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The Association Between Post–Kidney Transplant *De Novo* Glomerulonephritis and Alloimmunity

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Although kidney transplant (KT) success has largely been attributed to improvements in 1-year allograft survival, improvements in long-term survival have lagged behind,[1] making allograft failure the fourth most common cause of kidney failure in the USA.[2]

Post-KT glomerulonephritis (GN), typically classified under nonalloimmune etiologies, is a significant cause of allograft failure.[3] It can be classified as recurrent, *de novo*, and very rarely donor derived. Despite the presumed high incidence of *de novo* GN,[4] its natural history and pathogenesis remain poorly understood. Some studies have demonstrated that a proportion of allograft biopsies with *de novo* GN have concurrent T cell–mediated rejection or antibody-mediated rejection (AMR).[5–9] We conducted this study to understand the clinicopathologic correlates of *de novo* GN with a particular focus on its possible association with alloimmunity. We retrospectively studied 46 cases of *de novo* GN and compared them with 77 cases of recurrent GN, which served as post-KT GN controls.

RESULTS

Patient, Clinical, Laboratory, and Transplant Characteristics

De Novo *GN*

Eighty percent of the patients were male,11% were African American, and 52% received a deceased donor transplant. Patients had a median age of 52 years (interquartile range 33, 66) at the time of transplantation (Table 1). The median time to development of *de novo* GN after transplantation was 4.3 years. Eleven percent had a simultaneous kidney and other solid organ transplant, and 35% had a prior organ transplant (Table 1). As demonstrated in Table 2, 55% of patients received anti-thymocyte globulin for induction immunosuppression, whereas 34% received an interleukin-2 receptor antagonist. Fourteen percent had positive donor-specific antibodies (DSAs) at the time of transplantation, and 37% had positive DSAs at the time of *de novo* GN diagnosis. Seventeen percent of biopsies at *de novo* GN diagnosis were diagnostic of AMR (Table 3).

The different GN types diagnosed in allograft biopsies are reported in Table 2. Twenty-one patients in the *de novo* group had immune complex–mediated glomerulonephritis (ICGN) that did not fit a specific GN, which was the most common form of *de novo* GN. These ICGN, which included large numbers of membranoproliferative glomerulonephritis of unknown etiology, were classified as ICGN not otherwise specified (ICGN-NOS) (Figure 1). Others included IgA nephropathy ($n = 11$) and membranous nephropathy ($n = 8$) (Figure 1). *De novo* GN also included 4 cases of hepatitis C virus–related GN and 2 infection-related GN (Table 2).

Graft failure occurred in 24% of patients at a median of 7.9 years from transplantation (interquartile range 4.5, 12.7), and at a median of 1.4 years (0.2, 3.5) from *de novo* GN diagnosis (Table 2, Figure 2). The cause of graft failure was attributed to the *de novo* GN in 5 of 11 (46%) of patients, and to concomitant rejection and *de*

Table 1. Demographic characteristics of the study population

Characteristics of the Study Population	*De novo* GN (n = 46)	Recurrent GN (n = 77)	*P* value
Male	37/46 (80.4)	55/77 (71.4)	0.3
African American	5/46 (10.9)	9/77 (11.7)	>0.9
Deceased donor	24/46 (52.2)	24/77 (31.2)	0.02
Age at the time of transplantation[a]	52.3 (33.4, 65.5)	37.5 (32.9, 50.6)	0.003
Years from transplantation to GN[a]	4.3 (2.2, 7.4)	2.7 (0.2, 8.2)	0.06
Simultaneous organ transplant	5/46 (10.9)	0/77 (0)	0.006
Prior solid organ transplant	16/46 (34.7)	14/77 (18.2)	0.05
Kidney Transplant	10/46 (21.7)	14/77 (18.2)	0.8
Nonkidney solid organ transplant	6/46 (13.0)	0/77 (0)	0.002

GN, glomerulonephritis.
[a]Values are median (25th, 75th percentile).
Unless otherwise noted, values are n (%).

novo GN in 2 of 11 (18%) of patients. Two patients lost their allograft due to diabetic nephropathy and 1 due to nonresolving acute tubular necrosis.

