Recurrent Diseases in the Renal Allograft

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ABSTRACT

Although recurrent diseases in the renal transplant are becoming increasingly recognized as graft survival continues to improve, they account for less than 2 to 4% of all allograft failures. The most frequent cause of recurrent disease is recurrent glomerulonephritis. Among the recurrent glomerulonephritides, type II membranoproliferative glomerulonephritis, immunoglobulin A nephropathy, and focal and segmental glomerulosclerosis have the highest rates of recurrence. The observation continues to be substantiated that recurrence rates are increased in recipients of living-related transplants, particularly in those whose original native kidney disease was focal and segmental glomerulosclerosis, immunoglobulin A nephropathy, membranous glomerulonephritis, Henoch-Schönlein purpura, or the hemolytic uremic syndrome. Additionally, although renal transplantation has been felt to be contraindicated in patients with Fabry's disease, more recent experience with improved patient survival and decreased morbidity would suggest that transplantation may be a viable alternative for this systemic illness.

Key Words: Recurrent disease, renal transplantation

Many of the same pathologic entities that affect the native kidney recur in the allograft. However, in addition to recurrent disease, there are other histopathologic changes that affect the allograft other than classic rejection. These include de novo disease and an entity called transplant glomerulopathy. The de novo diseases are predominantly glomerular in origin, and transplant glomerulopathy is felt to be the consequence of chronic rejection. In a review of Cheigh and colleagues (1), it was found that the most common cause of proteinuria after transplantation, which accounted for up to two thirds of all patients with posttransplant nephrotic syndrome in that series, was transplant glomerulopathy. In comparison, recurrent glomerular diseases accounted for ~25% and the rest, or ~10%, were due to de novo glomerulonephritis (GN).

The recurrent diseases can be categorized into the glomerular and nonglomerular forms, and the glomerular diseases can be further divided into primary and secondary glomerulopathies.

Transplant glomerulopathy, also called rejection glomerulopathy, deserves mention because it can resemble type I membranoproliferative GN (type I MPGN) histologically. This disorder is felt to be the consequence of chronic vascular rejection, because there is a significant relationship between presentiment to human leukocyte antigens (HLA) and the occurrence of glomerular lesions (2). It is felt that repetitive episodes of endothelial wall injury with microthrombosis lead to the reparative changes in the vessel walls (3). Early on, by light microscopy, the glomeruli show swelling of the endothelial and mesangial cells (4). In the advanced form, there are pronounced changes with reduplication of the basement membrane. These histologic changes in the glomeruli are indistinguishable from those of type I MPGN. By fluorescence microscopy, there is predominantly immunoglobulin M (IgM) and fibrinogen staining in the mesangial regions. By electron microscopy (Figure 1), there is reduplication of the basement membrane which is the result of mesangial interposition. The lamina densa is preserved but is separated from a subendothelial layer of new basement membrane material by a wide electron-lucent zone of finely fibrillar or flocculent substance. Early on, the vessels show swelling of the endothelium which is followed later by myointimal proliferation. In the advanced stages, intimal fibrosis replaces myointimal proliferation, which leads to obliteration of the luminal space (4). It has been the general experience that the majority of these allografts will eventually lose function.

In a recent review, Mathew (5) stated that recurrent
Primary Glomerulopathies

FSGS. It is difficult to establish an exact recurrence rate for FSGS because of the focal nature of the distribution of glomerular lesions and the associated sampling error in graft biopsies (Table 1). Additionally, this histologic finding may be the consequence of hyperfiltration injury due to a reduction in nephron mass or the result of earlier episodes of focal glomerular proliferation or necrosis.

