Association of HLA Typing and Alloimmunity With Posttransplantation Membranous Nephropathy: A Multicenter Case Series.

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Association of HLA Typing and Alloimmunity With Posttransplantation Membranous Nephropathy: A Multicenter Case Series

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Abstract

Rationale and objectives

Post-transplant membranous nephropathy (MN) represents a rare complication of kidney transplantation that can be classified as recurrent or *de novo.* The clinical, pathological, and immunogenetic characteristics of post-transplant MN and the differences between *de novo* and recurrent MN are not well understood.

Study Design

Multicenter case series.

Setting and Participants

We included 77 patients from five North American and European Medical Centers with post-kidney transplant MN (27 *de novo* and 50 recurrent). Patients with MN in the native kidney who received kidney allografts but did not develop recurrent MN were used as non-recurrent controls (n=43). To improve understanding of post-transplant MN, we compared *de novo* MN with recurrent MN and then contrasted recurrent MN with non-recurrent controls.

Findings

Compared to recurrent MN, *de novo* MN was less likely to be classified as primary MN (OR, 0.04; P<0.001), and had more concurrent antibody-mediated rejection (OR, 12.0; P<0.001) and inferior allograft survival (HR for allograft failure, 3.2; P=0.007). HLA-DQ2 and HLA-DR17 antigens were more common in recipients with recurrent MN compared to those with *de novo* MN; however, the frequency of these recipient antigens in recurrent MN was similar to that in non-recurrent MN controls. Among the 93 kidney transplant patients with native kidney failure attributed to MN, older recipient age (HR per each year older, 1.03; P=0.02), recipient HLA-A3 antigen (HR, 2.5; P=0.003), steroid-free immunosuppressive regimens (HR, 2.84; P<0.001) and living-related allograft (HR, 1.94; P=0.03), were predictors of MN recurrence.

Limitations

Retrospective case series, limited sample size due to rarity of the disease, non-standardized nature of data collection and biopsies.

Conclusions

De novo and recurrent MN likely represent separate diseases. *De novo* MN is associated with humoral alloimmunity and guarded outcome. Potential predisposing factors for recurrent MN include recipients who are older, recipient HLA-A3 antigen, steroid-free immunosuppressive regimen, and living-related donor kidney.

Keywords: Membranous nephropathy (MN), pathology, allograft, HLA, HLA-A3, recurrent glomerulonephritis, *de novo* glomerulonephritis, allograft biopsy, phospholipase A_2 receptor (PLA_2R), antibody-mediated rejection (AMR), humoral alloimmunity, renal transplantation, allograft survival, steroid-free immunosuppression, case series

Introduction

Membranous nephropathy (MN) is an immune complex-mediated glomerulopathy characterized by subepithelial electron dense deposits. It is the most common cause of nephrotic syndrome in adult individuals of European ancestry and progresses to kidney failure in at least one third of patients [1]. Most cases (75%) of MN lack an identifiable cause (primary MN) [2], and the majority of primary MN cases are associated with antibodies against phospholipase A_2 receptor (PLA_2R) detectable in the serum and in the subepithelial deposits [3]. In those of European ancestry, several studies have shown an association of primary MN with specific HLA types, such as HLA-DR3 (HLA-DR17) and the closely linked *HLA-DQA1*05:01-*

*DQB1*02:01* haplotype, which is detected by serologic typing as HLA-DQ2 [4–7] In addition to inherited factors, MN in the native kidney may be associated with immune triggers [8].

Post-kidney transplantation MN can manifest as a recurrent or *de novo* disease. Our understanding of the pathogenesis and natural history of post-KTx MN is incomplete. Most, but not all, studies have found post-KTx MN (both *de novo* and recurrent) to be associated with inferior allograft survival [9–15]. With regard to pathogenesis, a few reports have suggested that *de novo* MN is linked to alloimmunity [13,16,17] Data on genetic predisposing factors for recurrent MN are very limited. While there is some evidence that recipient *HLA-DQA1*05:01* (DQ2 by serology) [18] and donor HLA-A3 [19] may predispose to recurrent MN, these findings have not been confirmed. Importantly, although HLA-DQ2, HLA-DR17, and HLA-A3 antigens are common in the general population [20–30% [20,21], 25% [22], and 20–25% [23–25], respectively], a systematic evaluation of the association of recurrent MN with each of these antigens in the donors and recipients has not been performed.

