Recent advances in our understanding of recurrent primary glomerulonephritis after kidney transplantation

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Recurrent glomerulonephritis (GN) is an important cause of kidney allograft failure, particularly in younger recipients. Approximately 15% of death-censored graft failures are due to recurrent GN, but this incidence is likely an underestimation of the magnitude of the problem. Overall, 18% to 22% of kidney allografts are lost due to GN, either recurrent or presumed *de novo*. The impact of recurrent GN on allograft survival was recognized from the earliest times in kidney transplantation. However, progress in this area has been slow, and our understanding of GN recurrence remains limited, in large part due to incomplete understanding of the pathogenesis of these diseases. This review focuses on recent advances in our general understanding of the pathophysiology of primary GN, the risk of recurrence in the allograft, and the consequences for kidney graft survival. We focus specifically on the most common forms of primary GN, including focal segmental glomerulosclerosis, membranous nephropathy, membranoproliferative glomerulonephritis, and IgA nephropathy. New understanding of the pathogenesis of these diseases has had direct clinical implications for transplantation, allowing better identification of candidates at high risk of recurrence and earlier diagnoses, and it is expected to lead to significance improvements in the therapy and perhaps even prevention of GN recurrence. More than ever, it is essential to fully characterize GN before transplantation as this information will direct our management posttransplantation. Further, the relative rarity of recurrent GN dictates the need for multicenter studies in order to evaluate, test, and validate recent advances and therapies.

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Glomerulonephritis (GN) is the primary cause of end-stage kidney disease in a large proportion of kidney allograft recipients, reportedly as high as 50% in the Australian–New Zealand population[1], 48% in China,[2,3] and ~30% in the US population (United States Renal Data System 2015 report).[4] Likely the prevalence of GN is higher than reported as many candidates do not undergo kidney biopsies before transplantation and remain undiagnosed. Recipients with GN are generally younger than recipients with other diagnoses, emphasizing the need to strive for the absolute longest graft survival possible in these patients.

Early kidney transplantation literature note that GN recurrence does occur and is associated with a high likelihood of allograft injury and failure.[5,6] Recurrent GN has been the subject of several high-quality reviews.[1,7–11] This review focuses on recent advances in our understanding of the behavior of the most common types of primary GN after transplantation, including focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), membranoproliferative GN (MPGN), and IgA nephropathy (IgAN). We recognize that our understanding of recurrent GN is not based on randomized studies or large retrospective observations. However, by focusing this review on this area. we hope to stimulate multicenter studies on these rare diseases. This review does not include a discussion of secondary forms of GN and their recurrence in renal allografts.

GN in kidney allografts

Allograft GN can be due to recurrence of a native disease or can develop *de novo*. In most previous studies, the diagnosis of allograft GN was based on clinical biopsy, and the distinction between recurrent and *de novo* GN was not made consistently. The reported incidence of clinical allograft GN increases with the time posttransplantation. For example, in 1 study, graft GN was diagnosed in 4% of 227 biopsy specimens obtained early posttransplantation (median, 0.8 years) and in 13% of 423 biopsy specimens obtained late posttransplantation (median, 7.5 years).[12] Other studies reported incidences of clinical graft GN between 3.4% and 18%,[8,13,14] this variability likely due to the inclusion of recurrent GN versus all allograft GNs and also due to wide variations in observation time.[1] Studies based on clinical and protocol biopsies (i.e., biopsies done at fixed times

posttransplantation, not guided by clinical indications) showed a higher incidence of allograft GN than in previous studies. Thus, among 1965 kidney recipients who underwent transplantation at our center between 1998 and 2011 and followed for 86 ± 49 months, the cumulative incidence of allograft GN was 5.2%, 18.2%, 21.7%, 35.8%, and 42.3% or recipients at 1, 3, 5, 8, and 10 years posttransplantation, respectively. These results were reported in part previously.[4] These data support the postulation that the incidence of allograft GN has been previously underestimated. This may be due to several reasons: we certainly do not know how often biopsies are done in patients with posttransplantation proteinuria, hematuria, and/or declining kidney function. Furthermore, allograft biopsy specimens are not routinely processed for immunofluorescence and/or electron microscopy studies required for a GN diagnosis. Finally, for some diseases, notably IgAN, long periods of observation are required as recurrence becomes clinically evident late, often 5 to 10 years posttransplantation.

The distinction between recurrent and *de novo* allograft GN is important but likely not very precise because pretransplantation native kidney biopsies are often not performed. Thus, it is likely that some graft GN considered *de novo* are in fact recurrent. Supporting this assumption, Figure 1 displays the incidence of allograft GN in patients with a diagnosis of GN before transplantation and in patients with pre-transplantation diagnoses other than GN. As expected, the incidence of graft GN is higher, and GN is diagnosed earlier in patients with GN pre-transplantation. However, some cases of *de novo* graft GN are diagnosed very early posttransplantation, suggesting that these are in fact recurrent, as *de novo* allograft GN commonly develops late posttransplantation. Table 1 displays the incidence of different types of recurrent primary GN diagnosed at our center by either protocol or clinical biopsies.

