Recurrent Glomerulonephritis in the Renal Allograft: An Update of Selected Areas

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Glomerular diseases, including diabetes and various forms of glomerulonephritis, account for more than 70% of patients undergoing renal transplantation. Among these patients, more than 40% develop significant proteinuria, and around 15% develop persistent nephrotic syndrome. The most common cause of posttransplantation proteinuria is chronic allograft nephropathy (60%), followed by recurrent (15%) and de novo (10%) glomerulonephritis. Persistent proteinuria is associated with a significantly reduced rate of graft survival but often can be controlled with non–disease-specific therapy including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers with favorable effects on long-term prognosis.

Recurrent or de novo glomerulonephritis occurs in 6%-20% of patients overall and is more common in patients transplanted with glomerulonephritic organs. Glomerulonephritis in the allograft is also associated with a reduction in long-term (5-year) graft survival (40% vs 70%). The most common diseases associated with allograft glomerulonephritis and their recurrence rates in transplantation patients are idiopathic focal glomerular sclerosis (20%-30%), IgA nephropathy (25%), membranoproliferative glomerulonephritis (type 1, 25%; type 2, 80%), membranous nephropathy (30%), and hemolytic-uremic syndrome (classic, 10%; atypical, 40%; familial, 60%).

This article reviews new developments in the understanding of 3 of these diseases—focal glomerular sclerosis, membranous nephropathy, and hemolytic-uremic syndrome—as they relate to the incidence of recurrence, the effects of recurrence on graft survival, risk factors for recurrence, and management issues for nephrologists caring for patients with renal allografts. Proper donor selection, early diagnosis in high-risk patients, and appropriate management can prolong graft survival and improve long-term outcomes.

Key words: Glomerulonephritis, Transplant, Focal sclerosis, Membranous nephropathy, Nephritic syndrome

The issue of recurrence of the original glomerular disease in renal allografts has been a topic of interest since 1968 when Glassock and coworkers first reported that 11 of 17 recipients of isografts from monozygotic twins, who were not receiving immunosuppression and had end-stage renal disease (ESRD) due to glomerulonephritis (GN) also had clinically significant recurrences of GN in the isograft [1]. Seven of the patients with recurrences became nephrotic, and 5 lost the graft from recurrent disease. Since then, a significant amount of literature has accumulated on this subject including several recent reviews [2-4]. It is apparent from the now-extensive clinical experience in this area that most immunologically mediated forms of GN can recur in allografts as well as in isografts (although they do so with varying frequencies) (Table 1), that there is a negative impact on long-term allograft survival due to recurrent disease, that improvements in immunosuppressive regimens for rejection have not diminished this problem significantly and may have increased it, and that the likelihood of recurrence is sometimes an issue in donor selection.

The purpose of this paper is not to reiterate information that is covered in previous reviews but
rather, to focus on 3 diseases where new insights into their pathogenesis have emerged quite recently that impact our thinking about recurrent disease and donor selection. The reader is referred to other, more-extensive reviews for more-detailed information on other disease entities [2-4].

The Problem

Clinically, recurrent GN manifests primarily as an increase in proteinuria in the allograft, usually associated with progressive loss of renal function or chronic kidney disease (CKD). Proteinuria occurs in about 10% of transplants [5]. It is transient in 1% and persistent in 9%. About 6% of allograft recipients in most studies develop nephrotic syndrome [5]. The differential diagnosis of proteinuria in transplants includes chronic allograft nephropathy (60%), recurrent GN (20%), de novo GN (10%), and several other, less-common conditions (10%) [5].

Development of recurrent disease, not surprisingly, has a negative effect on long-term allograft survival. In a study of more than 1500 patients, Hariharan and coworkers reported that graft survival was the same at 3 years, but at 5 years it was 64% in patients without recurrent versus 57% in patients with recurrent GN ($P < 0.05$) [3,4]. At 8 years, that difference had increased to 53% versus 34% ($P < 0.05$). Since progression of CKD of any kind tends to parallel proteinuria, and patients with recurrent GN have more proteinuria than patients without recurrent GN, the effects of recurrent GN on allograft survival may reflect interstitial changes consequent to proteinuria more than the glomerular changes in the allograft [6].