This multicenter case series examined the risk factors and natural history in 27 *de novo* and 50 recurrent MN cases, with particular focus on the role of alloimmunity and HLA serotypes. We sought first to compare *de novo* MN and recurrent MN and then to contrast recurrent MN with non-recurrent controls.

Methods

The data for the case series were collected across 5 medical centers: Columbia University Irving Medical Center (CUIMC, USA), Cornell University (USA), Oregon Health & Science University (OHSU, USA), Laval University (Canada), and Necker Hospital (France). Each center obtained demographic, clinical, laboratory and pathology data under approval by their Institutional Review Boards (IRB) and de-identified data were shared with CUIMC. The reported clinical and research activities are consistent with the Principles of the Declaration of Istanbul. In this pathology-based retrospective case series, the requirement for informed consent was waived by the institutional review board.

Allograft biopsies with MN were identified retrospectively from 2005 to 2018. Membranous lupus nephritis, monoclonal MN, and MN that developed in the kidney allograft of patients whose kidney failure in the native kidney was of unknown etiology were excluded. From a total of 33,119 allograft biopsies interpreted at the 5 medical centers between 2005 to 2018, the final cohort comprised 77 patients with one or more biopsies showing post-KTx MN [CUIMC (n=38), OHSU (n=15), Cornell University (n=9), Laval University (n=8), and Necker Hospital (n=7)]. The first post-transplant biopsy with MN was considered as the “index biopsy”. At all centers, allograft biopsies were performed for graft dysfunction and/or proteinuria; in addition, all recipients at OHSU and Necker Hospital underwent protocol biopsies at 3 and 12 months post-transplantation. Post-KTx MN was classified as *de novo* MN or recurrent MN, based on the native kidney disease. The primary outcome was death-censored graft failure, defined as re-initiation of dialysis or re-transplantation. Steroid-free regimens were defined as steroid-free maintenance immunosuppression from the time of initial hospital discharge after kidney transplantation, without re-introducing maintenance steroids at any time prior to the diagnosis of post-KTx MN (for cases of *de novo* or recurrent MN), or the end of follow-up (for non-recurrent controls).

HLA Typing and Assessment of Alloimmunity

Recipients and donors were serologically typed for HLA-A, -B, -DR, and -DQ. Circulating donor-specific antibody (DSA) were assessed by Luminex single antigen beads (One Lambda, Canoga Park, CA) and considered positive if at least one of the HLA antibodies was directed against donor antigens [according to each center’s positive cutoff of mean immunofluorescence intensity values].

Pathologic assessment

Allograft biopsies were stained with hematoxylin and eosin, periodic acid–Schiff, Masson trichrome, and Jones methenamine silver. Immunofluorescence staining for IgG, IgM, IgA, C3, C1q, albumin, fibrin, kappa and lambda light chains, and C4d was performed. Electron microscopy was available for 35 patients. Data on PLA_2R glomerular staining was available for 39 patients and serum antibody was available for 2 additional patients. Data on glomerular staining for IgG subclasses with clearly dominant or less intense staining for IgG4 in comparison to other subclasses was available for 10 additional patients [IgG4-dominant (n=3), weaker IgG4 staining (n=7)]. A diagnosis of primary MN was suggested based on either PLA_2R positivity, or dominance of IgG4 subclass when data on PLA_2R were not available.

Histologic parameters were evaluated according to Banff criteria for kidney allograft pathology [26–28]. Antibody-mediated rejection (AMR) was defined according to Banff 2017 criteria while acute T-cell-mediated rejection (TCMR) was defined by the presence of borderline changes (as defined by Banff 1997 criteria) or greater changes (grades IA-III).