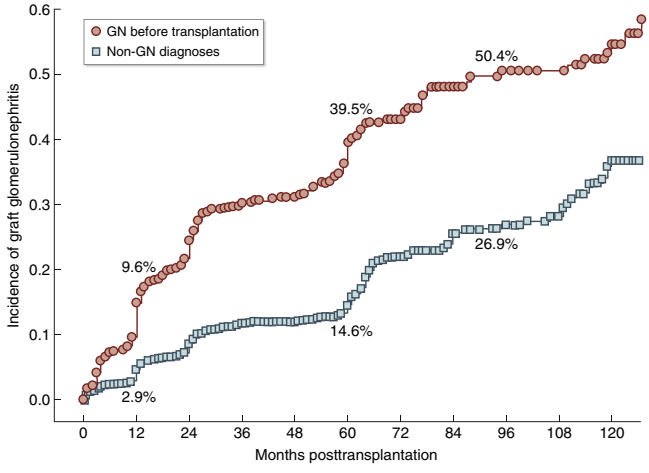

Figure 1 | Cumulative incidence (Kaplan-Meier plot) of graft GN in patients with GN before transplantation (N = 414, ○—○) and in patients with a diagnosis other than GN prior to transplantation (N = 1282, □—□). Median follow-up was 88.5 months (interquartile range, 53.9–120). Log-rank $P < 0.0001$. GN, glomerulonephritis.

Studies of protocol biopsies revealed 2 additional important findings: First, the clinical diagnosis of recurrent GN is often made late as recurrence can remain clinically silent for months to years.[15,16] Second, the histology of early GN is often different from that of advanced GN diagnosed in native biopsy specimens. For example, cases of early recurrent FSGS have no glomerular sclerosis but only diffuse podocyte foot process fusion. Similarly, the histology of early recurrent MN often does not include subepithelial electron-dense deposits and/or glomerular C3 deposits, although glomerular basement membrane granular C4d deposits are prominent.[16,17] The significance of bright mesangial IgA staining by immunofluorescence without mesangial deposits by electron microscopy is under investigation. However, often, but not always, subsequent biopsy samples in these patients will meet the classic histologic criteria of IgA nephropathy. Early recurrent MPGN often appears on light microscopy as "bland" mesangial proliferative GN without duplication of glomerular basement membranes or glomerular lobulation (Figure 2a and b). However, over time, early glomerular lesions evolve into traditional histologic patterns, sometimes rapidly (Figure 2c and d). It is important to keep these very early histologic changes in mind as adherence to strict diagnostic criteria can result in an erroneous diagnosis.

Impact of recurrent GN on graft survival

We should address 3 issues: (i) risk of graft failure in recipients with specific forms of GN before transplantation; (ii) the risk of graft failure in recipients in whom recurrent GN develops; and (iii) the overall impact of allograft GN and specifically recurrent GN on death-censored allograft survival.

Regarding the first issue, previous studies reported that, compared with control populations, the risk of graft failure is significantly higher in recipients with pre-transplantation type 1 MPGN and FSGS but not in patients with other primary GNs.[1,18] We should be cautious in interpreting these results as, even in these relatively large registry data sets, the number of cases of recurrent GN was low and the posttransplantation follow-up period was relatively short (<5 years). In assessing graft survival in patients with GN pre-transplantation, we also need to examine closely the cause of graft failure. Thus, recent studies showed that graft survival did not differ significantly between patients with primary MN and age-matched recipients with polycystic kidney disease. However, 5 of 11 graft losses (45%) in patients with MN were due to recurrent disease.[16] Thus, recurrent GN clearly has a detrimental effect on graft survival in patients with MN.

To assess the impact of allograft GN on death-censored graft survival, we need to consider that the timing of recurrence varies widely posttransplantation. Thus, statistically these analyses should consider recurrent GN as a time-dependent variable. Figure 3 displays the results of these analyses (Cosio *et al.*, data presented American Transplant Congress, 2015). Compared with recipients with GN in the native kidney but without recurrence, recurrent GN was associated with an increased risk of graft failure (Figure 3),

Table 1 | Recurrence of primary GN diagnosed by protocol or clinical biopsies

Diagnosis pre-transplantation[a]	N	Year 1, %	Year 3, %	Year 5, %[b]	Actual graft survival, %	P[c]	Follow-up (mo)
No GN	1282	–	–	–	82.6	–	87.5 ± 46
FSGS	148	10.5	30.7	35.1	73.0	0.009	90.3 ± 49
MN	49	18.9	45.4	55.0	79.6	0.908	99.7 ± 51
MPGN	52	18.3	41.4	41.4	53.8	<0.0001	81.3 ± 49
IgAN	165	12.5	42.0	51.0	80.9	0.382	96.2 ± 45[d]

FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; IgAN, IgA nephropathy; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis.
[a]Pre-transplantation diagnoses in 1965 kidney recipients who underwent transplantation at our center from 1998 to 2011. Not included are 269 recipients with other GN types before transplantation.
[b]The relatively low numbers of patients in each group did not allow accurate determinations of incidence of recurrence beyond 5 years posttransplantation.
[c]Log rank test comparing death-censored graft survival in recipients with each of the GN diagnoses with that of recipients with pre-transplantation diagnoses other than GN.
[d]Patients with IgAN had a significantly longer follow-up time ($P = 0.028$).