Table 2. Clinical and pathologic characteristics of the study population

Clinical and Pathologic Characteristics	*De novo* GN (n = 46)	Recurrent GN (n = 77)	*P* value
Induction agent[a]			
Antithymocyte globulin	24/44 (54.6)	46/68 (67.7)	0.2
Alemtuzumab	5/44 (11.4)	11/68 (16.2)	0.6
Interleukin 2 receptor antagonists	15/44 (34.1)	10/68 (14.7)	0.02
Total HLA mismatch (0–6)[b,c]	4 (2, 5)	3 (2, 5)	0.2
DSA[d]			
Pre-KT DSAs	5/36 (13.9)	8/64 (12.5)	>0.9
DSAs at time of GN discovery	15/41 (36.6)	10/59 (17.0)	0.03
Glomerulonephritis at index biopsy			
Anti-GBM GN	0/46 (0)	1/77 (1)	>0.9
C3 glomerulopathy	0/46 (0)	9/77 (12)	0.03
IgA nephropathy	11/46 (24)	46/77 (60)	0.0002
Membranous nephropathy	8/46 (17)	14/77 (18)	>0.9
HCV-related GN	4/46 (9)	0/77 (0)	0.02
Infection related GN	2/46 (4)	0/77 (0)	0.1
ICGN-NOS	21/46 (46)	7/77 (9)	<0.0001
Graft outcomes			
Graft failure	11/46 (23.9)	21/77 (27.3)	0.8
Time from KT to graft failure, yr[c]	7.9 (4.5, 12.7)	6.8 (4.9, 12.2)	0.9
Time from GN discovery to graft failure, yr[c]	1.4 (0.2, 3.5)	1.2 (0.7, 2.6)	0.7
Last creatinine if graft has not failed[c]	1.8 (1.3, 2.5)	1.7 (1.4 2.6)	0.8

Anti-GBM, anti–glomerular basement membrane; DSA, donor-specific antibody; GN, glomerulonephritis; HCV, hepatitis C virus; HLA, human leukocyte antigen; IGCN-NOS, immune complex–mediated glomerulonephritis not otherwise specified; KT, kidney transplant.
[a]Induction agent is unknown in 2 subjects in the *de novo* group and in 9 subjects in the recurrent group. One patient in the recurrent group did not receive any induction therapy as the transplant was from a twin sibling.
[b]HLA typing is missing in 2 patients in the *de novo* group and in 7 patients in the recurrent group.
[c]Values are median (25th, 75th percentile).
[d]DSAs at the time of transplant is missing in 10 patients in the *de novo* group and in 13 patients in the recurrent group. DSAs at the time of index biopsy is missing in 5 patients in the *de novo* group and in 18 patients in the recurrent group.
Unless otherwise noted, values are n (%).
HLA mismatch is calculated based on A, B, and DR antigens.

Table 3. The association between GN and rejection

Rejection Type	*De novo* GN, n (%) (n = 46)	Recurrent GN, n (%) (n = 77)	*P* value
Concurrent AMR	8/46 (17.4)	2/77 (2.6)	0.006
Concurrent TCMR or borderline	11/46 (23.9)	20/77 (26.0)	0.8
Previous AMR	3/46 (6.5)	2/77 (2.6)	0.4
Previous TCMR or borderline	11/46 (23.9)	11/77 (14.3)	0.2

AMR, antibody-mediated rejection; GN, glomerulonephritis; TCMR, T cell–mediated rejection.

Recurrent GN and Comparison Between Groups

Given the relatively increased frequency of patients with DSAs, we decided to further explore the potential association of *de novo* GN and alloimmunity by comparing *de novo* GN to a group of 77 patients with recurrent GN. The different recurrent GN types are reported in Table 2. Demographic and clinical characteristics of recurrent GN are presented in Tables 1 and 2.

A higher percentage of patients with *de novo* GN received allograft from deceased donors (52% vs. 31%, odds ratio [OR] = 2.41, P = 0.02) and interleukin-2 receptor antagonist for induction immunosuppression (34% vs. 15%, OR = 3.0, P = 0.02). Patients with *de novo* GN were more likely to have a history of prior solid organ transplants (35% vs. 18%, OR = 2.4, P = 0.05). There was no difference between groups in rates of pretransplant DSAs, T cell–mediated rejection, or AMR preceding the index biopsy, nor in T cell–mediated rejection at the time of index biopsy. However, at the time of GN diagnosis, *de novo* GN showed increased incidence of AMR (17.4% vs. 2.6%, OR = 7.9, P = 0.006) (Table 3) as well as concurrent DSAs (37% vs. 17%, OR = 2.8, P = 0.03) (Table 2). The latter became more obvious when patients with known cause of *de novo* GN, namely, infection-related (n = 2) and hepatitis C virus–associated (n = 4), were excluded from the analysis (14/28 [50%] vs. 10/59 [17%], OR = 4.9, P = 0.002). Finally, there was no difference in post-transplant or postbiopsy allograft survival between these 2 groups (Figure 2).