The overall recurrence rate is ~20 to 30% with a range of 20 to 100% in various series (1,2,7,9,17-25). However, there is a distinct subgroup of patients with a recurrence rate of ~50%. These individuals tend to be younger, usually less than 20 yr of age, and have had a malignant clinical course, with the interval from diagnosis of FSGS to end-stage renal disease (ESRD) being less than 3 yr (8,18,22). In comparison, recurrence rates in patients whose interval from the onset of the nephrotic syndrome to ESRD is greater than 3 yr, have a recurrence rate of 10 to 20% (22). Moreover, once there is a recurrence in the first allograft, the risk for recurrence in the subsequent allograft is enhanced (26,27) and may be as high 75% (24). Histologically, there is typical segmental glomerular sclerosis with hyalinosis. These lesions may be preceded by a focal and segmental proliferative lesion (28), possibly of the epithelial cells (29), which is later followed by focal and segmental scars.

Clinically, these patients usually present with nephrotic range proteinuria which can occur immediately posttransplant; graft loss is generally seen in about 30 to 40% of patients (17-20,22). This is in contrast to patients with de novo FSGS who usually develop proteinuria 3 months after transplantation and generally have been noted to have better graft survival (17). Another factor which has been noted to increase the likelihood of recurrence and graft loss is mesangial proliferation, especially if this is a dif-
TABLE 1. Recurrent primary glomerulopathies

<table>
<thead>
<tr>
<th>Recurrence Rate</th>
<th>Graft Loss</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSGS</td>
<td>20 to 30%</td>
<td>30 to 40%</td>
</tr>
<tr>
<td>Membranous GN</td>
<td>3 to 7%</td>
<td>Rare</td>
</tr>
<tr>
<td>Type I MPGN</td>
<td>20 to 30%</td>
<td>30 to 40%</td>
</tr>
<tr>
<td>Type II MPGN</td>
<td>&gt;80%</td>
<td>10 to 20%</td>
</tr>
<tr>
<td>lgA nephropathy</td>
<td>~50%</td>
<td>~10%</td>
</tr>
<tr>
<td>Anti-GBM nephritis</td>
<td>~12%</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Fuse process, in association with typical lesions of FSGS in the native kidney (20,23,24).

There is no consistently beneficial therapy for recurrent FSGS. An 8-wk course of cyclophosphamide was not found to be helpful in a single patient (18). Plasmapheresis in concert with dipyridamole administration in a patient with a second recurrence stabilized graft function (30). The graft was still present at 49 months, whereas the first was lost at 30 months after transplantation (30). Plasma exchange was attempted on two pediatric patients with recurrent FSGS between 1 and 6 months posttransplantation which apparently led to a remission in both patients (31). In a 19-yr-old female with recurrent FSGS, plasma exchange decreased the proteinuria from 10 to 1 g and stabilized graft function (32). However, plasmapheresis has not been found by others to be beneficial (18). Finally, with the use of meclofenamate, a nonsteroidal anti-inflammatory agent, in a dose of 300 mg/day in a single patient, proteinuria declined from 10 g to ~2 g and allograft function stabilized. The investigators suggested that meclofenamate may act by altering glomerular hemodynamics or affecting capillary wall permeability (33). Although there are reports of partial remission of the nephrotic syndrome secondary to FSGS with the use of cyclosporin A (CsA) (34,35), generally, CsA has not been found to prevent the recurrence of FSGS after transplantation (19,36–39).

The current recommendation in patients with a high risk for recurrence, including those with a malignant course and those with a prior history of recurrence in an earlier allograft, is to avoid the use of an allograft from a live donor. Recurrence should not preclude an attempt at cadaver transplantation, because not all patients will develop recurrent disease (40) and universal graft loss is not the rule. Some also suggest that if a first graft is lost to recurrence, a second transplant (which should be cadaveric) should be delayed for 1 to 2 yr, presumably to allow for disappearance of circulating nephritogenic factors; however, this is purely speculative.

Membranous GN. Recurrence of membranous GN is relatively rare with an incidence of 3 to 7% (5,41), although rates of 20% (9) and 57% (7) have been reported. It accounts for 25% or less of all posttransplant membranous GN (41,42).