which was highest in patients with recurrent MPGN type 1 and FSGS. Recurrent IgAN was also associated with higher risk of graft failure, which is in agreement with some studies[19] but not with others.[1,18]

Allograft GN (both recurrent and *de novo*) accounts for 18% to 22% of death-censored kidney allograft failures,[13,20] making it the second most common cause of death-censored graft failure[20] and the third most common cause of uncensored graft failure.[1,18] In 1 study, 33 of 153 (21.5%) death-censored graft losses were due to allograft GN, including 23 cases of recurrent GN (15% of all losses) and 10 cases of novo GN (6.5% of losses).[20] The second study evaluating this issue did not differentiate between recurrent and *de novo* GN.[13]

Recurrent FSGS

Approximately 30% of cases of primary FSGS will recur after transplantation, and recurrence can occur immediately or months to years posttransplantation (Table 1). Late recurrence is difficult to diagnose as such because FSGS is relatively common late posttransplantation, perhaps secondary to reduced renal mass, other glomerular injuries, and/or drugs.[20,21] Genetic forms of FSGS, including those related to high-risk APOL1 genotype, have a very low risk of recurrence.[22–24] In contrast, 1 study suggested that podocyn mutations (*NPHS2*) are commonly found in patients with FSGS and not associated with a reduced risk of recurrence.[23] Assessing the risk of FSGS recurrence relies principally on clinical parameters. Thus, risk is higher in younger patients,

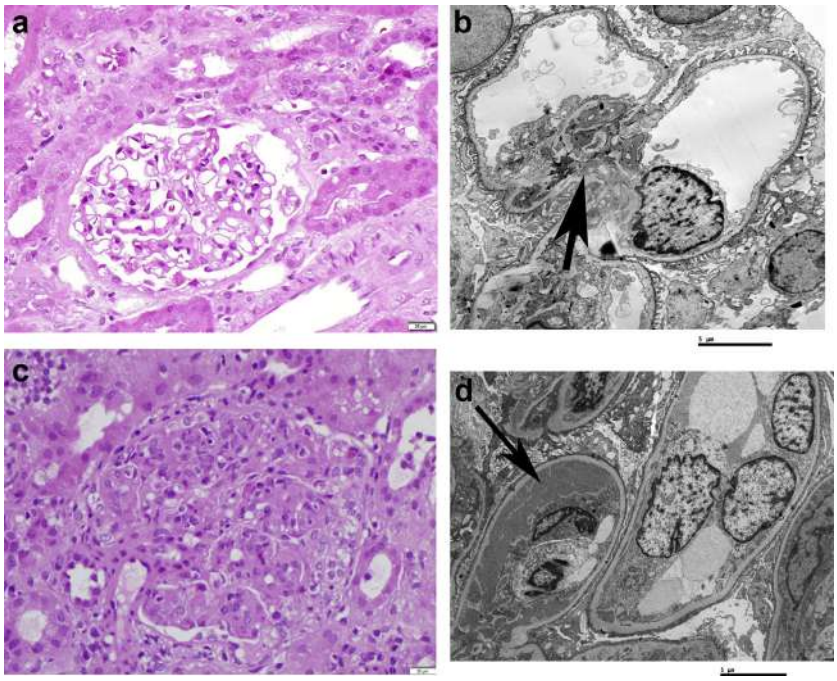

Figure 2 | Representative glomerular findings in serial biopsy specimens obtained in a patient with MPGN with monoclonal Ig glomerular deposits before transplantation. (**a**) Glomerular morphology on light microscopy in a protocol biopsy specimen obtained 3 months after transplantation. Immunofluorescence (not shown) was positive for IgG3-κ deposits. (**b**) Electron microscopy of the same 3-month biopsy specimen showing small electron-dense mesangial deposits (arrow). (**c**) Glomerular morphology on light microscopy in the same patient 6 months posttransplantation (3 months after biopsy [**a**]) demonstrating striking mesangial and endocapillary proliferation and lobular accentuation (MPGN). Immunofluorescence (not shown) was strikingly positive for IgG3-κ deposits. (**d**) Very large subendothelial electron-dense deposits in the 6-month biopsy specimen (arrow). MPGN, mesangioproliferative glomerulonephritis. Photomicrographs courtesy of Drs. Lynn D. Cornell and Mariam Alexander.

