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IN FOCUS

Recurrent IgA nephropathy in the renal allograft: not a benign condition

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Primary IgA nephropathy (IgAN) patients usually represent ideal candidates for a renal graft, because they are often relatively young and exhibit little comorbidity. For this reason, they constitute a significant share of transplant patients; for example, 13% of all transplant patients in the ANZDATA system [1] have IgAN. It is well established that up to 60% of the patients will experience a histological recurrence of the disease, in particular if protocol biopsies are obtained [2, 3]. At present, there are no firm data to suggest that either risk stratification or prevention of IgAN recurrence is possible.

Although initially assumed to be a relatively benign condition with little impact on graft function [4], this view has changed considerably during the last few years as follow-up of such patients became continually longer after transplantation [5]. Recurrence-related graft dysfunction is rare before 3 years after transplantation, but thereafter recurrent IgAN becomes clinically relevant and significantly contributes to graft failure. At 5 years, 10–15% of all patients exhibit some recurrence-related graft dysfunction and ∼5% have lost their graft due to recurrence [5]. In our own study [6], we also noted that the impact of recurrent IgAN could have been diminished by the more rapid manifestation of chronic allograft nephropathy or due to other reasons for graft failure. Nevertheless, graft survival in the first years after renal transplantation is generally better than that of other transplant patients [5]. This may relate to the over-reactivity of the IgA system in IgAN with the occurrence of alloreactive IgA anti-HLA antibodies, which may be less pathogenic than IgG anti-HLA antibodies and thus result in less severe or fewer acute rejection episodes [7].

Up to 10 years after transplantation, neither patient nor graft survival differs between those patients with an underlying IgAN and patients with other types of non-diabetic primary renal disease [1, 8, 9]. However, after 10 years, matters seem to tip, and Choy *et al.* [10] were the first to report that at 12 years the graft survival became worse in IgAN patients than in controls. In this issue of NDT, Moroni *et al.* [11] extend these data by describing their single centre, 30-year experience in 190 Italian transplanted IgAN patients when compared with 380 non-diabetic controls. The median follow-up in both the groups was almost 10 years. Whereas patient survival was similar, the death-censored graft survival at 15 years was about 10% lower in IgAN patients when compared with controls (63 versus 72%). The latter appeared largely due to recurrent IgAN as graft survival in non-recurrent patients was similar to that of controls, whereas it was only 51% in the recurrent patients at 15 years. Finally, the authors describe that recurrence of IgAN appeared to have diminished between 1981 and 2010.

Why is the study of Moroni *et al.* [11] so notable? The key features of that analysis are the relatively large group of patients but in particular the extremely long follow-up. In addition, 60% of the patients received at least one graft biopsy during follow-up and 24% received two or more biopsies. Thus, even though

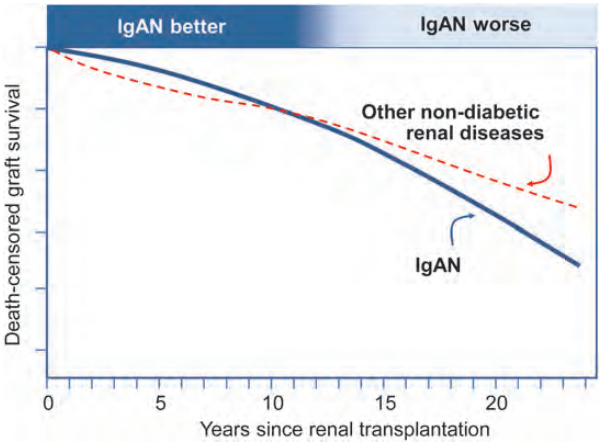

FIGURE 1: Impact of recurrent IgAN on the function of kidney allografts.