### Table 1. Causes and Risks of Recurrent Glomerulonephritis in Renal Allografts

<table>
<thead>
<tr>
<th>Disease</th>
<th>Risk of recurrence (%)</th>
<th>% of all recurrent GN</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGS</td>
<td>30 - 50</td>
<td>40</td>
</tr>
<tr>
<td>MPGN</td>
<td>30 - 100</td>
<td>15</td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>10 - 30</td>
<td>10</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>40 - 6</td>
<td>15</td>
</tr>
<tr>
<td>Anti-GBM</td>
<td>&lt; 5</td>
<td></td>
</tr>
<tr>
<td>HUS</td>
<td>50</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>SLE</td>
<td>&lt; 5</td>
<td></td>
</tr>
</tbody>
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GN: glomerulonephritis  
FGS: focal glomerular sclerosis  
MPGN: membranoproliferative glomerulonephritis  
GBM: glomerular basement membrane  
HUS: hemolytic-uremic syndrome  
SLE: systemic lupus erythematosus

### Recurrence in 3 Individual Glomerular Diseases

Table 1 lists the glomerular diseases most frequently associated with recurrence and the approximate frequency of recurrent disease associated with each. Because of space limitations, focus here is on only 3 of these entities, emphasizing where new insights into disease pathogenesis have shed light on the mechanisms involved and also may have broader implications for transplantation and donor selection in general.

#### A. Focal glomerular sclerosis

Focal glomerular sclerosis (FGS) is the disease entity that carries the highest incidence of clinically significant recurrent disease with the greatest impact on graft survival of any of the glomerular diseases. Although the rate of recurrence varies substantially with the presence of various risk factors, the overall recurrence rate in FGS is about 30%, and 50% of these grafts are lost from recurrent disease in 5 years [2-4,7-9]. The mean time to recurrence of FGS is short, 10-14 days, but recurrences have been reported within hours and up to 6 months after transplantation [7-9]. Up to 50% of patients with recurrent FGS also develop acute renal failure, 80% become nephrotic, and hypertension and hematuria are common [8,9].

Many factors have been identified as risk factors for recurrent FGS, although none of these is highly predictive in an individual patient. Clearly, recurrence is more common in younger patients. Patients under 5 years of age have a 50% likelihood of recurrence versus only 10%-15% in patients older than 30 years [8]. This likely reflects the higher prevalence of primary FGS in children, with more secondary FGS (which does not recur) in adults (see below). Mesangial hypercellularity also has been associated with recurrence in some studies, probably reflecting a greater severity of disease and steroid resistance in such patients [8]. White recipients seem more likely to have recurrences than African-Americans. Rapid progression of the underlying disease from initial diagnosis to development of ESRD, particularly if it occurs within 3 years, also predicts recurrence. And recurrence itself is a very bad prognostic sign that predicts recurrence in second allografts. Over 70% of such grafts have another recurrence and most are lost [7,8]. Thus, a history of graft loss from recurrent FGS virtually precludes subsequent successful transplantation in that recipient.
The pathogenesis of idiopathic, primary FGS remains unknown, but the rapid recurrence in some patients strongly suggests that a circulating factor is involved [7]. The initial glomerular lesion in patients with recurrent FGS is that of minimal change nephrotic syndrome with diffuse foot process effacement present in many glomeruli before sclerotic lesions develop, supporting the idea that both diseases are due to similar mechanisms. Indeed, in rare cases in which a normal kidney has been transplanted into a recipient with minimal change nephrotic syndrome, immediate recurrence of nephrotic range proteinuria is observed [10], and proteinuria resolves quickly if kidneys with minimal change disease are transplanted into normal recipients [11].

Many investigators have tried to identify circulating permeability factors, particularly in patients with recurrent FGS, which should identify patients likely to have such factors. Savin and coworkers have provided the most information in this area, utilizing an in vitro assay in which alterations in the albumin reflection coefficient of the capillary wall can be calculated by measuring changes in glomerular volume following incubation with putative factor-containing serum or fractions in albumin solutions [12]. Although this group initially reported good correlations between the presence of a circulating factor and recurrent disease in allografts [12,13], later studies by other groups have reported less robust correlations and less specificity, with serum from patients with other diseases also sometimes demonstrating permeability factor activity [14]. However, it seems likely that some form of permeability factor is operative in these patients with rapid recurrence of the idiopathic form of FGS, although the difficulties in measuring, isolating, and characterizing it have impeded progress in this area. Savin and colleagues have reported their factor is a nonimmunoglobulin protein that is stable for 3 years at 20°C, heat labile, protease sensitive, and between 30-50 kDa [13].