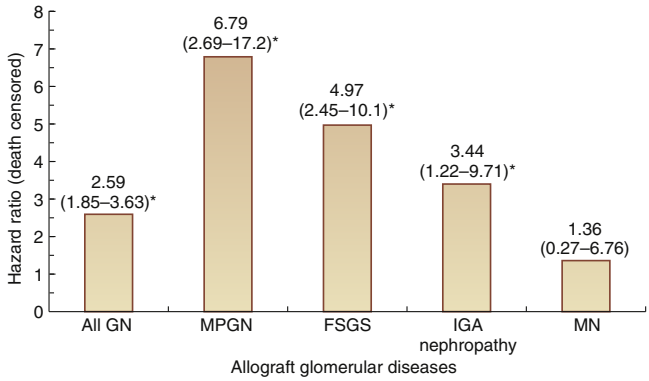

Figure 3 | Risk of death-censored graft failure associated with recurrent GN overall and in recipients with specific primary GN diagnoses (*x* axis). Values in the figure represent hazard ratios and 95% confidence intervals considering recurrent GN as a time-dependent variable. Data derived from the transplant population described in Figure 1 and Table 1. Compared with patients with the same GN diagnoses pretransplantation but without recurrence, recurrent FSGS, MPGN, and IgAN are associated with an increased risk of graft failure, but MN is not (*$P < 0.0001$). FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; IgAN, IgA nephropathy; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis.

those who progress to end-stage renal disease within 3 years of diagnosis, and those with higher levels of proteinuria pre-transplantation.[25,26] Unfortunately, this assessment lacks specificity, and of first kidney transplant recipients considered to be at high risk, only 50% had a recurrence.[27] Among these risk factors, younger age at diagnosis (younger than 15 years of age[25]) conveys the highest risk of recurrence. Rapid progression of FSGS in the native kidney is also associated with a higher risk of recurrence. However, in an earlier study, 70% of patients with a recurrence had a "slow" progression of disease pre-transplantation.[25] Furthermore, current therapies may slow down the course of FSGS. Thus, assessing rate of disease progression is now more difficult. The most reliable risk factor for recurrence is recurrence in a previous allograft, which is associated with an 80% likelihood of recurrence in the second allograft.

The pathogenesis of recurrent primary FSGS remains unknown. The clinical presentation of recurrence clearly suggests the presence of a circulating factor(s).[6,28–31] However, despite years of research, this putative circulating factor(s) remains elusive. The histology of early recurrent FSGS suggests that this factor(s) targets glomerular podocytes, causing diffuse podocyte foot process fusion[6] and proteinuria. Early in the process, this podocyte injury is clearly reversible.[30] Recent reports suggested an association between circulating soluble urokinase plasminogen activator receptors (suPARs)[32] and FSGS. However, those findings have not been confirmed by other investigators.[33–38] Similarly, the possible relationship between podocyte injury and the B7-1 pathway[39] has not been reproduced by other investigators.[37]

Serendipitously, it was discovered that recurrent FSGS may resolve after administration of anti-CD20 antibodies (e.g., rituximab).[40] This interesting observation sparked a great deal of interest and hope, suggesting that the soluble factor(s) causing podocyte injury might be derived directly or indirectly from B lymphocytes. Alternatively, it has been proposed that anti-CD20 antibodies may act directly on glomerular podocyte SMPDL-3b protein, modifying the actin cytoskeleton.[41]

Expanding experience on the use of rituximab in patients with recurrent FSGS suggests that the effectiveness of the drug is limited to a subset of patients. However, this information is derived from case studies and small series of patients and therefore should be interpreted with caution given the bias for publishing positive studies. Limited case studies suggest that FSGS develops in patients responsive to anti-CD20 antibodies in their native kidneys early in life.[42,43] Also it has been observed that rituximab-responsive individuals require very few doses of the drug, suggesting that the variability in responses is not due to dose exposure.[42] Interpreting the response of recurrent FSGS to rituximab is further complicated by the fact that most of these patients receive plasmapheresis (PP) concomitantly. PP is effective in some patients with FSGS, presumably by removing the circulating factor(s) causing the disease.[29,44] Unfortunately, the responses of recurrent FSGS to PP are also inconsistent and unpredictable. Of interest, a previous publication described a small group of patients, mainly pediatric, with recurrent FSGS responsive to but dependent on PP who were able to discontinue PP after administration of rituximab.[27] Other authors suggested that the therapeutic effects of PP and rituximab may be additive.[45]

Clearly, there is a wide spectrum of responses of recurrent FSGS to PP, anti-CD20 antibodies, and even other therapies.[39,43,46] Whether this variability indicates that there are several pathogenic subtypes of primary FSGS is speculative. Despite the realization for decades of the important negative impact of recurrent FSGS on graft survival, we still lack well-designed prospective prophylactic or therapeutic studies. Attempts have been made to remove the putative FSGS permeability factor(s) by PP to prevent recurrence. One study suggested that pre-transplantation PP may be effective in preventing recurrence,[44] whereas another did not confirm the observation.[27] A clinical protocol using anti-CD20 pre-transplantation to prevent recurrence in clinically defined high-risk patients is ongoing at our center. Early results have been encouraging, but the number of patients is still small, and prevention has not been complete.

