

# IgA Nephropathy in Renal Allografts-Recurrence and Graft Dysfunction

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With time after transplantation, the recurrence of IgA nephropathy (IgAN) becomes a relevant cause of graft dysfunction and failure. However, only limited information has been published regarding the related clinical and histological features. In this article, we review studies on recurrent IgAN in the English literature and describe our own clinical experience. The clinical and histological features related to recurrence are still indeterminate, but features associated with graft dysfunction include proteinuria, glomerulosclerosis, mesangial proliferation, glomerular crescents and interstitial fibrosis.

**Key Words:** IgA nephropathy, renal transplantation, recurrence, histology, proteinuria

Almost 30 years have been passed since the first report of recurrence of IgA nephropathy (IgAN) in a renal allograft. In 1975, Berger reported mesangial IgA deposition of allografts in 7 of 12 patients with IgAN as a cause of end-stage renal failure.<sup>1</sup> The patients had no or minimal glomerular changes, mild proteinuria and/or microscopic hematuria before, after or at time of diagnosis, and enjoyed good graft function 2 to 7 years after transplantation. This observation was confirmed later by the same author in a review which recruited more cases.<sup>2</sup>

Contrary to Berger's description of good prognosis in recurrent IgAN,<sup>1,2</sup> worrisome reports on the prognosis have been published since the mid 1990s.<sup>3-8</sup> Although chronic rejection still remains a

major cause of graft failure, recurrence of IgAN becomes a relevant cause of graft failure around five years after transplantation in some transplantation centers.<sup>8,9</sup> We can reasonably assume that IgAN recurrence will increase as graft survival period increases. There will be a concomitant increase of graft dysfunction and loss due to recurrent diseases.<sup>10,11</sup> However, only limited information has been obtained regarding factors related to recurrence and graft dysfunction.<sup>12,13</sup> The purpose of this article is to summarize observations on the clinical and histological features of recurrent IgAN reported in the English literature and to describe our experience in Yonsei University Medical Center.

## RECURRENCE OF IgAN IN RENAL ALLOGRAFTS

The recurrence rate of IgAN in renal allograft was between 13 and 65% in different series<sup>3-7,10,13-16</sup> and the mean time from transplantation to biopsy was 31-54 months (range: 0.3-213 months).<sup>4,7,10,13</sup> The different results may be explained by time or indication of biopsy and diagnostic criteria for recurrence (clinical vs. histological). In most of the studies, biopsy was taken more than 2 years post-transplantation and to reveal the causes of graft dysfunction and/or urinary abnormality. It could be assumed that the recurrence rate will increase if microscopic hematuria without graft dysfunction is included in biopsy indication<sup>17</sup> or protocol biopsy is performed. Clinical recurrence as depicted by urinary abnormality (microscopic hematuria or proteinuria more than 0.5 g per day that was not attributable to other causes) was 18.5

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months earlier than the histological recurrence reported by Ponticelli et al.<sup>13</sup> Clinical recurrence rate was generally lower than histological recurrence rate (Table 1).

### Clinical factors

No factors have been clearly associated with recurrence except for time from transplantation. Odum et al.<sup>3</sup> reported that the time to allograft biopsy or nephrectomy was 45.9 months versus 15.3 months post-transplantation in patients with and without recurrent IgA deposits, respectively, and that the difference was significant. However, time from transplantation was 39.8 months in recurrent patients and 33.9 months in non-recurrent patients by Kessler et al.,<sup>4</sup> and 54 months and 47 months, respectively, by Wang et al.<sup>20</sup> and these differences were not significant. Other clinical factors including rapid progression of original IgAN have been shown to have no predictive

value in recurrence in most studies (Table 2). Coppo et al.<sup>26</sup> reported that frequencies of macromolecular IgA (conglutinin IgA immune complexes and IgA-fibronectin aggregates) and IgA binding to type IV collagen were higher in the recurrence group, but had no predictive value in recurrence. Patients in the recurrence group showed higher proteinuria than those in the non-recurrent group.<sup>6,9</sup> Recently, Ponticelli et al.<sup>13</sup> reported that increased plasma creatinine and proteinuria at 6 months and age at transplantation were associated with the risk of IgAN recurrence. However, it is unclear whether proteinuria is a cause or result of IgAN recurrence. The role of cyclosporine has been disputed, and the role of mycophenolate mofetil or rapamycin on recurrence has not been settled.<sup>13,27</sup>

