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.

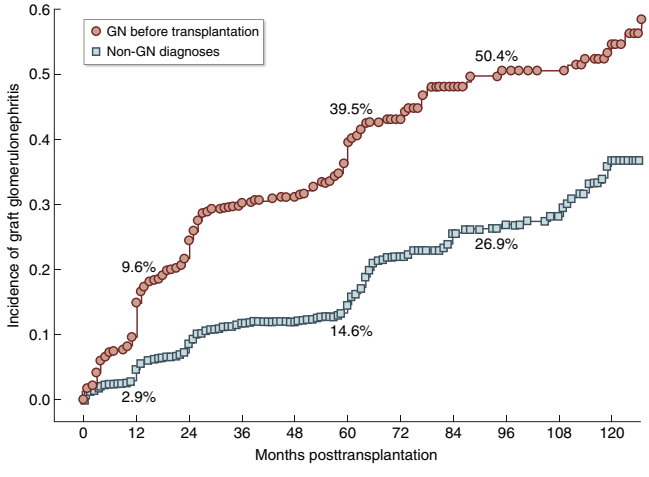

Figure 1 | Cumulative incidence (Kaplan-Meier plot) of graft GN in patients with GN before transplantation (N = 414, ○—○) and in patients with a diagnosis other than GN prior to transplantation (N = 1282, □—□). Median follow-up was 88.5 months (interquartile range, 53.9–120). Log-rank $P < 0.0001$. GN,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