Clinically, most patients present with nephrotic range proteinuria. Because of the small number of patients with recurrent membranous GN, it is difficult to provide an accurate estimate of graft loss. Although, graft loss appears to be rare (25), some report graft loss as high as 30% (42). Mathew (5) reported that, of 13 evaluable grafts, 8 have failed, although it was difficult to exclude the role of rejection in these patients. In contrast, patients with de novo membranous GN usually have the onset of proteinuria at an average of 18 months posttransplantation (41). However, patients with de novo membranous GN may also experience graft loss rates of up to 50%; again, it is difficult to exclude the role of rejection in some of these patients (43,44).

There is also the suggestion from the literature that patients with HLA-identical living-related transplants are at a higher risk for recurrence (41,45,46) and that recurrence occurs earlier, usually in the first 1 to 3 months, when compared with those who receive cadaver grafts, where the onset of proteinuria is seen at 7 to 25 months (41). It is, therefore, suggested that living-related transplants should be used
with caution in these patients. With regard to treatment, there seems to be no benefit with additional administration of steroids (41).

**Type I MPGN.** Type I MPGN has a recurrence rate of ~20 to 30% (5,25,47) but may be as high as 40 to 70% (7,8). Some believe that these reported rates may actually represent an overestimate because the histology can resemble transplant glomerulopathy. Additionally, because this is a descriptive diagnosis, secondary causes of MPGN which have been described with native kidney disease should also be kept in mind.

Histologically, on light microscopy, classic double contours of the GBM are observed. With electron microscopy, there are electron-dense subendothelial deposits and new basement membrane formation due to mesangial interposition. It has been suggested that glomerular changes which appear to be more severe and are disproportionate to the interstitial and vascular pathology (47), as well as the presence of glomerular crescents and subendothelial dense deposits (Figure 2), argue for the presence of recurrent type I MPGN rather than transplant glomerulopathy.

Clinically, patients usually present with proteinuria or hematuria or both. The C3 level in the serum is not helpful in the diagnosis or prognosis of the disease (47,48). Approximately 28 to 42% of patients with recurrent type I MPGN will lose their allograft (7,8). There is no known beneficial therapy but, in one patient, plasma exchange was shown to decrease the recurrent exudative and proliferative changes and to induce a remission (50).

**IgA Nephropathy.** IgA nephropathy, which was the most common cause of glomerular disease leading to graft failure in Australian (5), has a recurrence rate of about 50% and a reported range of 20 to 75% (7-9,15,25).

Clinically, the usual presentations are microhematuria and proteinuria. It has been noted that recurrence is more common in allografts from living-related donors (15,16,51). Bachman et al. noted a recurrence rate of 83% in patients receiving a living-related transplant (15), and there may be an increased susceptibility with certain HLA, particularly B35 and DR4 (15,16). It has also been noted that patients with recurrence of their disease may have higher titers of IgA rheumatoid factors (51). Graft loss is generally noted to occur in less than 10% of patients. Therefore, despite the high recurrence rate, living-related transplants are not discouraged because graft loss is minimal. However, there is one report of probable transmission of IgA nephropathy from a living-related donor which progressed to graft failure; a subsequent second living-related graft, initially free of IgA deposits, also progressed to graft failure (16).

The introduction of CsA was felt by one transplant center to decrease the incidence of recurrent IgA nephropathy from 50 to 16% (37) whereas others have found no impact of CsA (38,52).

**Anti-GBM Disease.** If defined as the presence of linear IgG staining of capillary walls on fluorescence microscopy, then anti-GBM disease recurs at a rate of ~50% (5). However, only 25% of patients with histologic recurrence will have clinical nephritis. Interestingly, Cameron reported no recurrence in five cadaver kidneys grafted in four patients (25). The low
Incidence of recurrence was felt to be the result of delaying transplantation until anti-GBM antibodies had subsided.

