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Kidney Transplant Recipients With Primary Membranous Glomerulonephritis Have a Higher Risk of Acute Rejection Compared With Other Primary Glomerulonephritides

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Background. Despite being the leading cause of graft failure, there is a lack of published data about the rates of rejection in kidney transplant patients with glomerulonephritis as the cause of end-stage renal disease. **Methods.** We examined all consecutive adult (>18 years) renal transplant recipients with biopsy-proven native renal glomerular disease who underwent kidney transplant between 1994 and 2013. Glomerulonephritis groups included were IgA nephropathy (IgAN) (N = 306), focal segmental glomerulosclerosis (FSGS) (N = 298), membranous nephropathy (MN) (N = 81), and lupus nephritis (LN) (N = 177). **Results.** In the total cohort of 862 patients, 363 patients had an episode of acute rejection during the follow-up period of 19 years (incidence rate of 7.2% per year). Forty-five of 81 patients with MN had an episode of acute rejection during the follow-up period. Patients with MN had significantly higher incidence of acute rejection (12.1 per 100 person years, $P < 0.05$) in comparison to IgAN (7.2 per 100 person years), FSGS (7.4 per 100 person years), and LN (7.9 per 100 person years). Patients with MN had 1.9 times higher risk of developing acute rejection after transplant in comparison to IgAN ($P < 0.005$). In patients with MN, 33 of 45 (73.3%) rejection events were acute cellular rejection, 8 (17.8%) of 45 were acute antibody-mediated rejection and 6 of 45 (13.3%) were combined cellular and antibody-mediated acute rejection. Despite higher rates of acute rejection, 10-year allograft survival was similar in all subgroups. **Conclusions.** Patients with MN have higher incidence of acute rejection after kidney transplant but have similar 10-year allograft survival in comparison to the other glomerular diseases like IgAN, FSGS, and LN.

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Graft rejection is more common than glomerular disease recurrence in transplant patients with end-stage renal disease (ESRD) due to glomerulonephritis.[1,2] Acute rejection events after kidney transplant are known to be associated with poor graft survival.[3] Many single-center and registry studies have published data on the recurrence rates of glomerular diseases after transplant.[4-7] However, despite rejection being more common, there is a lack of published data about rejection rates in this subgroup of transplant patients especially in different types of glomerulonephritis.

The inherent characteristics of patients with glomerulonephritis as the cause of ESRD can influence the incidence of rejection after transplant. First, many patients with glomerulonephritis have alterations in regulation of the immune

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system due to underlying autoimmune disease. Second, they have exposure to immunosuppressants pretransplant for treatment of their native glomerular disease, which further alters their immune system. Thus, patients with glomerulonephritis have immune system dysregulation before transplant. This may affect their alloimmune response and rejection rates after transplant in comparison to patients who have ESRD due to diabetes or hypertension. The goal of this study is to estimate the incidence rate of rejection and the effect of rejection on allograft survival in patients with ESRD due to glomerular disease.

MATERIALS AND METHODS

The University of Wisconsin Madison Institutional Review Board and Human Subjects Committee approved this study. Data were obtained from Organ Procurement and Transplantation Network registry from United Network for Organ Sharing and the Wisconsin Allograft Recipient Database. All consecutive adult (>18 years) renal transplant recipients with biopsy-proven native renal glomerular disease who underwent kidney transplant at the University of Wisconsin Hospital and Clinics between January 1, 1994, and June 30, 2013, were included. The cohort included primary transplant and retransplanted patients. The 4 major types of glomerular diseases included in the study are IgA nephropathy (IgAN), membranous nephropathy (MN), focal segmental glomerulosclerosis (FSGS), and lupus nephritis (LN). All patients included in the study had biopsy-proven primary glomerular disease. Patients with a presumptive diagnosis without a biopsy confirmation were excluded. Patients were followed up until graft loss, death, or last available follow-up. Allograft biopsy was performed for cause based on a rise in serum creatinine or proteinuria. Acute rejection was diagnosed using kidney biopsy per the clinical renal pathologist's final diagnosis. Acute cellular rejection and acute antibody-mediated rejection were combined to define an episode of acute rejection.