### Histological factors

To the best of our knowledge, there have been

**Table 1.** Recurrence of IgAN in Renal Allografts

No. of cases	Time to biopsy	Biopsy indication	Recurrence		Reference
			Clinical	Histological	
13	1 - 32 m	not described	38.5%	46%	Bachman et al., 1986 <sup>18</sup>
32		H, P or protocol biopsy		53%	Berger et al., 1988 <sup>2</sup>
46	45.9 m	prospective & retrospective		60.7%	Odum et al., 1994 <sup>3</sup>
71	39.8 m	graft dysfunction or abnormal urinalysis		46.4%	Kessler et al., 1996 <sup>4</sup>
53		H and P accompanied by renal dysfunction	26%	19%	Frohnert et al., 1997 <sup>5</sup>
61	65.3 m	not described	4.5%	23%	Ohmacht et al., 1997 <sup>6</sup>
61	31 m	H and/or P and graft dysfunction	29.5%		Bumgardner et al., 1998 <sup>7</sup>
79	13 - 145 m	P > 2 g/d, unexplained renal dysfunction	9%	53%	Andresdottir et al., 2001 <sup>19</sup>
90		H, P, creatinine elevation		44.2%	Kim et al., 2001 <sup>14</sup>
106	49 m	H, P, renal dysfunction, protocol biopsy		64.9%	Ponticelli et al., 2001 <sup>13</sup>
48	54 m	H or P with or without graft dysfunction		77.8%	Wang et al., 2001 <sup>20</sup>
75	67.7 m	P, gross H, renal dysfunction		40%	Choy et al., 2003 <sup>9</sup>

H, hematuria; P, proteinuria.

**Table 2.** Clinical and Immunologic Factors Which Have Been Studied in the Recurrence of IgAN in Allografts

	Related	Not-related
Type of donors (living vs cadaver)	15, 16, 21*	5, 7, 13, 14, 20, 22
Recipient age	13	7, 20
Race		7, 20
Gender		4, 7, 13, 20
HLA		
A2	20	9
B12		3, 14
B35	21, 23	3, 9, 19
DR4	21	3, 9, 14
ACE genotype		6
Time to end stage renal failure	3, 15	9, 13, 20
Immunosuppression	16, 24, 25	3, 4, 5, 6, 7

\*reference number.

no reports on histological factors influencing recurrence in native kidney.

### GRAFT DYSFUNCTION AND LOSS IN RECURRENT IgAN

Graft dysfunction was reported from 29% to 71%.<sup>3,5</sup> Graft survival was lower in patients with recurrence than in those without recurrence. The ten-year graft survival rate of recurrent IgAN in 2 large studies, one our own, was 66.5%<sup>14</sup> and 75%<sup>15</sup> and was not influenced by donor type. Compared to other renal diseases, graft survival of recurrent IgAN was reported to be better in the short-term (2 years),<sup>19,28</sup> not different at around 5 years<sup>7,14,29,30</sup> and lower at 12 years.<sup>9</sup> The major cause of graft loss in recurrent IgAN is chronic rejection.<sup>31,32</sup> Acute rejection rates of recurrent IgAN were lower<sup>19</sup> or similar to<sup>7,13,29</sup> those of other allografts, but no different from non-recurrent IgAN patients.<sup>13</sup>

### Proteinuria

Mild proteinuria is not rare in recurrent IgAN and even nephrotic syndrome can develop.<sup>33,34</sup>

Proteinuria is not only associated with graft dysfunction and failure,<sup>4,33</sup> but is also correlated with renal allograft histology.<sup>12</sup> Ponticelli<sup>13</sup> demonstrated that proteinuria (>1 g/day) at 6 months was an independent risk factor for graft failure in recurrent IgAN. He also reported preliminary treatment results with angiotensin converting enzyme inhibitors (ACEI) in 21 patients, showing a tendency of lower graft failure rate than that in patients without this treatment.<sup>13</sup>

### Immunologic factor

Graft survival decreased with better HLA-DR match in one study,<sup>7</sup> but there was no difference in others.<sup>20</sup> Lim et al.<sup>35</sup> proposed that IgA antibody to HLA antigen was associated with high graft survival in IgAN patients by blocking IgG antibodies or inhibiting cellular immune response.

