Invited Comment

Recurrent glomerulonephritis following renal transplantation: an update

Jürgen Floege

Division of Nephrology and Immunology, University of Aachen, Germany

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Introduction

Based on the literature, recurrent disease is observed in 4–20% of the patients receiving a kidney transplant and will lead to graft failure in 2–5% [1–6]. In a large study of the University of Wisconsin/USA that evaluated 1557 patients, followed for a mean of 7.3 years after transplantation, recurrence of the underlying disease was observed in 98 cases, i.e. 8% [7]. More than 75% of these cases were recurrent glomerulonephritides (GN) and the present discussion will therefore be limited to these disease entities. However, before going into detail, it should be realized that the above data need to be treated with great caution for a number of reasons.

- Patient groups in many studies are small and variable.
- Studies have frequently followed patients for relatively short times after transplantation.
- In particular in countries with a restrictive renal biopsy policy, up to 50% of the underlying diseases are unknown.
- Recurrent GN is often not adequately classified and in particular electron microscopic examination of the graft biopsy is too infrequent.
- The differential diagnosis of transplant glomerulopathy, de novo GN, transplanted GN (i.e. GN transmitted from the donor) and real recurrence may be difficult.
- Definition of recurrent GN is variable (e.g. clinical vs histological recurrence).
- Systemic diseases such as diabetes mellitus and hypertensive renal damage can also 'recur' in the graft. In particular, hypertension both pre- and post-transplant significantly impacts on graft survival [8].

Most importantly, however, chronic renal graft dysfunction has a multifactorial origin and results from both immunological mechanisms, in particular chronic allograft rejection, as well as non-immune mechanisms such as hypertensive damage, hyperlipidaemia, cyclosporin nephrotoxicity etc. Usually, detailed clinical data and biopsy findings (in particular when examined by immunohistology and electron microscopy as well) can with some certainty allow differentiation between the relative contribution of dysfunction due to recurrent disease and other reasons, in particular chronic alloreactive damage. For example, clinically manifest recurrent IgAN is often associated with persistent microhaematuria and proteinuria exceeding 0.5 g/day as well as the demonstration of mesangio proliferative GN, i.e. not just recurrent mesangial IgA deposits, upon graft biopsy. Even when all such findings are present, however, the available data on recurrent IgAN need to be interpreted with the caveat that other mechanisms may have amplified recurrence-related graft damage in an additive or even synergistic manner. These considerations also imply that caution should be applied when interpreting studies in which few clinical data are provided.

Impact of recurrent glomerulonephritis on graft survival

The overall impact of recurrent GN on graft survival is controversial. In the study cited above [7], graft survival in patients with recurrent disease at 5 years after transplantation was 7% lower than in the entire population, and was 17% lower at 8 years. Similar findings have been reported by other previous studies [9]. Very recently, a large Australian study on 1505 patients with biopsy-proved GN in the native kidneys reported that graft loss due to recurrent GN \((n=52)\) was, after chronic rejection and death with a functioning graft, the third most frequent reason for loss of
Table 1. Overview of recurrence and recurrence related graft loss as reported in the literature

<table>
<thead>
<tr>
<th>Clinical recurrence rate</th>
<th>Graft loss after 5–10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>(% of transplanted patients)</td>
<td>(% of transplanted patients)</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>10–25 (≥ 50 histologically)</td>
</tr>
<tr>
<td>FSFGS</td>
<td>20–40</td>
</tr>
<tr>
<td>MPGN type I</td>
<td>20–50</td>
</tr>
<tr>
<td>MPGN type II</td>
<td>&gt; 80 (histologically)</td>
</tr>
<tr>
<td>Membranous GN</td>
<td>5–30</td>
</tr>
<tr>
<td>Anti-GBM nephritis</td>
<td>Exceptional</td>
</tr>
</tbody>
</table>

*Most important differential diagnosis is transplant-glomerulopathy; distinction can be made via glomerular IgG and C3 deposits in MPGN and electron microscopic findings, in particular subendothelial immune deposits [53].

Note 3-fold higher rate of de novo membranous GN [54].

the graft after 10 years [10]. In that study the 10-year incidence of allograft loss was similar among transplant recipients with biopsy-proved GN and among those with other causes of renal failure (n = 2159). The situation is completely different and the effect of recurrent GN becomes particularly relevant in those cases where a first graft has already been lost due to recurrence [11].