But the story is more complex. Of particular importance in studying FGS is that the focal glomerular sclerotic lesion is not specific for a particular disease or underlying disease process, although the term unfortunately often has been attached to a specific clinical disease entity. Thus, the lesion is seen in the idiopathic form of FGS in patients with idiopathic nephrotic syndrome where permeability factor involvement seems likely. A similar sclerotic lesion occurs as a secondary phenomenon in many diseases where the podocyte is the target, including hemodynamically mediated progressive disease due to reduction in nephron number and other proteinuric primary glomerular diseases such as membranous nephropathy [15]. Of major recent interest is the rapidly expanding list of proteinuric diseases with the lesion of FGS caused by mutations of podocyte-specific genes [7]. The classic example of this is congenital nephrotic syndrome due to mutations in nephrin, a component of the glomerular slit diaphragm [16]. However, several other examples of inherited podocytopathies with FGS on biopsy have now been reported including defects in podocin, alpha actinin 4, and CD2AP [7, 15-19]. Recent studies suggest that around 15% of patients with what previously would have been called idiopathic FGS have inherited or acquired defects in podocyte proteins that underlie their diseases [7]. One would anticipate that placing a normal kidney into such recipients would not risk recurrent disease since the donor kidney is genotypically normal. However, further complicating the permeability factor story is the observation that recurrence does develop in about one third of such patients [17], and that it may be associated with the presence of a measurable permeability factor [7,14].

So a story that seemed simple a decade ago and offered the promise that identification of permeability factors, and perfection of more-specific assays for them, could eliminate the important clinical problem of recurrent FGS in transplants has now become much more complex. Do some permeability factors, albeit not antibodies, represent immune responses by recipients with abnormal podocyte genotypes to kidneys that contain normal genes and proteins? Do permeability factors somehow interact with and enhance the clinical expression of abnormal genotypes? Or, as has recently been suggested, do “permeability factors” actually represent not the presence of something bad that should not be there but instead, the absence of something good that should be [13]? Because of the surge of interest in podocyte biology with the discovery of disease-associated podocyte genes and proteins starting with nephrin, the topic of recurrent FGS is now at the center of a rapidly evolving story that has not yet been fully told.
B. Membranous nephropathy

Recurrent membranous nephropathy (MN) is not a problem of the same magnitude as recurrent FGS but is a disease of considerable interest because of its relative frequency, its common occurrence as a de novo disease in allografts, and the new insights that have been made into its underlying mechanisms. Recurrence rates for MN are between 10% and 30% depending on the series, and de novo MN is more common, causing about twice as many cases of MN in transplantation recipients [20]. Recurrent MN occurs sooner (10-24 months) and de novo later (24-36 months). Both present primarily as nephrotic syndrome, and both are associated with about a 50% rate of graft loss a decade later. Risk factors for recurrent MN include male sex, rapid course of the initial disease (less than 3 years from onset to ESRD), and living-related donor kidneys (in which the disease recurs 3 times more often as it does in cadaver kidneys) [20].

In MN, issues of both therapy of the disease in native kidneys and predicting disease in transplants are complicated by the fact that the nature of the pathogenic antibody and its antigenic target are unknown. However, in an animal model (rats), the disease very closely mimics Heymann nephritis, in which it has been established that the target antigen is a large protein called megalin, along with a smaller receptor, associated protein (RAP), together referred to as the Heymann nephritis antigenic complex (HNAC) that is expressed on the cell membrane of podocyte foot processes [21]. In Heymann nephritis, the IgG autoantibody binds in situ to the podocyte membrane to produce the subepithelial immune complex deposits that characterize MN. Proteinuria is mediated by formation of the C5b-9 membrane attack complex of complement, which inserts in sublytic quantities into podocyte membranes and activates the cell to produce several molecules that damage the underlyingglomerular basement membrane (GBM), particularly oxidants and proteases [21]. Although attempts to document a similar mechanism in the human disease have been unsuccessful for more than a decade, Ronco and colleagues recently were successful in doing so. They reported the birth of an infant with nephrotic syndrome and typical MN to a mother who was genetically deficient in neutral endopeptidase (NEP), a protein expressed on the podocyte cell membrane [22]. The mother developed antibodies to NEP that crossed the placenta and induced MN in the fetus. These same antibodies were capable of transferring the disease to normal rabbits [22]. Although this observation was published less than 3 years ago, more such patients with both inherited and acquired NEP deficiencies have already been discovered, and the search for other similar antigens is underway [23].