Controls

To identify variables predictive of recurrent MN, all patients who could be identified from all five participant centers to have kidney failure attributed to MN, transplanted between 2005–2017, and did not have evidence of recurrent MN (either clinically and confirmed by a dysfunction biopsy or incidentally detected on a protocol biopsy) were recorded. Only patients who were followed-up for longer than 2 standard deviation (SD) from the mean time to recurrent MN (≥2512 days post-transplantation) were included in the control group [n=43, CUIMC (n=13), Laval University (n=10), Necker Hospital (n=10), OHSU (n=9), and Cornell University (n=1)]. This cutoff value was selected to avoid misclassifying patients as not having recurrent MN merely because of inadequate follow-up.

Statistical analysis

Statistical analysis was performed using Prism 5 2007 (GraphPad Inc., San Diego CA) and SPSS Statistics 24 (IBM, Armonk, NY). Continuous variables were compared using Mann-Whitney test while categorical variables were compared using Fisher's exact test. Allograft survival was assessed by the Kaplan-Meier method and univariate comparisons were performed using log rank test. Univariate Cox proportional hazards (PH) analyses for several demographic and clinico-pathologic variables were used to guide the selection of variables for multivariable analysis whenever these results were significant. P values <0.05 with two-sided hypothesis testing were considered statistically significant.

RESULTS

Demographic, clinical, and pathological characteristics

The case series was composed of 77 patients with post-KTx MN that was classified as *de novo* (n=27) or recurrent (n=50). As demonstrated in Table 1 , recipients had a median age of 47 years and included 22% women, 13% self-reported blacks, 54% recipients of grafts from living donors, and 53% who received induction therapy with thymoglobulin. Index biopsies were obtained a median of 291 days post-transplantation, with median serum creatinine of 1.8 mg/d, and median proteinuria of 1.3 g/d. Detailed pathologic features are presented in Table 2. Only a minority of post-KTx MN cases (9%) were detected in protocol biopsies. Post-KTx MN was classified as primary in 21 of 51 (41%) patients [the vast majority of which (n=20) were recurrent MN], based on PLA_2R positivity (n=18) or dominance of IgG4 staining (n=3) in cases where PLA_2R staining was not available. Concurrent rejection was present in 23 (30%) index biopsies, and was characterized as TCMR (n=12, including 3 characterized as borderline changes), AMR (n=6), and mixed rejection (n=5). In addition to subepithelial deposits, among the individuals for whom electron microscopy data were available, sparse subendothelial or mesangial deposits were detected in 23% of cases, and diffuse foot process effacement was observed in 68%.

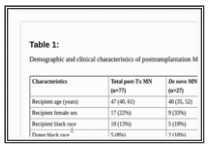

Table 1:

Demographic and clinical characteristics of posttransplantation MN

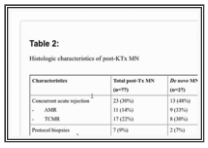

Table 2:

Histologic characteristics of post-KTx MN

Features of *De novo* MN

Information regarding PLA_2R status or IgG subtyping was available for 18 patients with *de novo* MN, who were classified as PLA_2R positive (n=1), PLA_2R negative (n=14), IgG1-dominant (n=2), and IgG3-dominant (n=1). Thus, only 1 of 18 (6%) of *de novo* MN cases was suggestive of primary MN, compared to 20/33 (61%) cases of recurrent MN (Table 2); the OR for de novo MN being classified as primary MN was 0.04 (95% CI, 0.005 – 0.3; P<0.001). Only a single recipient in the *de novo* MN group was HCV-positive versus none in the recurrent MN group (Table 1).

Compared to recurrent MN, *de novo* MN was encountered in younger recipients, occurred later in the course of transplantation, and had less foot process effacement, despite similar proteinuria levels (Tables 1 and 2). Furthermore, *de novo* MN was associated with individual features often encountered in AMR, including detectable DSA (Table 1), and higher scores for C4d staining in peritubular capillaries and for transplant glomerulopathy (Table 2). Indeed, as shown in Table 2, the diagnosis of overt AMR was more frequent in *de novo* MN compared to recurrent MN [9/27 (33%) vs. 2/50 (4%); OR, 12.0; 95%CI, 2.4–61; P<0.001].