Clinically, patients usually present with proteinuria and hematuria. Some will have spontaneous resolution of nephritis, and graft loss is rare (5,25). To minimize recurrence, the recommendation is to monitor circulating anti-GBM antibodies and, if antibody levels are undetectable over a 6- to 12-month period, it is safe to proceed with transplantation.

Idiopathic Rapidly Progressive GN (RPGN) or Idiopathic Crescentic GN. It is difficult to report rates of recurrence in this disorder because the literature experience is limited and examples of crescentic GN that were secondary to poststreptococcal GN, anti-GBM nephritis, or MPGN were not excluded in earlier reports (5,25). However, recurrences have not been reported (5,53) and, in one patient, led to graft loss (5).

Secondary Glomerulopathies

Henoch-Schöenlein Purpura. The rate of clinical recurrence of Henoch-Schöenlein purpura is probably less than 10 to 15% (54,55) (Table 2). Those patients with clinical recurrence including purpura and renal involvement had evidence of active disease within 8 to 18 months of allograft placement (54). Histologic recurrence with mesangial hypercellularity and mesangial IgA deposits, however, may be seen in ~30% of patients (25). In children, (histologic) recurrent rates as high as 75 to 88% have been reported (8,55) which have been noted to occur more frequently in recipients of living-related transplants (55).

Overall graft loss is ~10 to 20% but may approach 40 to 50% if histologic recurrence is accompanied by proteinuria or hematuria or both and if purpuric skin lesions are present (25,54,55). It is currently advised to wait at least 6 to 12 months, perhaps up to 2 yr, after the disappearance of purpura, before attempting transplantation.

Lupus Nephritis. In the early days of renal transplantation, it was feared that this prototype immune complex disease would recur frequently and lead to extensive graft loss. Experience, however, has shown that recurrence is rare, notably less than 1% (5,25,56), with only a few documented cases in the literature (57–61). This has supported the notion that once ESRD is reached, these patients have "burnt out" disease.

In those individuals with recurrence, clinical manifestations which occurred ~1 to 6 yr posttransplantation included a malar rash, Raynaud's phenomenon, and, usually, proteinuria of 1 to 3 g. In most patients, there may be an elevation in antinuclear antibody and anti-DNA titers, as well as depression of the complement levels. Allograft biopsy in most patients has demonstrated mesangial proliferative disease (57,58). In one case, the initial biopsy showed membranous GN which transformed to diffuse proliferative GN on repeat biopsy 6 months later (61). Treatment alternatives have included pulse steroids, which in one patient improved the serology and sta-

### TABLE 2. Recurrent secondary glomerulopathies

<table>
<thead>
<tr>
<th></th>
<th>Recurrence Rate</th>
<th>Graft Loss</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henoch-Schöenlein purpura</td>
<td>10 to 15%</td>
<td>10 to 20%</td>
<td>Mesangial IgA deposits seen in ~30%; graft loss with both renal/skin involvement</td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>&lt;1%</td>
<td>None</td>
<td>Recurrences successfully treated with steroids or plasmapheresis/chlorambucil</td>
</tr>
<tr>
<td>HUS</td>
<td>13 to 25%</td>
<td>40 to 50%</td>
<td>Use living related transplant and CsA with caution</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>100%</td>
<td>&lt;5%</td>
<td>Simultaneous renal/pancreas transplants may prevent diabetic renal lesions</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>5 to 30%</td>
<td>?</td>
<td>Overall high morbidity and mortality due to infections, cerebrovascular accident, cardiac amyloid disease</td>
</tr>
<tr>
<td>Wegener's granulomatosis</td>
<td>Reported</td>
<td>?</td>
<td>Recurrences successfully treated with cyclophosphamide and steroids</td>
</tr>
<tr>
<td>Essentially mixed cryoglobulinemia</td>
<td>?50%</td>
<td>?</td>
<td>Recurrence may occur despite clinical and serologic quiescence before transplantation</td>
</tr>
</tbody>
</table>
bilateral allograft function but did not affect the persistent proteinuria (57). Another treatment regimen consisted of a combination of plasmapheresis and chlorambucil which was able to stabilize graft function (58). In the patient who developed diffuse proliferative GN, monthly i.v. cyclophosphamide therapy was initiated when renal function deteriorated (61).

