transplantation Clinical Events	
Acute rejection	N = 6, 12%
Chronic rejection	N = 8, 16%
Previous infection with hospital admission	N = 5, 10%

Abbreviations: SD, standard deviation; BMI, body mass index; IgA, immunoglobulin A; mTOR, mammalian target of rapamycin.

The mean basal creatinine value was 1.67 ± 0.67 mg/dL and the mean creatinine value at the time of the biopsy was 2.53 ± 1.14 mg/dL. The mean 24-hour proteinuria was 6.9 ± 3.8 g and 26 patients (52%) presented with concomitant nephrotic syndrome. Regarding donor-specific HLA antibodies, they were positive in 15 recipients at the time of graft biopsy (30%).

Allograft Histology

The mean time post-transplantation at biopsy was 44 months (range, 24 months to 102.3 months). Histological findings of the 50 biopsy specimens are displayed in Table 2. The main primary histologic diagnoses were transplant glomerulopathy, recurrent glomerular diseases, and de novo glomerular diseases. Of the 11 patients with transplant glomerulopathy, 7 presented with positive C4d staining and donor-specific HLA antibodies (7 of 11, 64%) and were diagnosed with chronic humoral rejection. Regarding de novo glomerular diseases, 3 patients had undetermined cause for primary chronic kidney disease, whereas the others had chronic kidney disease due to nephroangiosclerosis (N = 2), diabetic nephropathy (N = 3), immunoglobulin A (IgA) nephropathy (N = 2), and membranous nephropathy (N = 1), with a different histological diagnosis on the transplant biopsy.

Interstitial fibrosis and tubular atrophy with glomerular sclerosis was present in 39 biopsy specimens (78%) but only in 8 specimens represented the primary diagnosis in the context of chronic allograft nephropathy.

Treatment

Maintenance therapy with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was performed in 16 patients (32%) with chronic allograft nephropathy,

Table 2. Findings in 50 Transplantation Biopsy Specimens in 44 Patients With Post-transplantation Nephrotic Proteinuria

Primary Diagnoses	N	%
Recurrent glomerular diseases	11	22
Diabetic nephropathy	3	
IgA nephropathy	3	
FSGS	3	
Primary hyperoxaluria	2	
Transplant glomerulopathy	11	22
De novo glomerular disease	11	22
Membranoproliferative GN with full house IF	4	
FSGS	3	
Membranous GN	1	
Mesangioproliferative GN	1	
Collapsing FSGS	1	
Crescentic GN	1	
FSGS + IFTA	8	16
FSGS + acute rejection	5	10
Other	4	8
Total	50	100

Abbreviations: IgA, immunoglobulin A; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; IF, immunofluorescence; IFTA, interstitial fibrosis and tubular atrophy.

and transplant glomerulopathy with important interstitial fibrosis and tubular atrophy. Increased immunosuppression was the approach in 18 patients (36%) with transplant glomerulopathy, recurrent glomerular diseases, and de novo glomerular diseases. Methylprednisolone pulses were performed in 9 patients (18%) including acute rejection imposed in chronic allograft nephropathy and de novo glomerular diseases. Therapeutic plasma exchange was performed in 5 patients (10%): 2 patients with antibody mediated rejection and 3 patients with recurrent focal and segmental sclerosis. Two patients received rituximab including 1 patient with membranoproliferative glomerulonephritis and 1 patient for chronic antibody mediated rejection.

Outcome

The median follow-up time was 93 months (range, 14 months to 190 months). Complete remission of the nephrotic proteinuria was observed in 5 patients (11%), three of them with de novo glomerular disease and two with recurrent glomerular disease. Thirty patients (68%) are dialysis-dependent, and there were three deaths registered. There was no difference between the immunosuppressive regimen used and the levels of proteinuria. There was no statistically significant difference between the histologic diagnosis nor the proteinuria levels and the outcome of the graft.

DISCUSSION

Previous studies report an average prevalence of 24-hour proteinuria >3 g/24-hour in KT recipients of 15% [5–7]. The present study reports post-transplantation proteinuria in 22.5% patients submitted to graft biopsies in a 10-year period. This high incidence might be related to the study design, as the general population includes patients undergoing biopsy, conditioning a selection bias.

Regarding etiology, the main histological findings in our report are concordant with the existing literature: recurrent glomerular diseases, de novo glomerulopathy, and transplant glomerulopathy [4,7].

In the KT population, the evidence base for the management of proteinuria is lacking for most cases, but routine monitoring of proteinuria as part of follow-up is recommended. Renin-angiotensin-aldosterone system blockade results in a significant reduction in proteinuria, but this benefit is frequently accompanied by a significant reduction in glomerular filtration rate and there is no evidence of improved patient or graft survival [4]. Some studies have noted an association between proteinuria and the use of sirolimus, especially in patients switched from calcineurin inhibitors [8]. We did not find any significant relation between the use of mTOR inhibitors and the level of proteinuria.

Our study reported a high rate of graft loss at time of follow up (69%). This might be related to the high prevalence of interstitial fibrosis and tubular atrophy found in our biopsy specimens, indicating chronic lesions regardless the glomerular changes. Also, the time of follow up was very variable and the majority of the patients were transplanted for more than 5 years at the time of biopsy. Although proteinuria is strongly associated with graft survival, other factors, such as donor age, may be equally significant [4,5,9].

CONCLUSION

In our report, the main causes of nephrotic range proteinuria in patients undergoing biopsy were transplant glomerulopathy, recurrence of the underlying disease, and de novo glomerulonephritis. Nephrotic range proteinuria was related to a high rate of graft loss.

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