Continuous variables were compared between groups with *t* tests and Kruskal-Wallis tests. Categorical variables were compared between groups with χ^2 tests. Univariable and multivariable Cox proportional hazards were used to assess independent associations between baseline characteristics and rejection rates in different subtypes of glomerulonephritis. Multivariable hazard ratio was calculated after adjusting for age, sex, race, dialysis pretransplant, duration of dialysis, panel reactive antibody, donor status, donor age, donor sex, prior transplant, delayed graft function, calcineurin use, and human leukocyte antigen mismatch. Time to event data were analyzed with Kaplan-Meier curves and log-rank tests. All analyses were performed using SAS statistical software version 9.1 (SAS Institute, Inc.).

RESULTS

Demographics

Between the years of 1994 and 2013, 862 patients with 4 of the major types of glomerulonephritis as the cause for ESRD received a kidney transplant. Of the total 862 patients, 306 had IgAN, 298 had FSGS, 177 had LN, and 81 had MN (Table 1). Patients were followed for a mean of 7.2 years (±4.7 years). The majority of patients were whites and received deceased donor transplants. An exception to this was seen in the IgAN group where 59.2% of the patients underwent living donor transplantation. Mean duration of dialysis before transplant was significantly lower in patients with IgAN at 14.6 months compared with FSGS, MN, and LN that had 24.5, 20.5, and 28.6 months, respectively. Prevalence of second transplant in all groups was similar ranging from 17% to 26%. All patients were on prednisone as

TABLE 1.

Patient characteristics for kidney transplant recipients with native glomerular disease as cause of ESRD

	IgAN (n = 306)	FSGS (n = 298)	MN (n = 81)	LN (n = 177)
Mean age, y	42.8	44.9	50.5	42.8
Male sex, N (%)	212 (69)	184 (62)	55 (68)	38 (21.5)
White patients, n (%)	259 (84)	233 (78)	71 (88)	140 (79)
Mean BMI, kg/m^2	27.4	27.6	27.0	25.1
Duration of disease before transplant, y	7.1	7.6	7.5	8.3
Mean duration of dialysis before transplant, mo	14.6	24.5	20.5	28.6
Deceased donor transplant, %	40.8	65.1	60.5	57.1
Donor age, y	41.5	41.7	40.2	40.1
Donor male sex, %	48	57	51.9	49.7
Donor white race, %	94.4	93.3	92.6	91
Retransplant, %	17.3	21.5	26	24.9
Peak PRA	5.9	10.2	15.3	18.3
Cold ischemia time, h	16.1	22.4	20	28.6
HLA total mismatch > 2, %	78.8	83.2	75.3	71.8
HLA A mismatch, %	74.8	78.2	65.4	65.0
HLA B mismatch, %	79.4	83.2	74.1	70.0
HLA DR mismatch, %	68.6	71.5	71.6	64.4
Prednisone use, %	100	99.7	100	100
Calcineurin inhibitor at discharge, %	93.8	87	91.4	93.8
Mycophenolate use, %	88.9	88.9	85.2	88.7
Delayed graft function, n (%)	31 (10.1)	61 (20.5)	11 (13.6)	30 (16.9)

TABLE 2.

Incidence of acute rejection and adjusted relative hazard ratio (95% confidence interval) of rejection, by native glomerular disease diagnosis

	Acute rejection events (n)/patients, n (%)	Incidence rate (per 100 person-years)	Time to event (median), mo	Adjusted relative hazard ratio[a]
IgAN	122/306 (39.9%)	7.2	3.9	1.0 (reference)
FSGS	120/298 (40.3%)	7.4	2.1	1.0 (0.7-1.3)
MN	45/81 (55.6%)	12.4*	3.1	1.9 (1.3-2.7)*
LN	76/177 (42.9%)	7.9	2.5	1.0 (0.7-1.4)

[a] Adjusted for age, sex, race, dialysis pretransplant, duration of dialysis, panel reactive antibodies, donor status, donor age, donor sex, previous transplant, delayed graft function, calcineurin use, HLA mismatch.
* $P < 0.005$ compared with IgAN.

part of their transplant maintenance immunosuppression, and greater than 85% were on calcineurin inhibitors and/or mycophenolate mofetil. Induction immunosuppression agents was similar in different glomerulonephritis (GN) subgroups - IgAN, FSGS, MN and LN (**Table S1, SDC,** http://links.lww.com/TXD/A53). Delayed graft function after transplant was significantly lower in patients with IgAN at 10.1% compared with 20.5% in FSGS, 13.6% in MN, and 16.9% in LN.