It would be beyond the scope of this short review to discuss the relevance of recurrent disease in detail for every GN entity. Based on data in the literature, the relevance of recurrence of the different disease entities is summarized in Table 1 [1–6,10,12–15]. Some specific aspects of individual forms of GN and new findings published in the last years include the following.

**Focal segmental glomerulosclerosis (FSGS)**

Recurrent disease is a very important clinical problem and usually occurs within the first 6–12 months after grafting. However, individual cases of apparent FSGS recurrence as long as 5 years after transplantation have been described [16,17]. Recurrence usually manifests in the form of heavy proteinuria, hypertension and/or loss of graft function. In patients with severe proteinuria in the course of FSGS recurrence, an increased risk of thromboembolic complications has been noted (as in other recurrent GNs with proteinuria exceeding 2 g/day) [18].

Risk factors for clinically relevant recurrence, the importance of which is additive, include young age, i.e. children, presence of mesangial proliferation in the original biopsy, rapid development of end-stage renal failure in the native kidneys, and a very short interval until recurrence of proteinuria and/or loss of graft function. In patients with severe proteinuria in the course of FSGS recurrence, an increased risk of thromboembolic complications has been noted (as in other recurrent GNs with proteinuria exceeding 2 g/day) [18].

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This later study, the central risk factor was young age and not the type of donor, as in the overall population, 84% of which were adults, the benefit of a living donor over a cadaveric donor was fully maintained [20]. Nevertheless, even in children with underlying FSGS, living related donor transplantation has been performed in small series with reasonable results [21,22]. Another recently recognized risk factor for recurrent FSGS appears to be white race, as African-Americans had significantly lower rates of graft loss attributed to recurrence [20].

Apart from supportive therapy with ACE inhibitors and/or angiotensin II receptor blockers, therapeutic options are increased immunosuppression and/or plasma exchange or immunoadsorption as recently outlined in the ERA guidelines on recurrent primary GNs [23]. In children, prophylactic plasmapheresis prior to transplantation appeared to be more effective in preventing recurrence than plasmapheresis after transplantation (FSGS recurrence in five of 15 vs four of six children, respectively) [24]. In those children with recurrence, eight of nine responded to the plasmapheresis [24] and individual cases have been maintained on plasmapheresis up to 6 years [25]. However, in adults with recurrent FSGS plasmapheresis appears less effective as compared to children and only five of 13 patients exhibited partial (n = 4) or complete responses (n = 1) [26]. Relapse after first successful treatment was reported in 10 cases. The median number of treatments received was less and the time from diagnosis to first treatment was greater for patients who relapsed. Early institution of treatment also appears important, since the presence of sclerosis on biopsy predicts treatment failure [17,27]. Consequently, early treatment after diagnosis with a regimen of three daily plasmapheresis treatments followed by six treatments on an alternate-day basis is recommended [26]. In other cases, patients have been maintained chronically on monthly plasmapheresis treatment [17].

The exact nature of the pathogenetic circulating factor(s) underlying rapidly recurrent FSGS [28–30] still remains elusive. Very recent data suggest that at least in some patients the circulating permeability-inducing factor may represent a novel protein or a family of small glycosylated proteins [31].
Recurrent FSGS needs to be distinguished from the pathological lesion of FSGS in the course of chronic allograft nephropathy. The latter, i.e. ‘de novo FSGS’ presents late after transplantation, in association with arteriolar hyalinosis and is a negative independent predictor of graft survival [32].

**Membranous glomerulonephritis**

No new data have been published since the large series (n = 30) described by Cosyns et al. in 1998 [13]. The actuarial risk for recurrence in that study was about 30% after 3 years and thereafter levelled. In those patients with recurrence, graft loss had occurred in half of them at 10 years. No risk factors for recurrence were identified. In a subset of the same patients, that was described earlier [33], three lymphomas were observed in the 19 transplanted patients with membranous GN as the underlying disease. Whether this represented a consequence of immunosuppressive treatment of the original disease could not be determined, but this observation implies that treatment of recurrent disease with intense immunosuppression might further aggravate the risk of malignancy.