Associations of HLA Serotype with Recurrent MN and Kidney Failure

To test whether HLA-DQ2, HLA-DR17, and/or HLA-A3 are associated with recurrent MN, we compared the frequencies of these HLA antigens in both recipients and donors with recurrent MN, *de novo* MN, and non-recurrent MN controls (whose characteristics are presented in Table S1). Recipients with recurrent MN had higher frequency of HLA-DQ2 antigen (P=0.02) and HLA-DR17 antigen (P=0.006) compared to those with *de novo* MN, but not compared to recipients classified as non-recurrent MN controls (Figure 1 and Table S2). In contrast, recipients with recurrent MN had higher frequency of HLA-A3 antigen compared to recipients with non-recurrent MN (P=0.01) and nominally more frequent HLA-A3 antigen compared to recipients with *de novo* MN, but this was not statistically significant (P=0.09) (Figure 1).

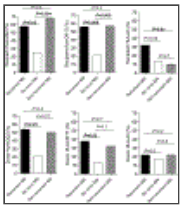

Figure 1:

Comparison of recipient and donor HLA-DQ2, HLA-DR17, and HLA-A3 antigens between recurrent MN, *de novo* MN, and patients with kidney failure secondary to MN in the native kidney who did not develop recurrent MN post-transplantation

With regard to donor HLA, patients with recurrent MN were more likely to have received grafts from donors with HLA-DQ2 antigen (P=0.03) and HLA-DR17 antigen (P=0.03) compared to patients with *de novo* MN but these were similar to those with non-recurrent MN. In contrast, the frequencies of donor HLA-A3 were similar amongst patients with recurrent MN, *de novo* MN, and non-recurrent MN (Figure 1).

Factors Associated with Recurrent MN

To identify variables predictive of recurrent MN, all patients from the 5 participating centers with native kidney failure attributed to MN regardless of the recurrent disease status were combined (n=93) and MN recurrence was considered as the outcome of interest. On univariate analysis, older recipient age (HR per 1 year older, 1.03; P=0.02), recipient HLA-A3 antigen (HR, 2.5; P=0.003), steroid-free regimen (HR, 2.84; P<0.001), and receiving a living-related allograft (HR, 1.94; P=0.03) were associated with recurrent MN (Table 3). Other demographic variables or induction therapy regimens were not significantly associated with recurrent MN. On multivariable analysis, older recipient age, recipient HLA-A3 antigen, and steroid-free regimens were significantly associated with recurrent MN while receiving an allograft from a living-related donor was numerically similar to the HR for recurrent MN from the univariate analysis, though it was no longer statistically significant (P=0.07) (Table 3). These results should be interpreted with caution due to the non-standardized collection of data and biopsies.

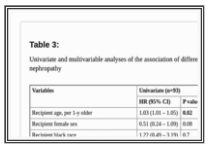

Table 3:

Univariate and multivariable analyses of the association of different variables with recurrence of membranous nephropathy

HLA antigens of donor-recipient pairs from the 15 patients with recurrent MN who received an allograft from a living-related donor were analyzed separately (Table S3). The most frequently shared antigens in each class were HLA-A1 [6 of 15 pairs (40%)], B18 [5 of 15 pairs (33%)], DR11 [6 of 15 pairs (40%)], and DQ2 [6 of 12 pairs (50%)]. Notably, the most frequent shared antigen (HLA-DQ2) was not a significant predictor for recurrent MN (Table 3).

Treatment, outcome, and prognostic indicators of post-KTx MN

Data on treatment was available for 72 patients (Table S4). Thirty-two (44%) patients were managed conservatively (12 *de novo* and 20 recurrent). Corticosteroids was used in 15 (21%) patients (7 *de novo* and 8 recurrent) while rituximab was administered in 22 (31%) patients (5 *de novo* and 17 recurrent). Plasmapheresis and/or IVIG were used for the remaining 3 (4%) patients (all with *de novo* MN). Graft failure developed in 23 (30%) patients at a median of 36 (IQR, 23–59) months after the index biopsy. When classified according to MN types, we found that graft failure occurred at an event rate of 11.7 per 100 person-years of follow-up in *de novo* MN compared to 3.7 per 100 person-years of follow-up in recurrent MN (Figure 2; HR, 3.2; 95%CI, 1.3 – 7.7; P=0.007 by Log rank test).