DISCUSSION

GN, both recurrent and *de novo*, is a significant cause of allograft failure.[2] The incidence of *de novo* post-KT GN is much higher than that of native kidney GN.[4] In most forms of GN, injury occurs secondary to the formation of antigen-antibody immune complexes formed by ligation of an immunoglobulin to an *in situ* or circulating antigen, often triggering complement activation and leukocyte influx.[S1] In the field of KT, most AMR is mediated by DSAs, which bind to kidney donor alloantigens and can trigger complement fixation, leukocyte influx, and rejection. Moreover, following stem

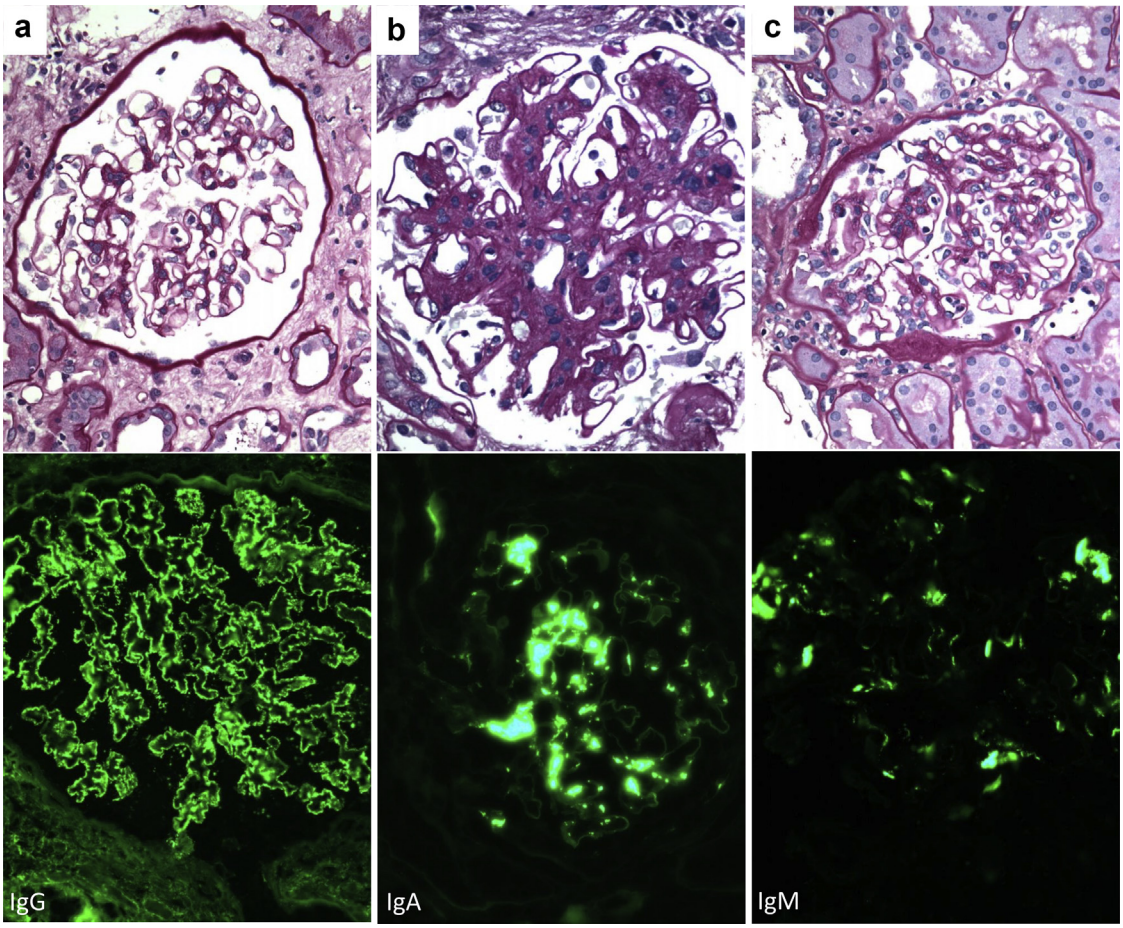

Figure 1. Representative photomicrographs of *de novo* GN of the kidney allograft. (a) *De novo* membranous nephropathy from a patient showing C4d-positive antibody-mediated rejection: from top to bottom, a normocellular glomerulus with unremarkable basement membranes but mild prominence of visceral epithelial cells and a few marginating leukocytes in the capillary Lumina (periodic acid–Schiff, original magnification × 400). This was associated with global granular staining for IgG along glomerular basement membranes in a subepithelial distribution (immunofluorescence, original magnification × 400). (b) *De novo* IgA nephropathy in a patient without features of antibody-mediated rejection who developed native kidney failure secondary to Alport's syndrome: from top to bottom, a glomerulus showing mesangial expansion and proliferation (periodic acid–Schiff, original magnification × 600). This was associated with global granular to confluent staining for IgA in the mesangium (immunofluorescence, original magnification × 400). (c) *De novo* IgM-dominant immune complex–mediated glomerulonephritis not otherwise specified from a patient showing C4d-positive antibody-mediated rejection: from top to bottom, a glomerulus showing mesangial proliferation and scattered leukocytes within the glomerular capillary lumina (periodic acid–Schiff, original magnification × 400). This was associated with global granular to confluent staining for IgM in the mesangium (immunofluorescence, original magnification × 400). GN, glomerulonephritis.

cell transplantation, alloimmunity in the form of graft-versus-host disease can manifest as ICGN that can mimic autoimmune GN both in human and in animal models.[S2–S4] Based on the limited but interesting data in the literature, we hypothesized that a portion of *de novo* GN in the allograft is associated with alloimmunity.