It has been suggested that in addition to clinical quiescence, serologic parameters of disease activity (antinuclear antibody, anti-DNA, and complement levels) should be minimal in order to prevent recurrence (59). In a case report, a patient with ESRD and clinically active disease (elevated anti-DNA and low C3 and C4 levels) was given CsA (6 mg/kg) and steroids while on hemodialysis (62). This therapy induced quiescence, and the patient was then successfully transplanted 4 months later (62).

HUS. Hemolytic uremic syndrome (HUS) has been associated with a variety of conditions including viral infections, pregnancy, malignant hypertension, systemic sclerosis, acute renal injury, and complement levels (63-65) although, in recipients of living-related transplants, the University of Minnesota found a recurrence rate of 50% (66). The disorder is characterized by intravascular coagulation which may be due to a primary intravascular coagulopathy leading to endothelial damage or primary endothelial damage leading to intravascular coagulation. Remuzzi and colleagues (67) have shown that some patients and their family members have decreased or absent plasma factor(s) which stimulate endothelial prostacyclin synthesis. Prostacyclin is a potent inhibitor of platelet aggregation, and its absence favors thrombosis. In addition, the ability of cyclosporine to favor synthesis of eicosanoids which promote thrombosis (68) has led to the suggestion that cyclosporine may increase the risk of recurrence (5,66,69). Cyclosporine has clearly been associated with de novo HUS/thrombotic thrombocytopenic purpura in bone marrow (70), liver (71), and renal allograft (72) recipients. Although it has been advised that CsA should be used with caution in patients whose original kidney disease was due to HUS, there are only a few (less than five) reports in the literature of recurrent HUS possibly precipitated by the use of CsA (5,65,66,69). In addition, the use of antilymphocyte globulin (ALG) is felt to be a potential risk based on data from the University of Minnesota group that described a substantial number of recurrences in patients who received ALG (66).

Clinically, patients present with microangiopathic hemolytic anemia, consumptive thrombocytopenia, and renal failure. It is difficult to provide an accurate rate of graft loss in this disorder. The group with the largest experience, the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry, reports that 3 of 27 patients with recurrent HUS lost their graft for a failure rate of ~10% (5). Culmination of other centers’ experience and various case reports suggests a higher graft loss rate of ~40-50% (63,64,66,73-77).

On the basis of these findings, a possible approach to the management of these patients includes the following: (1) one should use living-related transplantation with caution because of the possible familial inheritance of a prostacyclin synthesis abnormality (66). (2) One can attempt cadaveric renal transplantation with CsA immunosuppression. Additional measures to prevent recurrence include the indefinite use of low-dose salicylates and dipyridamole (66) and avoidance of the use of ALG and oral contraceptives (63,74). (3) In patients who develop recurrence, acute therapy with plasma infusions and plasma exchange which can be successful (64,75-77) should be attempted. (4) One should avoid the use of CsA if the first transplant was associated with rapid recurrence of HUS; an alternative approach with these patients would be the use of a higher dose azathioprine (3 mg/kg) or perhaps newer immunosuppressive agents (e.g., FK-506).

Diabetes Mellitus. Diabetes mellitus is the most common systemic disorder that leads to ESRD. In almost 100% of allografts, there will be recurrence of GBM thickening and mesangial expansion 2 yr beyond transplantation (78,79) and hyalinization of afferent and efferent arterioles by 4 yr (80). However, the typical nodular intercapillary glomerulosclerosis is rarely seen in these patients (81,82).

