Renal transplantation: recurrence of original disease with particular reference to primary glomerulonephritis

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Introduction

The recurrence in the transplanted kidney of the disease leading to renal failure in the native kidneys has been a matter of concern since the very early days of transplantation. One year after their first successful living donor transplantation in identical twins, Murray and Harrison in 1955 raised the question of whether the transplanted kidney would become affected with the same condition that destroyed the recipient’s own kidneys [1]. The patient survived a further 7 years before dying from coronary artery disease, although it was recognized that some form of unspecified glomerular disease had developed. It is now 30 years since Hamburger and his colleagues described glomerular changes in well-tolerated transplanted kidneys [2]. Three years later, during the first international congress of the Transplantation Society which was held in Copenhagen, the glomerular lesions of transplanted kidneys were further described [3] and recurrent glomerulonephritis documented [4]. At about this time, membranous-type changes were first described in renal allograft [5]. Since these early reports there have been many anecdotal case reports, registry reports [6], and several review articles [7,8] dealing with the question of recurrent disease after renal transplantation.

The incidence of recurrent renal disease is difficult to determine from the published reports. In assessing published reports one has to be careful to differentiate recurrence from failure, as not all recurrent disease will lead to failure of the transplant. The reported incidence of recurrent glomerulonephritis in large transplant series varies from 6% to 27% [7] and this wide variation in frequency is most likely due to the case mix of the studied patients. In situations where the primary renal disease is known for certain the incidence of recurrence varies between 10% (membranous nephropathy) [9], 30% (focal segmental glomerulosclerosis [9], 50% (IgA nephropathy) [10], and 90% (mesangiocapillary glomerulonephritis type II) [8]. Thus, any figure for a heterogeneous series of patients is meaningless and will only reflect the distribution of primary renal disease as a cause of initial renal failure in the patients studied. A number of publications have reported on the incidence of recurrent disease as a cause of graft failure. This has been variably recorded as between 1% and 2% [6,7]. Again, from what is now known regarding the incidence of recurrence of particular forms of renal disease, this figure can only give an overall impression of the number of patients in any general programme likely to lose their kidney as a consequence of recurrent glomerular disease.

Diseases known to recur

Those diseases known to recur in the transplanted kidney comprise three main categories: metabolic diseases, vasculitic diseases, and glomerular diseases (Table 1). Of the metabolic-type diseases, insulin-dependent diabetes mellitus recurs with a frequency of virtually 100% [11], oxalosis 90% [7], amyloidosis 33%, and cystinosis 5%. Of the vasculitic-type diseases there are well-documented reports of systemic lupus erythematosus, Henoch–Schönlein purpura, and Wegener’s granulomatosis involving the transplanted kidney. It is however in the area of glomerulonephritis that most information is available with the frequency of recurrence varying from 10% to 90% depending on the initial disease.

Table 1. Conditions known to be associated with recurrence of disease in the transplanted kidney

<table>
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<tr>
<th>Metabolic diseases</th>
<th>Vasculitic diseases</th>
<th>Glomerulonephritis</th>
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<td>Diabetes mellitus</td>
<td>Systemic lupus erythematosus</td>
<td>IgA nephropathy</td>
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<tr>
<td>Oxalosis</td>
<td>Wegener’s granulomatosis</td>
<td>Membranous nephropathy</td>
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<td>Cystinosis</td>
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<td>Mesangiocapillary glomerulonephritis (Type I and II)</td>
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<td>Crescentic glomerulonephritis</td>
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The appearance of significant proteinuria and haematuria in transplanted patients suggests an underlying glomerular lesion. This could be transplant glomerulopathy, recurrent glomerulonephritis or de novo glomerulonephritis. Transplant glomerulopathy has been described as a focal and segmental thickening of glomerular basement membrane associated with a focal and segmental mild increase in mesangial matrix without any significant increase in mesangial cells. Immunofluorescence examination is frequently negative, but may on occasions show a fine granular deposition of IgM in the glomerular capillary walls. On electron microscopic examination there is an expansion of the subendothelial space of the glomerular capillary wall with a deposition of amorphous material; in general, no deposits are seen in this expanded space. In addition there may be vascular changes.

De novo glomerulonephritis is most commonly a membranous-type nephropathy. It was first reported by Murphy et al. in 1973 [17] who described two patients with transplant membranous nephropathy, in whom the native kidney disease had been pyelonephritis and hereditary interstitial nephritis. It is now recognized as the second most common cause of the nephrotic syndrome in a transplant patient. It presents clinically on average 21 months (range 3 months to 6 years) after transplantation [18]. On biopsy there is, in addition, frequently evidence of chronic rejection and it may well be that the membranous lesion is a manifestation of rejection. It is interesting to note, however, that the development of de novo membranous nephropathy is more likely to appear in well-matched grafts.