Rates of Rejection in Different GN Subtypes

A total of 363 of 862 patients developed acute rejection during the follow-up period of 19 years (incidence rate of 7.2% per year). Patients with MN demonstrated a significantly higher incidence of acute rejection (12.4 per 100 person years) compared to IgAN (7.2 per 100 person years, $P < 0.005$) (Table 2). Incidence rates of acute rejection were similar among patients with IgAN, FSGS, and LN (3-year incidence rate of acute rejection in different time period for all subgroup is available in **Table S2,** http://links.lww.com/TXD/A53). Additionally, patients with MN had a 1.9 times higher incidence of acute rejection compared to IgAN even after adjusting for all the significantly different variables ($P < 0.005$). The number of patients with MN and a rejection-free functioning allograft were significantly lower compared with patients with IgAN (Figure 1A). Time to rejection in patients with MN was similar to IgAN at 3.1 and 3.9, respectively. Patients with FSGS had the first episodes of rejection earlier than other groups at 2.1 months, but this difference was not statistically significant ($P = 0.1$).

Types of Rejection in MN

We analyzed all the rejection episodes in patients with MN by reviewing individual biopsy reports to categorize episodes into cellular, antibody-mediated, and mixed rejection. Thirty-three (73.3%) of 45 rejection events were acute cellular rejection, 8 (17.8%) of 45 were acute antibody-mediated rejection, and 6 (13.3%) of 45 were combined cellular and antibody-mediated acute rejection (Figure 1B).

Allograft Survival in Different GN Subtypes

Patients with MN had a slightly worse 3-year allograft survival compared with IgAN, FSGS, and LN after rejection (Figure 2). However, 10-year allograft survival in patients with MN was like FSGS and LN. Patients with IgAN had a slightly better 10-year allograft survival after rejection when compared with other subgroups but the difference was not statistically significant.

DISCUSSION

We found that kidney transplant recipients with a diagnosis of native MN have the highest incidence of acute rejection when compared to recipients with IgAN, FSGS, or LN as the cause of ESRD. Patients with MN had a 1.9-fold higher risk of developing acute rejection after transplant compared with patients with IgAN ($P < 0.05$). Patients with MN also had decreased short-term allograft survival after rejection, but there was no significant difference in long-term allograft survival.

The risk factors that have been associated with high rates of acute rejection after kidney transplant are previous transplant,