Recurrent membranous nephropathy

Beck *et al.*[47] first described that 70% of patients with primary MN have autoantibodies against the podocyte antigen phospholipase A2 receptor (PLA2R). The percentage of kidney transplantation candidates with primary/idiopathic MN who have anti-PLA2R antibodies is essentially the same as in the general primary MN population (70%–80%).[16,48,49]

Overall, 40% to 50% of primary/idiopathic MN cases recur in the allograft.[15,16,50] However, the risk of recurrence is variable according to the pathogenic subtype of MN. Thus, patients with anti-PLA2R antibodies pre-transplantation have a 60% to 76% risk of histologic recurrence, whereas antibody-negative patients have a significantly lower risk (28%–30%).[16,49,51,52] The positive predictive value of pre-transplantation anti-PLA2R antibodies for disease recurrence is 83%.[49] Shortly after transplantation, anti-PLA2R antibody levels decline in ~50% of recipients, likely due to absorption of the antibody into the allograft and also reduced antibody production due to transplant immunosuppression. This decline is associated with reduced risks of recurrence and of disease progression if recurrence occurs.[49] In contrast, high anti-PLA2R antibody titers are associated with higher risk of recurrence,[51] and antibody levels may relate to disease progression or resistance to treatment in native MN and perhaps in allografts.[49] Of interest, in some populations, there is a genetic link between the risk of MN recurrence and some human leukocyte antigens. It is postulated that this association is due to variability in PLA2R antigen expression in podocytes.[53] We have not observed this association in US white populations,[15,16,54] perhaps because this population is genetically more diverse than European populations or because the numbers of patients in our study were too small.

Histologic recurrence of primary MN occurs most often during the first year posttransplantation, but a second period of high risk occurs around 5 years.[15,16] The histologic manifestations of recurrent GN can be observed on protocol biopsies as early as 1 to 2 weeks posttransplantation,[16,17] most likely because of deposition of circulating antibodies present at transplantation. Late MN recurrence is clearly the result of the production of new anti-PLA2R antibodies posttransplantation and needs to be differentiated from *de novo* MN that is not associated with anti-PLA2R antibodies.[48,55]

Accumulating information suggests that measuring anti-PLA2R antibodies at different times during the transplantation process is clinically useful (Figure 4) for assessing risk of recurrence, risk of progression, differential diagnosis of proteinuria in recipients with a history of primary MN, and response to therapy. It should be noted that in some patients, serum anti-PLA2R antibodies may become undetectable. In these cases, glomerular staining for PLA2R may be positive, indicating anti-PLA2R–associated MN[49,56] (Figure 4). Thirty percent of primary MN cases are not anti-PLA2R related. A small percentage of these patients may have antibodies against other antigens such as cationic bovine serum albumin and thrombospondin type 1.[57–59] At this point, we have no information about the relevance of these antibodies in disease recurrence.

Better understanding of the pathogenesis of primary MN paralleled advances in the treatment of allograft MN. Most recipients with recurrent MN are receiving calcineurin inhibitors, an effective therapy for MN in native kidneys.[60] The combination of alkylating agents (cyclophosphamide or chlorambucil) and corticosteroids[61] is also effective in treating MN in native kidneys and, in our experience, also in treating recurrent MN. However, this therapy may be complicated by severe leukopenia, and we recommend that mycophenolate mofetil be discontinued while the patient is receiving alkylating agents. Anti-CD20 antibodies are also effective in treating native MN and allograft MN.[48,54,62–65] Rituximab therapy for early MN recurrence leads to 80% complete or partial remission, and resolution of subepithelial deposits has been documented in 40% of patients.[16,54] Anti-CD20 therapy is associated with an increased risk of infections in transplant recipients.[16,54] However, in our clinical experience, this

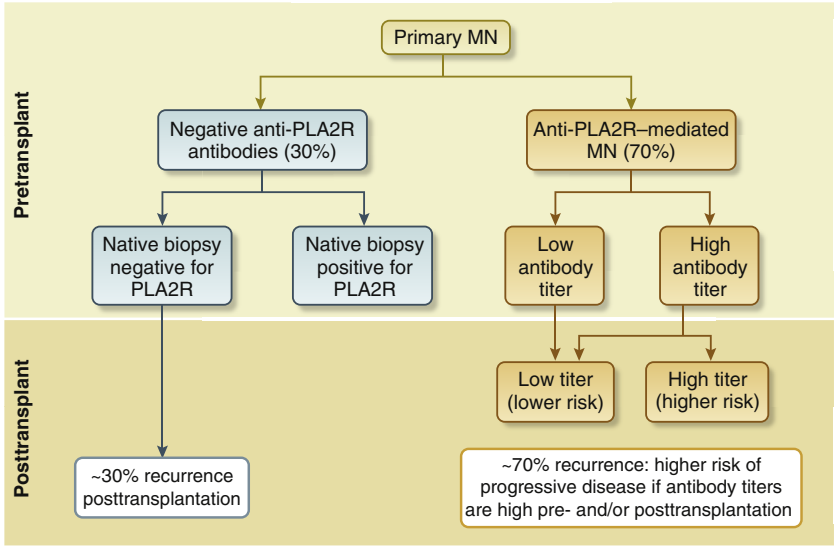

Figure 4 | Assessment of risks of MN recurrence and progression posttransplantation based on laboratory parameters obtained before and after transplantation. MN, membranous nephropathy; PLA2R, phospholipase A2 receptor.