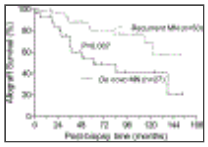

Figure 2:

Allograft survival in *de novo* and recurrent MN

Variables associated with allograft outcome were then analyzed. In *de novo* MN, serum creatinine at biopsy, transplant glomerulopathy scores, and C4d scores were associated with inferior allograft survival on univariate analysis although none of them remained significant on multivariable analysis (Table S5). In recurrent MN, the level of proteinuria and transplant glomerulitis scores were associated with inferior allograft survival and both remained significant on multivariable analysis (Table S6).

Discussion

This report represents the largest clinico-pathologic case series of post-KTx MN, which is a rare and understudied condition. Typically, MN occurs as *de novo* or recurrent disease. Our findings confirm previous reports that *de novo* MN is usually PLA_2R negative [29], unlike MN in the native kidney or recurrent MN. Based largely on immunostaining for PLA_2R, and to a lesser extent on the dominant IgG subclass, only 6% of *de novo* cases were classified as primary, compared to 61% of recurrent MN. Furthermore, our findings show that, compared to recurrent MN, *de novo* MN is encountered in younger recipients, occurs later in the course of transplantation, is associated with less severe foot-process effacement and is not associated with increased frequency of HLA-DQ2 or DR17 antigens in the recipients. Taken together, these results support the idea that *de novo* MN has different pathogenetic mechanisms. Some studies have suggested a relation between *de novo* MN and HCV [30,31], but in our case series, only 1 of 26 recipients of *de novo* MN had evidence of HCV infection. Some [16,17], but not all [29], more recent studies have suggested that *de novo* MN is associated with AMR. We found that 33% of index biopsies with *de novo* MN were diagnostic of overt AMR. This high incidence of AMR is significantly more than that encountered in recurrent MN (4%, P<0.001).

The association of subsets of MN with alloimmunity is backed by several lines of evidence: First, the occurrence of MN in neonates following production of IgG antibodies in mothers who are deficient in neutral endopeptidase [32], and in stem cell transplant recipients following graft vs. host disease [33,34]. Second, the strikingly higher incidence of *de novo* MN in kidney allograft recipients (≥1%) [35–37] compared to MN's annual incidence of 0.0012% in the general population [38].

Similar to MN in the native kidney, recurrent MN is usually PLA_2R positive [29,39] and recurrence after kidney transplantation occurs in 15–50% of patients with kidney failure secondary to MN [40,41]. Risk factors for recurrent MN are not well understood. A few studies have suggested that high titers of anti-PLA_2R antibodies prior to or at the time of transplantation can predict recurrent disease [18,42]. Receiving grafts from living-related and identical donors has been considered a potential risk factor for recurrent MN in some [14,19,43] but not all [44] studies. With regard to HLA antigens, the results are even more conflicting. While Quintana et al. showed that 6 of 7 (86%) recipients with PLA_2R-positive recurrent MN were carriers of the HLA allele *DQA1*05:01*[18], other studies have failed to replicate these findings [45,46]. Notably, these studies did not specifically address the role of donor HLA-DQ2/*DQA1*05:01-DQB1*02:01* in recurrent MN. Andrésdóttir and Wetzels found that 6/8 (75%) of patients who developed recurrent MN received grafts from donors with HLA-A3 antigen compared to 2/15 (13%) of patients without recurrent disease [19]. In addition to the small sample size, the Andrésdóttir and Wetzels study did not present data on HLA-A3 antigen in the recipients to address the potential confounding effects of HLA-A3 recipient-donor matching.

In our case series, both recipients with recurrent MN or with native kidney MN without recurrent disease had higher frequencies of HLA-DQ2 and HLA-DR17 compared to those with *de novo* MN and to the general population. These results suggest that HLA-DQ2 and HLA-DR17 are associated with MN in the native kidney irrespective of recurrent disease. Similar findings, albeit to a lesser extent, were observed for HLA-DQ2 and HLA-DR17 in the donors, probably reflecting considerable efforts to match class-II HLA in recipient-donor pairs.