### Table 2. Criteria for diagnosis of recurrent disease

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<tr>
<td>1</td>
<td>Accurate histological diagnosis of initial cause of renal failure</td>
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<tr>
<td>2</td>
<td>Accurate histological diagnosis of pathology in transplanted kidney</td>
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</tbody>
</table>

### Criteria for the diagnosis of recurrent disease

To be certain that the clinical and functional abnormalities of a transplanted patient can be attributed to recurrent disease there must have been accurate diagnosis of the original kidney disease, accurate histological diagnosis of the pathology in the transplanted kidney and knowledge that the transplanted kidney was normal at the time of insertion (Table 2). To differentiate between recurrence and other conditions which may affect the transplant tissue, diagnosis is essential, and in many instances will require electron microscopy and immunofluorescence studies. In 1983 the EDTA Registry reported that 1.5% of graft failure could be attributed to recurrent disease [14]. However, in this report it was recognized that the diagnosis was often made on clinical and not histological criteria.

Two years later the EDTA Registry tried to improve on these figures by sending a specific questionnaire to those centres that had previously reported recurrent disease [6]. Of the 110 questionnaires that were sent only 66 were returned and of these in only 31 patients could recurrent disease be confirmed as a cause of the graft failure. This clearly indicates the extreme difficulty in undertaking any study in this area.

Many patients entering an end-stage renal failure programme do not have a biopsy undertaken and furthermore, a number of transplanted patients with urinary abnormalities and/or failing function similarly do not have a biopsy performed. In the report of O'Meara et al. [15] 295 patients receiving a kidney allograft were considered to have had a diagnosis of glomerulonephritis as a cause of their kidney failure. Histological confirmation, however, was available in only 156 patients (53%). In the study of Vangelista et al. [16] in only 59 of the 509 patients transplanted (12%) was a histological diagnosis made of the original renal disease. In the EDTA Registry of those patients reported as having glomerulonephritis only about 25% had the diagnosis confirmed histologically. In view of the significant number of patients who progress to end-stage renal failure without an accurate histological diagnosis being made, any estimate of the incidence of recurrence of disease is likely to be an underestimate.

### Differential diagnosis

The appearance of significant proteinuria and haematuria in transplanted patients suggests an underlying glomerular lesion. This could be transplant glomerulopathy, recurrent glomerulonephritis or de novo glomerulonephritis.
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The prognosis is poor with approximately 30% progressing to end-stage renal failure within 4 years.

Type II mesangiocapillary glomerulonephritis (dense deposit disease) is the most common form of primary glomerulonephritis to recur in grafted kidneys. Recurrence is usually clinically evident within the first year, but may occur early. I have seen histological evidence of recurrence of disease as early as 1 week following transplantation. In the study of Vangelista et al., three of four patients recurred at 4, 9, and 48 months after transplantation. Progression to renal failure is common, but has been variably reported. The Australia and New Zealand Registry reported failure in seven of 52 patients with recurrent disease (13%) [7], a figure very similar to that reported by O'Meara et al. [15] who documented four graft failures from 32 patients with recurrence (12%). These reports contrast with others in which four of six patients progress to renal failure [19]. There is thus considerable variation in experience and although progression is common, many patients can continue with urinary abnormalities for many years without any change in overall function.

Membranous nephropathy

The first case report of recurrent membranous nephropathy was published in 1975 [20]. This patient had biopsy-proven membranous nephropathy and 2 months after receiving a cadaveric transplant he developed massive proteinuria. A graft biopsy revealed changes identical with those of his native kidney biopsy. It is widely reported that the recurrence rate of membranous nephropathy is approximately 10%, although only some 24 case reports have been published. Clinically, patients can present with nephrotic range proteinuria from as early as 1 week post-transplant up to 25 months post-transplant. Biopsy changes have been detected as early as 8 days [21]. The prognosis is poor with approximately 50% progressing to end-stage renal failure in a variable period of time. There is a suggestion that membranous nephropathy is more likely to recur in identical twins and those transplanted from a related donor. As far as can be determined no satisfactory treatment exists, although attempts have been made with high-dose alternate-day steroid therapy in a regimen similar to that employed in idiopathic membranous nephropathy.

Focal and segmental glomerulosclerosis

Recurrence of focal and segmental glomerulosclerosis was first described by Hoyer et al. in 1972 [22] and since then there have been many further reports of recurrence. The frequency of recurrence is estimated to be approximately 30% [8], but it is accepted that this may be an overestimate. Vangelista et al. [16] reported recurrence in four of 15 patients at 4, 7, 19, and 31 months post-transplantation, and O’Meara et al. [15] identified recurrence in eight of 15 patients. The clinical presentation is with haematuria and significant proteinuria. The overall prognosis is poor with approximately 30% progressing to end-stage renal failure within 4 years.
that one should be cautious with respect to transplantation in patients with Alport’s syndrome.

Conclusion

In conclusion recurrent disease in transplanted kidneys is well recognized and the incidence of such recurrence is dependent upon the nature of original disease. Recurrence may appear remarkably early following transplantation, but may not become clinically apparent for many years. Mesangiocapillary glomerulonephritis type I, focal segmental glomerulosclerosis, and IgA nephropathy are the forms of primary glomerulonephritis that are most likely to recur in a transplanted kidney. Although progression to failure may occur, it appears that most recurrent disease is less aggressive than the disease affecting the native kidneys. In those conditions known to recur and lead to failure, living donor transplantation should not be undertaken.

References