Recurrent IgA Nephropathy After Kidney Transplantation

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ABSTRACT

Background. Immunoglobulin (Ig)A nephropathy is the most common primary glomerulonephritis worldwide, with a high recurrence rate after kidney transplantation. The aim of this study was to assess allograft survival, impact of recurrence on allograft function, and risk factors for post-transplant IgA recurrence.

Methods. We identified 104 patients with IgA nephropathy who underwent kidney transplantation at our center between 1993 and 2014. Fourteen patients underwent more than one allograft.

Results. IgA recurrence was documented in 23 (19%) allografts. Median time to recurrence was 6.75 years (interquartile range, 1.4–9.2 years). Twelve of the 23 recurrences were from living related donors ($P = .07$), and those with younger age at transplantation (37.7 ± 2.3 vs 44 ± 1.3, $P = .05$) were at higher risk of recurrence. Mean allograft survival was reduced in those with recurrence (6.5 ± 5.1 years) compared with those without recurrence (10.4 ± 7.5 years). At 6 years after transplant, allograft failure was documented in 52% of the recurrence group compared with 10% in the non-recurrence group ($P = .002$).

Conclusions. IgA recurrence after transplant is an important cause of allograft loss. Living related donors and younger age at transplantation are associated with high recurrence rate. Close monitoring and treatment of recurrence are crucial.

IMMUNOGLOBULIN (Ig)A nephropathy is a very common primary glomerulonephritis worldwide that progresses to renal failure in approximately 15% to 40% of those afflicted [1]. Kidney transplantation is the treatment of choice for end-stage renal disease (ESRD) and is an excellent option for patients with ESRD caused by IgA nephropathy. Unfortunately, recurrence of IgA nephropathy after transplantation does occur and can lead to premature graft failure [2]. Prior studies of relatively small patient series report recurrence of IgA nephropathy after kidney transplantation at a rate of approximately 60% [3,4], and allograft loss due to recurrent disease in about 30% [4].

Recurrent disease is diagnosed by a combination of clinical and pathological findings. Clinically, recurrent IgA nephropathy manifests as microscopic hematuria and new or worsening proteinuria exceeding 0.5 g/day but usually remains below the nephrotic range, or an increase in serum creatinine. Pathologically, in addition to the mesangial IgA deposition, mesangioproliferative glomerulonephritis must also be observed in the kidney allograft biopsy to meet the diagnostic criteria of recurrent IgA nephropathy [3]. In rare cases, recurrent IgA nephropathy presents as crescentic glomerulonephritis with rapidly progressive renal allograft failure [3]. Patients who had a rapidly progressive course of ESRD in their native kidney tend to recur early after transplantation, with significant clinical manifestations [5]. Those with early allograft loss from recurrent IgA nephropathy may also be at risk of rapid recurrence after retransplantation [4].

Possible risk factors for recurrence of IgA nephropathy after transplantations include living donors, in particular receiving living related donor kidneys compared with deceased donor kidneys [5,6]. An analysis of the European

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Transplant Registry revealed that the 10-year graft survival was significantly lower among patients with IgA nephropathy and human leukocyte antigen (HLA)-B8 and HLA-DR3 [7]. Data from the Australian and New Zealand registry of 1354 patients with ESRD caused by IgA nephropathy showed that zero HLA-mismatched living donor recipients were more likely to develop recurrence [8]. There are limited data pertaining to therapeutic options for recurrent IgA nephropathy; therapies such as angiotensin-converting enzyme inhibitor (ACEi) or angiotensin-II type I receptor blocker (ARB) showed some benefits [9].

In this large-sized study, we aimed to identify the risk factors for recurrent IgA nephropathy after kidney transplantation in our kidney transplant recipients and to evaluate the impact of recurrence on the allograft function and survival.

METHODS

Patient Selection and Data Collection

We report the results of 104 patients with ESRD secondary to documented IgA nephropathy who underwent kidney transplantation at the Johns Hopkins Hospital between April 1993 and November 2014. During this period, 14 patients underwent repeat transplantation and therefore a total of 122 transplants were evaluated. Study approval was granted by the Institutional Review Board of our institution.