therapy is safer, better tolerated, and easier to administer than alkylating agents. Consequently, our current practice is to use rituximab as the primary therapy for recurrent MN. During this therapy, there is no need to modify transplant immunosuppression. Currently, there is insufficient information to determine whether the presence or absence of anti-PLA2R antibodies alters the response to rituximab; therefore, we use this drug regardless of antibody status. Patients unresponsive to anti-CD20 may respond to alkylating agents and vice versa.[16,63] Therapy with rituximab leads to progressive declines in anti-PLA2R antibody titers before the proteinuria declines.[48] Thus, serial measurement of antibody levels may be useful to predict disease responsiveness to therapy and also predict relapse.[66] In contrast to the approach taken for the treatment of native MN,[67] we advocate treatment of recurrent MN early in the disease when proteinuria is progressive and has reached 1000 mg/day as this approach has led to a very high percentage of therapeutic success.[16] Despite these therapeutic options, as many as 45% of death-censored graft losses in patients with primary MN are attributable to recurrent disease.[16] We postulate that early treatment is likely to reduce this percentage.

Theoretically, anti-CD20 antibodies administered 4 to 6 months before transplantation may be used to reduce anti-PLA2R antibody levels and prevent MN recurrence. We have not adopted this approach systematically because treatment of early recurrent MN with anti-CD20 antibodies is quite successful.[16,54,68] Furthermore, anti-PLA2R antibody levels may decline shortly after transplantation, reducing recurrence risk.[49] We have used preventive anti-CD20 therapy successfully in 2 patients who lost previous allografts due to recurrent MN within 3 years posttransplantation. Recurrence was not seen in either of these patients on protocol biopsies at 12 to 18 months posttransplantation.

Recurrent idiopathic MPGN

The classification of MPGN has evolved to now include both classic morphology and other features.[69,70] This new classification greatly enhances our ability to assess the risk of recurrence and the course of the disease in the allograft and its therapy. Specifically, assessing MPGN recurrence considering this lesion as a single entity (Table 1, Figure 3) hides the fact that there are great disparities in recurrence rates and graft survival in patients with different MPGN subtypes.

Table 2 displays the frequency of MPGN types by the new classification in adults referred to our service for kidney transplantation. Approximately 77% of MPGN cases were associated with glomerular Ig deposits, half polyclonal and half monoclonal. In 23% of cases, MPGN was associated with predominant glomerular C3 deposits, including mainly cases of C3 glomerulopathy (C3GN) and a rare case of dense deposit disease (DDD).

The behavior of MPGN with polyclonal Ig deposits (Table 2) posttransplantation is variable. However, generally, this disease has a relatively low risk of recurrence, usually presenting late during the first 5 years and progressing relatively slowly.[71] Late recurrent MPGN with polyclonal Ig deposits cannot be differentiated morphologically from *de novo* MPGN, also presenting late posttransplantation and usually with polyclonal Ig deposits.[20] In patients with MPGN and polyclonal Ig deposits, the presence of low complement levels (C3 and/or C4) identifies patients with higher risk of recurrence.[71,72] An important observation useful in differential diagnosis is that patients with MPGN and polyclonal Ig deposits have glomerular C4d deposits, indicating classic or lectin pathway complement activation. In contrast, glomerular C4d is absent in patients with C3GN and DDD, indicating alternative complement pathway activation.[73]

MPGN with monoclonal Ig deposits[74] (Table 2, Figure 2) recurs often (~66%), very early posttransplantation and often follows an aggressive course leading to a high-risk of graft failure.[71,75] In 70% of these cases, there is no evidence of monoclonal Ig in serum/urine, no evidence of a plasma cell dyscrasia in the bone marrow, and these patients have a low risk of multiple myeloma developing.[74,76] Although in this disease, glomerular deposits are most often composed of IgG3-κ[74], other Ig isotypes and/or light chains may be present. Whether these Ig variations have prognostic implications is still unclear.[75,77] In addition, we should consider that the antigen reactivity of these monoclonal proteins may also be relevant for disease pathogenesis. For example, there is an association between monoclonal glomerular deposits and C3GN,[78] suggesting that, in some cases, the monoclonal protein may alter the regulation of the complement cascade allowing overproduction of activated C3.[79] Thirty percent of patients with MPGN and monoclonal Ig deposits have serum monoclonal proteins,[74] although they may not have multiple myeloma. This group of patients fits into the category of diseases now called monoclonal gammopathies of renal significance.[80,81] It is likely that the risk of recurrence will be very high in these patients, mimicking observations made in fibrillary GN in which the presence of serum monoclonal Ig is associated with a higher risk of recurrence.[82]

C3GN (Table 2) is characterized by glomerular deposits of C3 with no or minimal Ig deposits.[83,84] C3GN and DDD share immunofluorescence features and pathogenic mechanisms. However, these 2 diseases have distinct morphology

Table 2 | Incidence of different pathogenic subtypes of primary MPGN in adult kidney transplant candidates