These recent observations in MN raise several issues related to both recurrent and de novo MN in the allograft. Is it finally possible to characterize the disease-causing antibody in MN such that prospective recipients with the disease might be screened and not transplanted if the antibody were present, as is currently done to prevent recurrent anti-GBM antibody disease? Does the more common de novo MN in transplants occur specifically in recipients who lack a particular podocyte antigen (such as NEP) and who then respond to that antigen in the allograft? How common are such renal antigen deficiencies (not manifested by a clinical phenotype) in the general donor population? Will the future see high throughput screening for many kinds of nontransplant proteins in both donors and recipients to avoid mismatching for antigens that may have more nephritogenic potential for the recipient than HLA-type mismatches do?

C. Hemolytic-uremic syndrome

Like recurrent FGS, recurrent hemolytic-uremic syndrome (HUS) is an unfortunate clinical situation with a poor outcome. As many as 50% of patients transplanted with non-Shiga toxin-induced (non-STX) HUS develop recurrent disease within 30 days, and 90% of these patients lose the graft within 2 years [24]. Thus, similar to FGS, the etiology of the original disease has a bearing on the outcome of the transplant.

About 90% of cases of HUS are diarrheal diseases induced by Shiga toxin, usually *E. coli* o157:H7. About half of these patients develop some degree of acute renal failure, but recovery is the rule, transplantation is rarely required, and graft survival is above average in these patients [24]. However, in the remaining 10% of non–STX-induced HUS, the situation is different. These cases have multiple etiologies including pregnancy, drugs, and familial causes. Calcineurin drugs are important causes, and 10%-15% of transplant patients receiving these agents show some
evidence of HUS. The rate of development of ESRD in non-STX HUS is 50%-60% in most series, and treatment is generally ineffective [24].

What is new and of particular interest in HUS is the increasing realization that many cases of HUS are linked to abnormalities in complement-regulatory proteins [25]. Up to 40% of familial cases and 20% of sporadic cases of non-STX HUS are linked to either genetic deficiencies or mutations in the factor H (HF1) gene or polymorphisms in the protein [24]. More recently, other cases have been linked to abnormalities in membrane cofactor protein (MCP) [26]. Factor H is a circulating protein and MCP a cell-bound one. Factor H mutated at the hit point for C3b has reduced binding affinity for polyanion on the endothelial cell and therefore, fails in its normal function of preventing the C3b product of C3 activation from binding to the cell surface and initiating further activation of the alternative complement pathway and cell injury [27]. Mutations of MCP, a cell-bound complement regulatory protein with similar function, also have been associated with non-STX HUS [24]. It is, of course, likely that these discoveries represent only the tip of the iceberg that will quickly lead to more observations sure to clarify why certain settings are associated with development of HUS in some individuals and not in others.

As this story unfolds, it is also likely that we soon will be able to screen recipients for circulating regulatory protein deficiencies that will render them particularly susceptible to developing HUS, recurrent or de novo, in transplants and avoid placing grafts in such individuals or treat to prevent development of severe HUS in the graft. Interestingly, those who develop HUS as a consequence of an MCP deficiency do not appear to be at increased risk for HUS in the allograft, presumably because the MCP is a cell-bound protein provided in the donor kidney [24]. Of course, development of an alloimmune response to kidneys containing such a “foreign” protein is another likely, as yet undescribed, event that could also result in loss of MCP function and de novo HUS in the allograft. Unfortunately, at present, there is no available complement protein assay that will reliably screen for HF1 or MCP gene defects or mutations, and molecular analysis is required. However, this will likely change rapidly as the clinical utility of this information in transplantation becomes more widely appreciated.

Conclusions

Recurrent GN continues to be a significant clinical problem in transplant nephrology with an adverse impact on long-term graft survival. Improvements in immunosuppressive regimens that have diminished acute rejection have not reduced the incidences or severity of recurrent GN or the development of de novo GN in allografts and may have increased them. However, recent advances in defining the pathogenesis of 3 more-common recurrent diseases—FGS, MN, and HUS—have led to improved understanding of these diseases that should reduce their incidence and improve therapy. In FGS, the increasing role of inherited and acquired podocytopenies in producing the lesion has shifted attention away from putative permeability factors to other proteins that permit better classification and more rational therapies of this group of diseases. In MN, demonstration of an alloimmune underlying mechanism in the native disease should allow better screening of patients at risk of recurrence and better prevention of the more common de novo disease. In HUS, the recently recognized role of complement regulatory proteins in the pathogenesis of non-STX HUS, and in the susceptibility of the allograft to both recurrent and de novo HUS, should open new approaches to treatment of this common cause of graft loss.

References