The mechanism for recurrence of diabetic nephropathy has not been fully elucidated. In studies examining the development of diabetic nephropathy in native kidneys, three pathogenetic theories have been proposed: genetic, metabolic, and hemodynamic factors (83). The genetic theory proposes that the development of microvascular complications is related to a genetic predisposition of the individual. Certain HLA phenotypes, notably DR4, B8, and B15, have been associated with nephropathy. With the metabolic theory, glycemic control either with exogenous insulin replacement or islet cell transplantation is felt to play a major role in the genesis of the disease. It has been demonstrated that strict glycemic control normalizes the glomerular filtration rate in insulin-dependent diabetics who were treated with an insulin pump compared with those in the conventional treatment group (84). Proponents of the hemodynamic theory state that changes in renal hemodynamics including increase in renal plasma flow and transcapillary hydraulic pressure in the glomerulus lead to diabetic kidney disease (85).
In the renal allograft, recurrence of diabetic nephropathy has been shown to be related in part to better glycemic control because patients who received simultaneous renal and pancreas transplants did not develop these glomerular and arteriolar lesions (78,86). There have been no studies to date addressing the role of hemodynamic alterations in the recurrence of disease. Clinically, most patients present with proteinuria and a slow decline in allograft function over a period of many years, with graft loss seen in the second decade posttransplantation in less than 5% of patients (87).

Amyloidosis. The largest series of patients with ESRD due to amyloidosis was reported by Pasternak and colleagues in 1986 (88). They compared the results of transplantation in 45 patients with amyloid with those in matched control transplant patients. The majority of patients, 42, had secondary amyloidosis due predominantly to rheumatoid arthritis whereas the rest had primary amyloidosis. There were a large number of deaths in the amyloid group (3-yr patient survival of 50 versus 80% in the control group) due predominantly to infectious and cardiovascular complications. However, if one looked at the 3-yr graft survival, and excluded deaths, the rates were comparable (53% in amyloid patients and 49% in controls), indicating that transplantation is a viable alternative for patients with ESRD secondary to amyloidosis. In this series, tissue specimens from grafts were available in 31 patients. Typical amyloid deposits were seen in 7 of 31, for a recurrence rate of ~20%; there was graft loss in 2 of these patients (2 of 7 or ~30%). In the ANZDATA Registry series, the recurrence rate was ~33% with trivial graft loss (5), whereas an earlier report quoted a recurrence rate of ~5% (89). In the latter review, patients with amyloid had a very high mortality rate due to sepsis, cerebrovascular accidents, cardiac amyloid disease, and viral infections (89).

TABLE 3. Recurrent nonglomerular diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Recurrence Rate</th>
<th>Graft Loss</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxalosis</td>
<td>90 to 100%</td>
<td>Majority</td>
<td>Improved success rates with renal/liver transplantation</td>
</tr>
<tr>
<td>Cystinosis</td>
<td>~10%</td>
<td>Rare</td>
<td>Recurrence with minimal impairment in graft function</td>
</tr>
<tr>
<td>Fabry's disease</td>
<td>Rare</td>
<td>?</td>
<td>Recent reports of improved patient survival</td>
</tr>
<tr>
<td>Sickle cell nephropathy</td>
<td>Rare</td>
<td>?</td>
<td>Recurrences observed in those with a malignant course</td>
</tr>
<tr>
<td>PSS</td>
<td>?</td>
<td>?</td>
<td>Small risk for development of anti-GBM disease</td>
</tr>
<tr>
<td>Alport's syndrome</td>
<td>Rare</td>
<td>Rare</td>
<td></td>
</tr>
</tbody>
</table>
macytic interstitial infiltration with tubular cast formation (96) or fibrillar crescentic GN (97). There has been impaired graft function in the latter entity.

Macroglobulinemic nephropathy has been reported to recur with IgM and lambda light chain staining in association with diffuse mesangiocapillary changes, but the histopathologic alterations were not felt to affect allograft function (98).

Examples of transplantation in patients with ESRD due to light chain nephropathy or light chain deposition disease with or without detectable serum monoclonal proteins have been described (99–102). Recurrent disease has been reported in six patients (99,101,102) which led to graft loss in two patients (99,102).