Renal Transplantation and Immunosuppression

The 122 kidney transplants reported here were from deceased, living related, or living unrelated donors. The majority of patients received induction with thymoglobulin and high dose of intravenous corticosteroid followed by triple maintenance therapy with tacrolimus, mycophenolate mofetil (MMF), and prednisone. Some patients received maintenance therapies with cyclosporine and azathioprine.

Diagnosis of Recurrent IgA Nephropathy and Graft Failure

Both clinical and pathological parameters were evaluated to establish a diagnosis of recurrent IgA nephropathy. Allograft function was evaluated by use of measurements of serum creatinine and estimated glomerular filtration rate (eGFR). Hematuria was quantified by means of the number of red blood cells (RBC) per high-power field (hpf) on urinalysis, and proteinuria was quantified by means of the urine protein-to-creatinine (UPC) ratio.

Renal allograft biopsies were performed for clinical indications including allograft dysfunction, proteinuria, and/or hematuria. All biopsies were reviewed by a dedicated renal pathologist. Immunofluorescence staining for IgA deposition was performed in all cases. Biopsies were evaluated according to Banff criteria relevant at the time of the biopsy [10,11]. Graft loss was attributed to recurrent IgA nephropathy if the renal allograft biopsy at the time of clinical graft failure demonstrated diffuse mesangial proliferation and glomerular sclerosis caused by IgA deposits. On the other hand, graft loss caused by chronic rejection was suggested in cases in which chronic inflammatory cells, vascular injury, and interstitial fibrosis with tubular atrophy were seen in the absence of IgA deposits.

Time to allograft failure was determined by means of the time elapsed between transplantation and the earliest of dialysis initiation, re-transplantation, or patient death. We assessed the pertinent parameters that may affect allograft survival and IgA recurrence in our cohort.

Statistical Analysis

Descriptive statistics were used to estimate the frequencies, means ± standard deviation (SD), and medians with interquartile range (IQR) of the study variables. The Student t test was used to assess P values. A 2-tailed P value of $\leq .05$ was considered statistically significant. Kaplan-Meier methodology was used to estimate allograft survival. Unadjusted hazard ratios were calculated by use of Cox models. All statistical analyses were performed with the use of STATA 12 (College Station, Tex, United States).

RESULTS

Demographics

Between April 1993 and November 2014, 104 patients with ESRD caused by documented IgA nephropathy underwent one or more kidney transplants, for a total of 122 transplants performed. Of these allografts, 45 (37%) were from deceased donors, 43 (35%) were from living related donors, and 34 (28%) were from living unrelated donors. For the overall cohort, the mean age ± standard deviation (SD) at diagnosis of IgA nephropathy was 32.9 ± 14.7 years (Table 1). For purposes of comparison and evaluation of risk factors, the cohort was divided into two groups, based on whether or not they developed recurrence over the study period. Recurrence of IgA nephropathy was documented in 23 allografts (19%), with a hazard ratio (HR) of 1.91 (0.79–4.60, $P = .15$), and the median time to recurrence was 6.75 years (IQR, 1.4–9.2 years). The non-recurrence group consisted of 99 allografts (81%).

Triple maintenance therapy was documented in 16 patients (70%) of the IgA recurrent group versus 89 patients (90%) of the non-recurrence group ($P = .07$).

Table 1. Demographics and Clinical Characteristics

Recipient Characteristics	
Male, n (%)	66 (63)
Race, n (%)	
White	65 (62)
Black	10 (10)
Asian	27 (26)
Other	2 (2)
Mean age at diagnosis of IgA nephropathy, years, ±SD	32.9 ± 14.7
Mean age transplant, years, ±SD	33.9 ± 11.4
Kidney transplants during study period, n (%)	
1	90 (87)
≥2	14 (13)
Donor characteristics	
Donor type, n (%)	
Deceased	45 (37)
Living related	43 (35)
Living unrelated	34 (28)