**Mesangiproliferative (mesangiocapillary) glomerulonephritis (MPGN)**

In a recent Dutch study in patients with type I MPGN [12] high recurrence rates of up to 50% at 5 years were reported that frequently led to graft failure. Recurrence rates appeared to be highest in patients receiving a second graft after prior recurrent MPGN (recurrence in 4/5 patients). Apart from the time after transplantation, HLA B8DR3 and living related donor were identified as risk factors for recurrence, but both later factors need to be interpreted with caution given the low numbers of patients [12]. The high risk of graft loss in patients with recurrent MPGN type I was also noted in an Australian registry, where the risk of graft loss due to recurrent MPGN even exceeded that of recurrent FSGS [10]. Specific therapy for recurrent MPGN type I is not established, and at best, case reports on successful treatment with long-term cyclophosphamide [34] or plasmapheresis [35] are available.

Recently, a series of patients (n = 13) with type II MPGN (dense deposit disease) has been described [36]. In these patients, 11 of 13 had a histological recurrence within 14 months, which, however, was associated with other lesions (rejection, ischaemia or cyclosporin toxicity) in eight. Importantly, immunohistology and electron microscopy were usually required for the differential diagnosis. In three patients it was felt that recurrence was the sole cause of graft loss within the first 3 years after transplantation [36].

**IgA nephropathy (IgAN)**

Many studies are now available on recurrent IgAN (summarized in Table 2).

With respect to predictors of clinically relevant recurrent IgAN, most current studies suggest that it represents largely a function of time post-transplantation. The only other predictor that was identified may be young age of the patient [37]. At present it is controversial whether living related donor kidneys are at a higher risk of recurrence and graft deterioration than kidneys from non-related donors. In this respect, many studies have failed to detect a significant difference [37–39], one study was indeterminate [40] and others noted a negative impact of a living related donor on graft outcome [41–43]. However, even in the studies, where the risk was increased with living related donors, graft survival of living related and

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients (n)</th>
<th>Follow-up in the whole study population (mean and range, months)</th>
<th>Graft dysfunction/loss due to recurrence (%)</th>
<th>Follow-up in patients with graft dysfunction loss due to recurrence of IgAN (mean and range, months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odum et al. 1994</td>
<td>46</td>
<td>n.a. (3–183)</td>
<td>11/2</td>
<td>62 (32–75)</td>
</tr>
<tr>
<td>Kessler et al. 1996a</td>
<td>28*</td>
<td>73 (4–120)*</td>
<td>21/14</td>
<td>84 (43–119)</td>
</tr>
<tr>
<td>Frohnert et al. 1997</td>
<td>51</td>
<td>n.a. (&lt;3 – &gt;156)</td>
<td>19/6</td>
<td>n.a. (12 – &gt;144)</td>
</tr>
<tr>
<td>Ohmacht et al. 1997</td>
<td>61</td>
<td>54 (7–127)</td>
<td>23/16</td>
<td>67 (32–102)</td>
</tr>
<tr>
<td>Bungardner et al. 1998</td>
<td>54</td>
<td>61 (n.a.)</td>
<td>16/10</td>
<td>75 (n.a.)</td>
</tr>
<tr>
<td>Freese et al. 1999</td>
<td>104b</td>
<td>67b (11–159)</td>
<td>13/6</td>
<td>n.a.</td>
</tr>
<tr>
<td>Kim et al. 2001</td>
<td>89</td>
<td>60 (2–164)</td>
<td>n.a./2</td>
<td>n.a.</td>
</tr>
<tr>
<td>Andresdottir et al. 2001</td>
<td>79</td>
<td>66 (n.a.)</td>
<td>9/2</td>
<td>n.a. (13–145)</td>
</tr>
<tr>
<td>Wang et al. 2001</td>
<td>48</td>
<td>52 (18–155)</td>
<td>10/8b*</td>
<td>95 (n.a.)</td>
</tr>
<tr>
<td>Ponticelli et al. 2001</td>
<td>106</td>
<td>70 (12–120)</td>
<td>n.a./4</td>
<td>74 (12–120)</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td><strong>67</strong></td>
<td><strong>63</strong></td>
<td><strong>15/7</strong></td>
<td><strong>76</strong></td>
</tr>
</tbody>
</table>

*Only patients who received a transplant biopsy because of graft dysfunction or urinary abnormalities are included in the data shown. Five patients suffered from underlying Henoch–Schönlein purpura.
*Four patients suffered from underlying Henoch–Schönlein purpura.
*50% of the patients had living donors.
*Median and range.
*Cause of graft loss not specified.
*n.a., Not available.
non-related grafts was identical at 5 years and failed to reach a significant difference at 10 years [42,43]. In comparison to patients with other underlying GNs or non-GN disorders, patient and graft survival up to 10 years after grafting in case of an underlying IgAN is not different [10,37,39,40].