The findings of ICGN and rejection have been described in a rat model of AMR. Kidneys harvested at 9 days and at 6 weeks after AMR had similar histopathologic findings to human kidney allograft AMR findings whereas those harvested at 26 weeks showed ICGN.[S5] Giannico *et al.*[S6] described the clinical and histopathologic features of 28 allograft biopsies with mesangial immune complex deposits. They found the biopsies to be associated with concurrent acute T cell–mediated rejection ($P = 0.023$) as compared to transplant controls without immune complex deposition. Interestingly, 54% of their patients with ICGN had detectable DSAs. Lloyd *et al.*[8] also identified 32 patients with *de novo* ICGN in the allograft. Of those, 37% had ICGN-NOS. This group had a high frequency of DSA positivity (88%) and a high incidence of concurrent AMR (67%). Recently, Chin *et al.*[9] identified 28 patients with allograft biopsies showing ICGN-NOS. Fifty-seven percent of those patients met criteria for definite or possible allograft rejection, including 43% with features of humoral alloimmunity, and 63% had detectable DSAs.

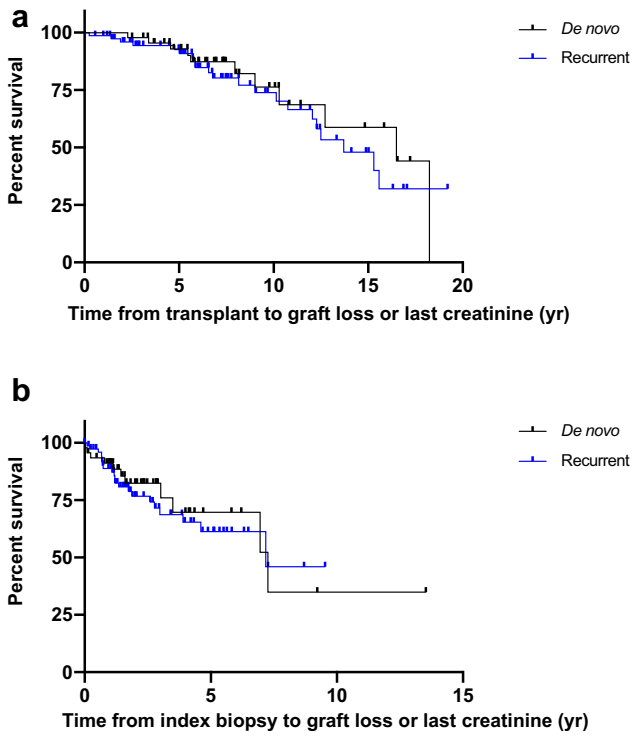

Figure 2. (a) Kaplan-Meier curve estimating the survival probability from transplant to graft loss or last follow up. Comparison between *de novo* and recurrent groups shows a hazard ratio (HR) equal to 0.8, 95% confidence interval (CI): 0.4–1.6. (b) Kaplan-Meier curve estimating the survival probability from index biopsy to graft loss or last follow-up. Comparison between *de novo* and recurrent groups shows an HR equal to 0.8, 95% CI: 0.4–1.7.

Our study is the largest to date to examine the association between *de novo* GN and alloimmunity and the first to use recurrent disease as post-transplant GN controls. Although the incidence of AMR and DSAs in our study was lower than the 2 aforementioned studies (17% and 37%, respectively), when we compared our 46 patients with post-KT *de novo* GN to 77 patients with recurrent GN, we found data suggestive of an alloimmune mechanism underlying the development of *de novo* GN, including a higher concurrent rate of AMR, higher DSAs at the time of diagnosis, a higher number of previous solid organ transplants, a higher frequency of allografts from deceased donors, and a less potent induction therapy.

Our study has a number of limitations, including the retrospective nature of the study and missing laboratory studies. Our center does not perform yearly protocol biopsies, which may underestimate the true incidence of both *de novo* and recurrent GN.

Our results support that a significant proportion of *de novo* GN may be related to humoral alloimmunity. This relationship deserves further investigation in order to elucidate the underlying pathophysiology and associated risk factors in order to develop strategies to prolong allograft survival.

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DISCLOSURE

The authors declared no competing interests.

AUTHOR CONTRIBUTIONS

OK and IB participated in the research design, data collection, data analysis and writing of the manuscript. JK, GS, and RV participated in data collection. RJC participated in the writing of the manuscript. GKD participated in the research design and writing of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods

Supplementary References

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