Glomerular deposits by immunofluorescence	Subtype	No. (%) (62)[a]	Recurrence risk (%)	Graft failure if recurrent
Igs	Polyclonal	24 (38.7)	30–35	10%
	Monoclonal	24 (38.7)	66	50%
Complement (C3)	C3GN	12 (19.3)	70	50%
	DDD	2 (3.2)	80–90	25%

C3GN, C3 glomerulopathy; DDD, dense deposit disease; MPGN, membranoproliferative glomerulonephritis.
Incidence of recurrence and death-censored graft failure rates associated with recurrence.
[a]Number of adult kidney recipients with idiopathic MPGN referred to our center for transplantation. All of previous native kidney biopsies of these patients were reviewed at our center.

and clinical features before and after transplantation, suggesting still unrecognized pathogenic factors. C3GN is associated with a very high risk of recurrence posttransplantation (~70%), which is often clinically aggressive, sometimes early posttransplantation and leading to a high risk of graft failure (~50%).[85] DDD is also associated with very high risk of recurrence and is associated with reduced graft survival.[86,87] However, DDD recurrence presents clinically late posttransplantation and generally progresses slowly in association with minor or no clinical manifestations.[86–89] Patients with C3GN and DDD generally have alterations in the regulation of the alternative pathway of the complement cascade, resulting in overproduction of activated C3 and at times also terminal pathway activation (C5–C9).[83,90,91] The causes of this dysregulation are variable, including the presence of autoantibodies against C3 convertases (C3 nephritic and C4 nephritic factors)[88,92,93] or against factor H[91] and mutations in genes related to complement regulatory proteins, principally factor H.[83,84,90,91,94–96] Recent studies suggest that polymorphisms in complement regulatory proteins, particularly those of the alternative pathway, may be common in all forms of MPGN and may relate to renal prognosis.[97] Similar genetic mutations are found in patients with atypical hemolytic uremic syndrome, resulting in a completely different disease phenotype.[98–100]

The morphologic/pathogenic classification of MPGN should also help guide therapy. It is reasonable to postulate that therapy of MPGN with Ig deposits should be directed at suppression of antibody production. There are no randomized trials using this approach before or after transplantation In uncontrolled studies, anti-CD20 antibodies has been reported to be effective in the treatment of MPGN with monoclonal Ig deposits in native kidneys and allografts.[71,77] There are several reports on the use of monoclonal antibodies that inhibit activation of the C5 component of complement (eculizumab) in patients with C3GN. Those reports are mixed.[101–105] Supporting the use of eculizumab in C3GN, this drug is effective in patients with atypical hemolytic uremic syndrome, a disease with similar pathogenesis, preventing and treating posttransplantation recurrence.[98,105–107]

Given the aggressive course of recurrent MPGN with monoclonal Ig deposits and of C3GN, we should consider prevention. A clinical protocol aimed at preventing recurrence of MPGN with monoclonal Ig deposits using anti-CD20 antibodies pre-transplantation is ongoing at our center. The initial results have been encouraging but still premature. Whether C5 complement inhibition (eculizumab) is effective in preventing recurrence of C3GN is unclear.[101–103,105] Patients with genetic mutations in complement regulatory proteins remain asymptomatic for many years until a putative triggering event leads to the development of pathology. Dysregulation of complement activation during organ ischemia-reperfusion at transplantation[108–112] may theoretically explain the very aggressive clinical course of C3GN in the allograft.

Given the highly variable behavior of MPGN subtypes, it is essential to classify these diseases before transplantation. Table 3 summarizes pre-transplantation information helpful in this classification. These investigations should include re-examination of previous native kidney biopsies, especially if they were done before our current understanding of MPGN pathogenic types. Importantly, the behavior of MPGN in native kidneys is a very poor predictor of its behavior post-transplantation. Specifically, a slow progressive course in the native kidney is not predictive of a similar slow course post-transplantation.

Recurrent IgA nephropathy

The reported incidence of clinically evident recurrent IgAN is often quoted as 30%,[113] but it varies considerably in different studies due to differences in diagnostic criteria and particularly length of follow-up as recurrent IgAN rarely manifests clinically before 5 years posttransplantation. Histologic recurrence of the disease is much more common and occurs earlier posttransplantation (Table 1).[114] A small percentage of cases of recurrent IgAN have a rapidly progressive course with crescents, and these cases generally have a poor prognosis.[113,115,116] It has been suggested that those recipients had a crescentic form of IgAN before transplantation.[117]

Our understanding of the pathogenesis of IgAN is incomplete.[118] However, 3 pathogenic components of the disease appear to be promising markers of disease activity and risk of recurrence. Thus, a higher risk of recurrence has been associated with higher levels of circulating galactose-deficient IgA1 and IgA-IgG immune complexes and with lower levels

Table 3 | Pre-transplantation characteristics helpful in classifying primary MPGN and predicting risks of recurrence and progression posttransplantation