Renal transplantation has also been reported in four patients with ESRD due to fibrillary GN (103,104). Recurrence, which was noted in two patients, led to graft failure in one (C. Alpers, personal communication) and probably also in the second patient (104).

Nonglomerular Disorders

Oxalosis. Oxalosis is a metabolic disorder resulting from an inborn error in glyoxalate metabolism, leading to excessive oxalate synthesis and excretion (Table 3). The end result is systemic oxalate deposition and renal failure. The management of renal failure is even more problematic because oxalate overproduction continues, and, in the presence of renal failure, there is oxalate retention which may lead to potentially lethal oxalosis. Hemodialysis and peritoneal dialysis can remove the oxalate anion but generally cannot keep up with production, and the patient continues with progressive oxalosis.

The early transplant experience was disappointing because recurrence occurred in almost all patients and led to allograft loss in the majority (5,89). This usually occurred in patients who did not undergo a vigorous dialysis regimen before transplantation to deplete the oxalate metabolic pool and in those who experienced primary nonfunction or rejection episodes. In some patients, the administration of high-dose pyridoxine (500 to 1,000 mg daily) has been shown to help maintain allograft function (105,106). Pyridoxine functions as a coenzyme in the conversion of glyoxalate to glycine; thus, pyridoxine could decrease the glyoxalate pool which is the immediate precursor to the oxalate pool.

However, currently, there are certain manipulations which may make transplantation more successful. These include: (1) early transplantation when glomerular filtration rate approaches 20 mL/min/1.73 m² to minimize the effect of oxalate retention, (2) aggressive preoperative dialysis to deplete the oxalate metabolic pool, and (3) maintenance of high rates of urine flow and avoidance of primary nonfunction and rejection episodes (107). The simultaneous or sequential placement of liver and renal allografts has improved success rates (108–110) because the liver provides the source of the missing enzyme that leads to oxalate overproduction.

Cystinosis. Cystinosis is a disorder which results from an inborn error of sulfur metabolism and usually affects the pediatric population. The biochemical defect leads to accumulation of cystine crystals in the renal interstitium leading to tubular atrophy, glomerular sclerosis, and calcific degeneration of tubules. Recurrence is seen in ~10% (5) of transplanted patients with minimal impairment of graft function (111). Transplantation is the recommended or preferred mode of treatment of ESRD in children with cystinosis (89,112).

Fabry’s Disease. Fabry’s disease is also due to an inborn error of metabolism. The biochemical defect results from a deficiency of the enzyme, α-galactosidase, leading to accumulation of glycosphingolipids which leads to renal failure. The early transplant experience was disappointing (89,113). Although recurrence of the disease in the graft was rare, patient mortality was high. Many of these patients died of sepsis, pulmonary hemorrhage, and thrombosis (89). Initially, it was hoped that the transplanted kidney would provide the source of the missing enzyme but this was not observed (114). However, more recently, there are reports of successful transplantation in these individuals (115–117) with a lower incidence of infectious complications (117). Likewise, according to the Collaborative Transplant Study, as of March 1990, 21 patients with Fabry’s disease were found to have a 3-yr graft survival of 80% (G. Opelz, personal communication). Therefore, the more recent experience may change the currently stated recommendation that transplantation should be withheld from patients with this disorder.

Sickle Cell Disease. There is a paucity of literature on renal transplantation in patients with sickle cell disease. The largest single center experience with eight patients was reported from the University of Alabama at Birmingham (118). Only two of eight patients had functioning allografts beyond 1 yr; one of the patients died, and the other one had chronic rejection. In four patients, the allografts were lost because of sickling. It was noted that the improvement in the hematocrit after transplantation may have contributed to the sickling episodes. Although the experience of that center has been dismal, cumulative data from other centers have shown that as many as 67% (23 of 34) of these allografts function beyond 1 yr (119). Therefore, it is difficult to give an absolute recommendation with regard to renal replacement therapy in these patients.