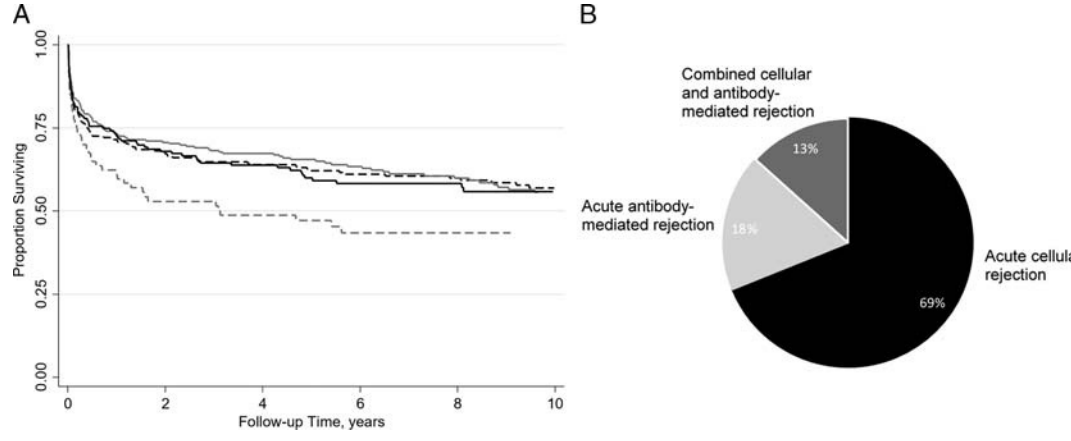

FIGURE 1. A, Kaplan-Meier curve of 10-year rejection free survival for kidney transplant patients by native glomerular disease diagnosis after acute rejection. IgAN (solid gray line), FSGS (dashed black line), MN (dashed gray line) or LN (solid black line). $P = 0.004$ for MN compared with IgAN. B, Types of acute rejection in patients with MN as cause of ESRD after kidney transplant. Acute cellular rejection (Black), acute antibody-mediated rejection (light gray), combined acute cellular and antibody-mediated rejection (dark gray).

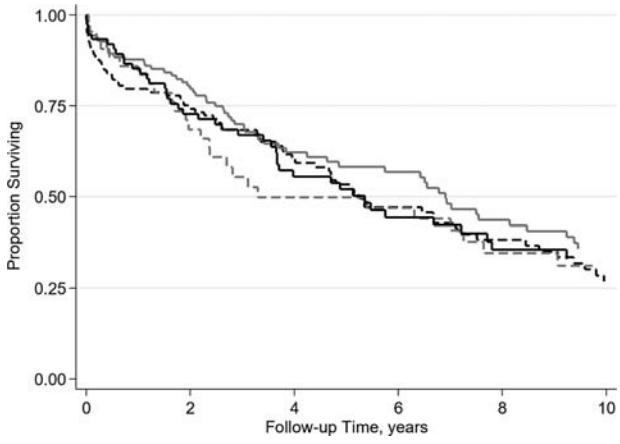

FIGURE 2. Kaplan-Meier curve of 10-year allograft survival for kidney transplant patients by native glomerular disease diagnosis after acute rejection. IgAN (solid gray line), FSGS (dashed black line), MN (dashed gray line) or LN (solid black line).

human leukocyte antigen mismatch, high panel-reactive antibody, delayed graft function, and African American race.[8-11] Patients with MN did have a higher rate of retransplant and high panel-reactive antibodies, but the difference was not statistically significant. Prevalence of delayed graft function was lower in patients with MN in comparison to FSGS and LN. In our study, patients with MN had higher incidence of acute rejection despite adjusting for all the abovementioned traditional risk factors associated with higher rates of acute rejection. Therefore, it is possible that the immunopathology of the disease itself predisposes the patients with MN to have higher rates of rejection. Antibody against antiphospholipase 2 receptor is known to cause the majority of primary MN.[12] Because MN is an autoantibody-mediated disease, there is a possibility of higher alloantibody-mediated rejection in MN. Therefore, we analyzed the types of rejection in patients with MN. Thirty percent of acute rejection events in patients with MN were antibody-mediated rejection, which is similar to previously published data in kidney transplant recipients.[13] The immunopathology in patients with MN that increases their risk of rejection is unclear and requires further study.

The patients with MN did have a lower 3-year allograft survival after rejection due to higher rates of acute rejection but their long-term allograft survival was similar to all other glomerular disease cohorts. One of the reason for similar 10-year graft survival could be that the allograft survival in these patients with glomerulonephritis is likely influenced more by other factors like glomerular disease recurrence rather than acute rejection.[2]

The incidence rate of acute rejection rates in our cohort is similar to those reported elsewhere.[1,14] One of the other limitation of our study is that this is a single center study and these results need further assessment in a more diverse cohort. Another limitation of our study is that biopsies were conducted for cause, and not per protocol, therefore potentially missing episodes of subclinical rejection.

We conclude that patients with MN have higher incidence of acute rejection after kidney transplant and slightly worse 3-year allograft survival, but have similar 10-year allograft survival in comparison to the other glomerular diseases like IgAN, FSGS, and LN.

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