Pre-transplantation studies	Lower risk of recurrence and progression	Higher risk of recurrence and progression
Native kidney biopsy Immunofluorescence (glomerular) Electron microscopy	Polyclonal Ig deposits[a]	Monoclonal Ig deposits[b] C3GN DDD, high risk of recurrence but often slow progression
Serum studies Complement levels (C3, C4) Monoclonal proteins	Normal Absent	Low C3 and/or C4 Present
Additional complement studies Alternative pathway activation? Classic/lectin pathway activation? Terminal pathway activation? C3Nef, C4Nef? Other autoantibodies? Genetic mutations?	Classic/lectin pathway activation (positive glomerular C4d) is associated with MPGN with polyclonal Ig deposits	Overactivation of alternative and/or terminal pathway Note: We do not know whether the mechanism of complement overactivation affects risk

C3GN, C3 glomerulopathy; C3NEF, C3 nephritic factor; C4NEF, C4 nephritic factor; DDD, dense deposit disease; MPGN, membranoproliferative glomerulonephritis.
[a]One of several Igs present with equal staining for κ and λ light chains.
[b]Disproportionate staining of 1 light chain (most often κ) over the other. IgG is the predominant Ig in these cases, most often IgG3. However, other Igs can be present.

of circulating complexes of IgA-soluble CD89, the myeloid cell receptor for IgA.[119] It should be noted that in those studies, there was considerable overlap between the levels of these proteins in recipients with or without IgAN recurrence. This overlap maybe due to the fact that recurrence in those studies was defined clinically, and we know that IgA recurrence can be clinically silent for many years. Thus, some patients without a recurrence likely had a recurrence.

Analyses of risk factors for IgAN recurrence have not provided consistent results. Recurrence appears to be more common in young recipients and perhaps in those with more rapidly progressive disease before transplantation. Some studies report an association between recurrence with the degree of human leukocyte antigen matching and/or the use of living versus deceased donors.[120,121] However, those observations were not confirmed in other studies.[113,114] There are inconsistent reports on the possible association between IgAN recurrence and polymorphisms in interleukin-10.[122,123] Registry data from Eurotransplant reported that patients with IgAN and the human leukocyte HLA-B8-DR3 haplotype have reduced graft survival.[124] To our knowledge, this report has not been confirmed. Of interest, the risk of IgAN recurrence appears to be higher in patients receiving steroid-free immunosuppression posttransplantation.[125,126] Some studies suggest that the histologic classification of recurrent IgAN may have prognostic implications.[19,127,128]

Overall, patients with IgAN have excellent transplantation outcomes compared with other GN types or other diagnoses (Table 1). In fact, several studies reported better graft survival in patients with IgAN compared with other diagnoses.[117,129,130] However, assessing the risk of IgAN recurrence requires long observation times. In fact, the evidence indicates that recurrent IgAN is harmful to the allograft. Thus, compared with patients with IgAN without recurrence, recurrence was associated with a higher risk of allograft failure[19,113,131,132] (Figure 3). Risk of recurrence and graft survival is reportedly similar in IgAN and in Henoch-Schönlein purpura.[129,130]

Our therapeutic options for IgAN are limited. It was reported that induction immunosuppression with antithymocyte globulin is associated with a reduced risk of IgAN recurrence.[133] It is our practice to maintain patients with IgAN on low-dose corticosteroids posttransplantation to prevent recurrence.[125,126,131] In contrast to this approach, recent studies suggested that immunosuppressive therapy does not improve outcomes in patients with native IgAN.[134] Studies from Japan report favorable outcomes after tonsillectomy in patients with recurrent IgAN.[135–137]

Role of transplant immunosuppression

Previous studies reported no significant associations between the type of transplant immunosuppression and the risk of GN recurrence.[138] However, in our opinion, the information contained in UNOS databases is not sufficiently granular or complete to assess recurrent GN. Furthermore, 3 observations suggest that transplant immunosuppression has at least a modulating effect on recurrent GN: First, there is an unexpected low incidence of clinical recurrence in some forms of GN, particularly systemic lupus erythematosus and antineutrophil cytoplasmic antibody–associated vasculitis.[9,10,139,140] Studies of protocol biopsies showed that there is histologic evidence of recurrent systemic lupus erythematosus in ~25% of patients, but the disease remains subclinical (Alexander *et al.*, ATC 2014, manuscript in preparation), suggesting that transplant immunosuppression may modulate disease progression rather than recurrence rate. Second, steroid-free immunosuppression appears to be associated with a higher risk of recurrent GN in pediatric patients and those with IgA nephropathy,[125,126,131] whereas it does not appear to increase the risk of FSGS recurrence.[141,142] Third, after transplantation, levels of anti-PLA2R antibodies often decline, perhaps due to reduced antibody production induced by transplant immunosuppression.[49]

The risk of graft failure due to graft GN and in particular recurrent GN is high, almost certainly higher than estimated in previous studies. Furthermore, the risk associated with recurrent GN expands the entire transplant course (Figure 1). Randomized studies on the prevention and treatment of allograft GN are essential to further improve graft survival. Multicenter studies on recurrent GN were not done in the past, perhaps because of skepticism about available therapeutic options and/or length of follow-up required to prove benefit. However, given these data, we believe that these arguments are no longer valid.

DISCLOSURE

All the authors declared no competing interests.

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