In a single case report, recurrent sickle cell neph-
ropathy was described. The biopsy showed prominent hemosiderosis as well as chronic ischemic damage, moderate interstitial fibrosis, and atrophy; the latter changes, however, may also be due to chronic rejection (120).

PSS. There are a few reports of transplantation in patients with ESRD due to progressive systemic sclerosis (PSS). On the basis of cumulative experience, the following is known: (1) the highest patient survival, whether dialysis or transplantation was the mode of replacement therapy, was noted in those individuals who have had bilateral native nephrectomies usually to control severe hypertension (121–127), and (2) the two patients with recurrence (126,127) [out of a total of 10 patients with ESRD secondary to PSS who underwent renal transplantation] had a malignant course. The time interval from the onset of PSS to transplantation was less than 1 yr (4 and 10 months, respectively). Recurrence was evident at 2 and 3 months after transplantation. Whereas the vascular changes of mucoid intimal thickening of the interlobular arteries and fibrinoid necrosis in the glomeruli may be difficult to differentiate from acute vascular rejection, the presence of antinuclear antibodies eluted from both of these grafts was felt by the authors to be highly suggestive of recurrent PSS because these latter findings are characteristic of scleroderma. The current advice is to establish that the patient is clinically stable without visceral activity before transplantation.

Alport’s Syndrome. Recurrence of typical lesions of Alport’s syndrome is extremely rare (2). In a single case, the disease was thought to have recurred in a 27-yr-old male with a second transplant (a cadaver) who developed typical lesions of foam cells in the glomeruli and interstitium. With electron microscopy, the basement membrane had a fibrillar appearance. In the 73 patients with Alport’s syndrome who received 83 transplants reported by the Renal Transplant Registry in 1975 (89), no recurrences were noted.

The more interesting phenomenon seen in these patients is the development of anti-GBM disease. Patients with Alport’s syndrome or hereditary nephritis lack a component of the GBM, perhaps a domain on type IV collagen (128), and do not bind anti-GBM antibodies isolated from patients with Goodpasture’s syndrome (129,130). Once the allograft which contains these “normal” antigens is placed, the recipient may mount a humoral response against these foreign proteins, which may lead to anti-GBM disease.

It is difficult to provide incidence rates based on the presence of serum anti-GBM antibodies. Linear anti-GBM staining in the allograft, and graft loss, because so few cases have been reported and because of the lack of uniformity with regard to monitoring of these parameters (131–136). However, anti-GBM antibodies have been detected in sera of patients with (133,135) and without (131,134,136) consequence to the allograft. Linear anti-GBM staining in the allograft may be associated with graft loss if accompanied by nephritis, usually crescentic GN (132,133).

In other patients, linear anti-GBM staining was accompanied by typical changes of rejection and the grafts were eventually lost (131,132). Additionally, in the report by Milliner and colleagues (131), 8 of 10 patients with urinary abnormalities including hematuria and proteinuria had normal renal function and only 1 of these 8 patients had circulating anti-GBM antibodies. The graft histology was not available from these patients.

SUMMARY

Almost all histopathologic disorders which affect the native kidneys have been reported to recur in the renal allograft. However, in general, recurrent disease has had a minimal impact on graft survival as less than 1 to 4% of all graft failures are accounted for by this entity. Type II MPGN, IgA nephropathy, FSGS, diabetic nephropathy, and oxalosis have the highest rates of recurrence. Recipients of living-related kidneys have been reported to have higher recurrence rates, especially if the native kidney disease was due to FSGS, IgA nephropathy, membranous GN, Henoch-Schönlein purpura, or HUS. In these latter patients, it is therefore advised that living-related transplantation should be performed with caution. Additionally, cyclosporine should be used with caution in patients whose renal failure was due to HUS because it may precipitate this disorder. Finally, with the current experience, transplantation is becoming a viable alternative for renal replacement therapy in patients with oxalosis (in concert with liver transplantation) and Fabry’s disease.

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