### Allograft histology

Little has been reported about histological factors, which are responsible for or related to graft dysfunction in renal allografts with recurrent IgAN.<sup>12</sup> In a clinicopathological study of recurrent IgAN in 7 children, allograft biopsies showed an

increase of glomerular size, ischemia-related lesions, and thickening of the endothelium, other than specific findings of IgAN.<sup>36</sup> Glomerular crescents were associated with acute graft dysfunction and failure in the early post-transplant period,<sup>37-41</sup> but rarely beyond this period.<sup>18</sup>

## YONSEI EXPERIENCE OF RECURRENT AND POST-TRANSPLANT IgAN

### Recurrent IgAN

In our study of 90 grafts in patients with IgAN as a cause of end stage renal disease, the duration from transplantation to diagnosis was not significantly different between recurrence (43.4 months) and non-recurrence (34.4 months). However, cumulative histological recurrence rate (35%) at 5 years was increased to 44% at 10 years post-transplantation. HLA mismatch and donor type have been shown to have no predictive value in recurrence. Graft survival did not differ between patients with recurrence and those without. The ten-year graft survival rate in recurrent IgAN patients was 66.5% and was not influenced by donor type. Graft loss was reported in 4 of 19 grafts (21.1%) during a follow-up of more than 10 years. The causes of graft loss were chronic rejection and IgAN recurrence in 2 grafts each.<sup>14</sup>

Glomeruli in recurrent IgAN were enlarged or small and wrinkled. They showed a tendency of mesangial expansion compared to those in renal allografts without glomerulonephritis.<sup>42</sup> Regarding the relationship between proteinuria and graft histology, our preliminary study of 20 cases of recurrent IgAN showed that proteinuria at 3 g/day or more was associated with advanced glomerular and tubulointerstitial lesions.<sup>12</sup> When we expanded a patient pool to 27 cases and set the proteinuria level at 1 g/day, the mean percentages of glomerulosclerosis, the proportion showing mesangial proliferation, and the prevalence of mesangial IgG deposition increased in cases with higher proteinuria (unpublished data). Therefore, histological parameters of progressive IgAN in native kidney, including glomerulosclerosis, interstitial fibrosis and mesangial hypercellularity,<sup>21</sup> seem to be also effective with regard

to graft dysfunction in recurrent IgAN.

### Graft histology and dysfunction in post-transplant IgAN

IgAN developing after renal transplantation (post-transplant IgAN) includes glomerular disease having mesangial IgA deposits regardless of information on original disease. Recurrence was confirmed in less than 20% of the cases at the time of transplantation in our institution.<sup>43</sup>

Graft histologies of post-transplant IgAN were variable and not different from those of renal allografts without IgA deposits. In a study of 54 cases of post-transplant IgAN,<sup>43</sup> glomerular hypertrophy and segmental sclerosis were present and associated with proteinuria, which was in agreement with a study from Japan.<sup>44</sup> We assumed that segmental glomerulosclerosis was a manifestation of progressive renal injury, since biopsies showing segmental sclerosis also showed advanced tubulointerstitial fibrosis. We also observed the beneficial effects of ACEI on proteinuria in ten post-transplant IgAN patients.<sup>43</sup> ACEI treatment was reported to be beneficial in transplant patients with proteinuria including a study of post-transplant IgAN.<sup>44-47</sup> The use of ACEI may be expanded in post-transplant IgAN, as well as recurrent IgAN patients with proteinuria, unless tubulointerstitial lesion is advanced.<sup>45-47</sup>

We also looked for the significance of glomerular crescents. Although glomerular crescents were reported to be rare one year after transplantation in a Japanese study,<sup>44</sup> they were not rare in our study.<sup>43</sup> Four of 54 post-transplant IgAN patients showed crescents, which accompanied mild urinary abnormality. In another study, 71 patients underwent a renal allograft biopsy at least 6 months post-transplantation with indications of either creatinine elevation, proteinuria of 1 g/day or more, or microscopic hematuria. Crescents were observed in 10 patients (14.1%) and grafts failed in all 5 patients who had 30% or more crescents on allograft biopsy.<sup>48</sup>

In summary, the histological features related to graft dysfunction in recurrent and post-transplant IgAN include not only those described in native IgAN but also those findings related to nephron underdosing. More studies will be needed to

determine the clinical and histological factors able to predict disease progression and to establish strategies for early intervention for functional deterioration.

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