No immunosuppressive drug, including newer drugs such as mycophenolate mofetil (MMF) or rapamycin can prevent histological recurrence of IgAN [37]. However, some preliminary data suggest that MMF may affect the clinical course of recurrent IgAN [44]. Unfortunately, all other data available up to now on MMF in patients with underlying IgAN involve short-term follow-up and it will therefore take several years to establish the role of this potential new approach for the prevention of recurrent IgAN. Until then, we are left with more conventional approaches, in particular the use of ACE inhibitors, to prevent progression of renal failure in such patients [45].

In contrast to recurrent IgAN, much less is known of the course of Henoch–Schönlein purpura (HSP), considered by many to represent the systemic variant of IgAN, after renal transplantation. The data available to date suggest that recurrence of clinically relevant IgAN in patients with underlying HSP is similar to that observed in patients with underlying IgAN [46,47]. In other studies [40,48] comprising nine and 12 HSP patients, respectively, no clinically evident recurrence of IgAN or graft loss was noted even with follow-up to a mean of 13 years. The only large study published also suggests that delaying transplantation until 1 year after the disappearance of purpura has no effect on the recurrence rate [47].

Anti-GBM nephritis

No new data have been published recently. Renal recurrence appears to be rare (i.e. below 5%) as long as anti-GBM antibody titres are negative for 6–12 months prior to transplantation [15].

**Recommendations on how to follow patients with underlying glomerulonephritis after renal transplantation**

In view of the above, the following considerations should be taken into account when transplanting patients with underlying GN.

- Attempt to obtain an exact diagnosis of the primary disease wherever possible.
- Attempt to clarify causes of prior graft losses as thoroughly as possible.
- Possibly modify immunosuppression according to underlying disease (controversial).
- Closely follow patients peri- and post-operatively. Pathological laboratory findings should be clarified aggressively including graft biopsy where necessary.
- Living related donors should be evaluated with particular attention and may require a renal biopsy prior to donation in cases of potential familial disease (e.g. clinically unapparent familial cases of IgA nephropathy); in our policy, living related donors are acceptable in patients with membro-proliferative GN (types I and II), membranous GN, IgA nephropathy and anti-GBM nephritis. Living donors, even after an explicit discussion of the risk, should be accepted in a restrictive fashion in patients with FSGS and a high chance of recurrence, i.e. those patients with an age of less than 15 years, mesangiotrophic changes upon renal biopsy and/or duration between diagnosis and renal failure of less than 3 years. However, as noted above, living donation is not absolutely contraindicated in these cases and in children needs to be balanced against the problems associated with continued dialysis treatment.

- If a prior graft has been lost due to any type of recurrent GN in the past, living donation should be discouraged in general and reserved for exceptional circumstances, as the risk for a second recurrence and graft loss appears inappropriately high [11].

In conclusion, recurrent GNs are now the third most frequent cause of allograft loss at 10 years. With increasingly better transplant survival rates [49], for example due to better HLA-matching and/or better immunosuppression, the importance of recurrent GNs will continue to increase in the future [10, 50]. While epidemiological data have been accumulating for most of the individual GN types, information on therapy is still very limited. In patients with recurrent GN, no effect of the introduction of cyclosporin on the prevalence of recurrent disease has been demonstrated. Whether cyclosporin has led to a lower rate of graft loss due to recurrence is controversial [51]. There is no evidence to support the notion that bilateral nephrectomy prior to transplantation prevents recurrence; if at all, higher recurrence rates have been noted [52]. At present, in the vast majority of patients with recurrent GN therefore, no specific therapy has been established, with the possible exception of recurrent FSGS (see above), and only good supportive care, similar to that instituted in the primary diseases, can be offered. Given this situation, it is clear that multicentre studies on how to treat recurrent GN will be needed in the near future. In this respect, recurrent GN offers the unique opportunity of not only early but also preventive therapy.

**References**