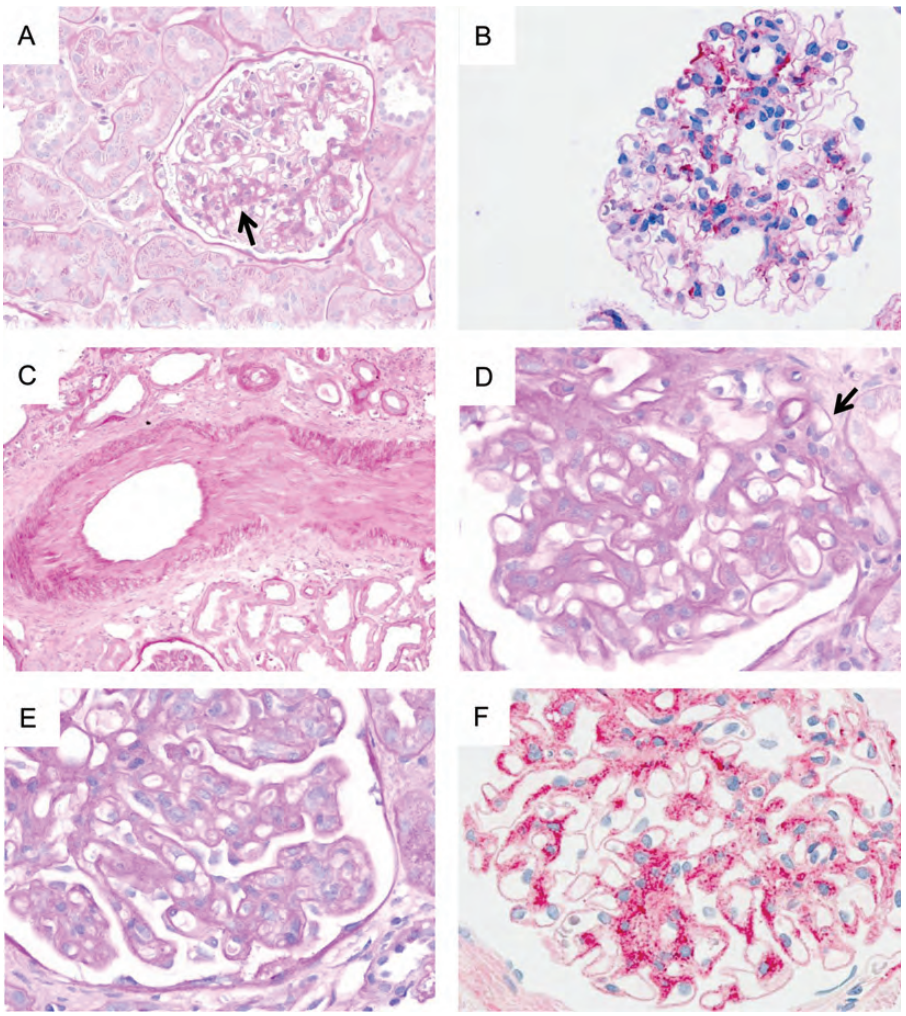

FIGURE 2: (**A**) Recurrent IgAN with slight segmental mesangial proliferation (arrow) and (**B**) IgA deposits in the mesangium. (**C**) Nephrosclerosis can lead to deterioration of renal function. (**D**) Focal segmental glomerulosclerosis (arrow) can be a consequence of IgAN as well as nephrosclerosis. (**E**) Transplant glomerulopathy may show mesangial proliferation and matrix expansion and (**F**) may be positive for IgA in the mesangium. 2 A, C, D, E: PAS stain; 2 B and (F) IgA detection by APAAP immunohistochemistry.

no protocol biopsies were available and clinical findings prompted biopsies, a large portion of the patients had some histological assessment. Furthermore, this is the first study to apply the IgAN Oxford classification [12, 13] to recurrent IgAN. Not surprisingly, worse histology scores were noted in those patients where IgAN recurrence led to graft loss as opposed to others with IgAN recurrence [11]. The study by Moroni *et al.* [11] thus further extends our knowledge of recurrent IgAN and supports the notion that the very long outcome is not as good as initially believed (Figure 1).

Again, other findings of the study by Moroni *et al.* [11] are nicely confirmatory of prior studies (reviewed in [5, 14, 15]): First, 8 of 42 patients with recurrence initially presented with isolated proteinuria and 4 of 42 with an isolated increase in plasma creatinine, i.e. haematuria is not universal in recurrent IgAN and in 7 of 42 all urinary abnormalities even regressed during further follow-up. Second, 50% of the grafts with recurrent IgAN were ultimately lost (about half of them assumed due to IgAN recurrence only and another quarter with at least a contribution of recurrent IgAN). Third, in particular, recurrence with crescents was associated with a high rate of graft loss, and fourth, recurrence was not different between kidneys of living and deceased donors. However, the study was not powered to detect small differences between these types of donors as only 36 (19%) of the grafts were from a living donor.

What are the limitations of the study by Moroni *et al.* [11]? The duration of the study period, i.e. 30 years, is the strength, but at the same time also a weakness of the study. In fact, the observation of the authors that the recurrence rate of IgAN seemed to decrease progressively has to be interpreted with great caution given the potential for uncontrolled confounders. The true incidence of recurrence in this study, as in many others before, is unknown, given that transplant biopsies were obtained only if clinically indicated. Furthermore, despite the relatively large-study population, the group of patients with documented recurrent IgAN is still small at 42 and this renders any firm statements on predictors of recurrence or recurrence-related graft loss difficult.