In contrast to HLA-DQ2 and HLA-DR17, the rate of HLA-A3 positivity in recipients with recurrent MN was considerably higher than in control recipients without recurrent MN, and was nominally higher than that of *de novo* MN. Furthermore, recipient HLA-A3 antigen was a predictor for recurrent MN, whereas donor HLA-A3, donor or recipient HLA-DQ2, and donor or recipient HLA-DR17 were not (Table 3). While intriguing, these findings require replication in other cohorts. A steroid-free regimen also emerged as a predictor of MN recurrence, suggesting that steroids may work as immune modulators to mitigate potential immunologic triggers for recurrent MN. However, these results should be interpreted with caution, given the longer follow-up (and thus, the greater potential for introducing steroid maintenance over the long-term) in non-recurrent controls compared to recurrent MN. Other predictors for MN recurrence included older recipient age and receiving grafts from living-related donors; the latter may reflect intrafamilial genetic predisposition. Assessing HLA of donor-recipient pairs from the patients with recurrent MN who received allografts from living-related donors could not identify a single HLA antigen that was overwhelmingly shared in the majority of these patients. These findings support

further search for additional risk factors in the donor, including non-HLA markers, which may help in recipient-donor matching to reduce the incidence of recurrent MN.

With regard to prognosis, *de novo* MN had worse allograft survival than recurrent MN. Given the small sample size for *de novo* MN, it is difficult to tease out the prognostic effects of *de novo* MN per se vs. AMR. Indeed, in univariate analysis, poor outcome in *de novo* MN was associated with transplant glomerulopathy, C4d staining in peritubular capillaries, and serum creatinine, all of which may well be related to AMR. In contrast to *de novo* MN, worse allograft survival in recurrent MN was associated with higher proteinuria and transplant glomerulitis scores. Given the lack of other features supporting AMR in recurrent MN, this glomerulitis may reflect non-specific margination of leukocytes within the glomerular capillaries. In the native kidney, similar leukocyte margination has been described in some patients with renal vein thrombosis, and has been linked to worse outcome [47].

Limitations of our case series include its retrospective nature and incomplete data, notably precluding assessment of anti-PLA_2R antibody levels in predicting recurrent MN. Additionally, due to retrospective analysis of the HLA data, we are unable to control for potential population stratification in our HLA analysis. Given the lack of information on haplotype blocks that are in high linkage disequilibrium, and taking into account that HLA-A3 is differentially distributed across worldwide populations, there is a possibility that our association of HLA-A3 with MN recurrence is confounded by the aforementioned factors. Thus, a genetic study that properly controls for ancestry and other HLA antigens is needed to confirm the role of recipient HLA-A3 in predicting recurrent MN.

In summary, although *de novo* MN and recurrent MN share similar pathologic features (subepithelial deposits), they appear to represent separate diseases. Recurrent MN is frequently PLA_2R-mediated, often encountered in older recipients, and occurs early post-transplantation whereas *de novo* MN is PLA_2R-negative, encountered in younger patients, and occurs later in the course of transplantation. The association of *de novo* MN with overt AMR, as defined by Banff criteria, supports that *de novo* MN may represent a manifestation of humoral alloimmunity. While our data support the association of HLA-DQ2 and HLA-DR17 antigens with MN in the native kidney, the presence of these HLA antigens, in either the donor or recipient, were not predictive of recurrence. Our findings suggest that both intra-renal donor factors (e.g., living-related allograft), extra-renal recipient factors (including older age and the presence of HLA-A3 antigen) and immune modulators (e.g. steroid-free immunosuppressive regimen) are important contributors in the development of recurrent MN. Genetic studies in donors and recipients will be required to dissect more precisely intra-renal from extra-renal predisposing effects. Exploring the potential interactions between PLA_2R polymorphisms, HLA antigens, non-HLA genetic risk factors, and antigen presenting cells in the recipient and donor are potentially rewarding avenues for future research.

Supplementary Material

1

Click here to view.(213K, pdf)

2

Click here to view.(26K, docx)

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Footnotes

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