Another major limitation, which applies to all studies of this kind, is the difficulty of relating clinical to histological observations. Graft loss may be difficult to ascribe to recurrent IgAN (Figure 2A and B) when histology is not available shortly before a significant decline in renal function occurs. There are usually several morphological phenomena which contribute to loss of function; some are not explicitly mentioned in the current study. These morphological lesions may manifest simultaneously and result in a complex histopathological pattern. Thus, IgAN in non-transplant patients is often associated with obliterating nephrosclerosis (Figure 2C). The latter may also occur independently of IgAN in allografts and both may lead to focal segmental glomerulosclerosis (Figure 2D). Next, transplant glomerulopathy (Figure 2E) can have similar clinical features as recurrent IgAN. Transplant glomerulopathy may be accelerated by IgAN recurrence and both can lead to mesangial proliferation and IgA deposits (Figure 2F). The differential diagnosis can only be tentatively resolved by electron microscopy in some cases (Figure 3). It is not evident which criteria were used to perform EM in only one-third of the biopsies. Finally,

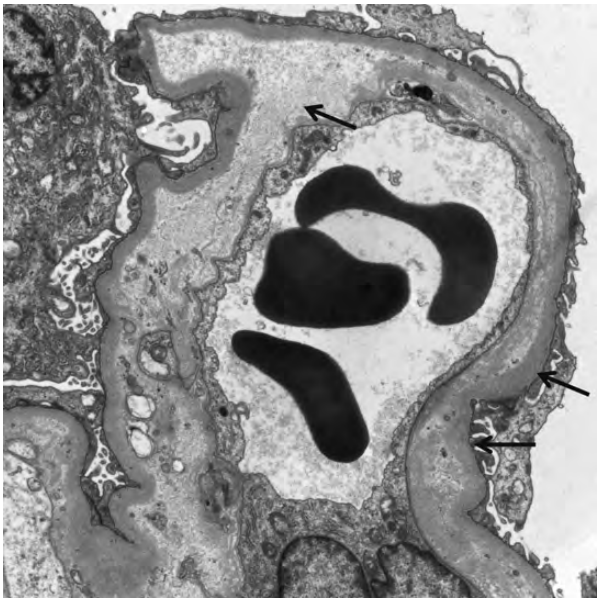

FIGURE 3: Electron microscopy can help in the differential diagnosis and demonstrate broad duplicated basement membranes and electrolucent subendothelial space (arrows) in transplant glomerulopathy, i.e. features not to be seen in IgA nephritis. Magnification ×5000.

tubulointerstitial fibrosis and atrophy do not aid in the differential diagnosis, as these are common sequalae of a large variety of insults to the transplant kidney. And last, an unusual feature of the study by Moroni *et al.* [11] is the high prevalence of crescents (crescents in at least 30% of glomeruli were present in 9 43 recurrent IgAN cases). In our experience, the vast majority of recurrent IgAN do not show segmental necrosis and/or extracapillary proliferation, suggesting that the Italian cohort is a very selected group of patients.

Finally, even though the study by Moroni *et al.* [11] is a relatively large case series, once again there is little insight as to how to treat recurrence of IgAN. Most patients with recurrence were given ACE inhibitors but more than half of them lost their graft. About 20% were also given methylprednisolone pulses and again more than half lost their graft. Moroni *et al.* also identified immunosuppression with less than three drugs as an independent predictor of recurrence. However, this was not significant ($P = 0.055$) and so far there has been little indication that the choice of immunosuppression affects IgAN recurrence in the allograft [5]. This is the reason why within the ERA-EDTA Immunonephrology Working Group, we recently initiated a registry on recurrent glomerular diseases with a particular focus on the treatment given and the outcomes (www.recurrentgn.net). Even though this will be a non-systematic collection, we sincerely hope that by gathering a large body of cases and treatment experiences, some common patterns evolve that can then form the basis for interventional studies and strategies aimed to ultimately reduce the impact of recurrent IgAN.

(See related article by Moroni *et al.* The long-term outcome of renal transplantation of IgA nephropathy and the impact of recurrence on graft survival. *Nephrol Dial Transplant* 2013; 28: 1305–1314.)

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IN FOCUS

End-stage renal disease epidemic in diabetics: is there light at the end of the tunnel?

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The world is facing an epidemic of diabetes, especially type 2 diabetes, which appears likely to endure for decades to come. Worldwide prevalence of diabetes was estimated at 2.8% in 2000. Between 2000 and 2030, the number of adults with diabetes is expected to increase by 50–70% in developing countries and by 20% in developed countries [1, 2]. In 2030, the prevalence of diabetes is projected to be 4.4% of the world population. The most important change in this prevalence appears to be an increase in the proportion of patients older than 65 years.

This change is related to the aging of the population, especially in developed countries [1, 2], and to the burden of obesity [3] that affects the prevalence of type 2 diabetes so strongly. Unfortunately, similar trends are also observed in