All forms of primary GN may recur after kidney transplantation and potentially jeopardize the survival of the graft. IgA nephritis (IgAN) may recur in approximately one third of patients, more frequently in younger patients and in those with a rapid progression of the original disease. However, with the exception of few patients with rapid progression, there is no evidence that recurrence of IgAN has a deleterious effect on graft survival at least up to 10 years. Recurrence of focal segmental glomerulosclerosis (FSGS) is often associated with nephrotic proteinuria and is more frequent in children, in patients with rapid progression of the original disease, and in those who lost a previous transplant from recurrence. The natural course of recurrent FSGS is usually unfavorable. Early and intensive plasmapheresis may obtain complete or partial response in several patients. Good results have also been reported with rituximab. Idiopathic membranous nephropathy (IMN) may recur in 30% to 40% of patients. The graft survival in patients with IMN is not different than that of patients with other renal diseases. Good results with rituximab have been reported. Membranoproliferative GN (MPGN) may recur in 27% to 65% of patients. The recurrence is more frequent and the prognosis is more severe in type II MPGN. Although recurrent GN is relatively frequent and may worsen the outcome of renal allografts in some patients, its effect is diluted by several other risk-factors that may have a greater effect than recurrent GN on the long-term graft survival.

IgAN

IgAN is a primary GN characterized by the dominant or co-dominant diffuse mesangial deposition of IgA, usually IgA1. The deposits consist of an aberrant galactose-deficient form of IgA1 and IgA or IgG autoantibodies to the aberrantly glycosylated IgA1 (4,5). The disease usually runs an indolent course but may lead to ESRD in 30% to 50% of patients after 25 years or more of follow-up. IgAN is one of the most common recurrent GN after transplantation (6).

A review of the literature reported that recurrences develop in approximately 33% of patients with large differences, ranging between 9% and 61%, among the different series (7). Several reasons can account for these large discrepancies. The indications for undergoing a graft biopsy were variable in the different studies and it is likely that several patients with asymptomatic hematuria and/or proteinuria never received biopsy. The follow-ups were quite different and the risk of recurrence was probably underestimated for patients followed for short times. Longer follow-up times yield higher recurrence rates. There are different racial and geographical distributions of IgAN. In some cases, IgA deposits could be already present in the donated kidneys. As an example, in a Japanese series, mesangial IgA deposits were present in 16% of 510 donated kidneys (8), although it is not clear if the deposited IgA were abnormally glycosylated.

Recurrences of IgAN can be “immunopathologic” only; discovered on a “protocol” renal biopsy in an asymptomatic patient; or “clinical,” which is delineated by abnormalities in the urine and/or renal function leading to a renal biopsy. Clinical recurrence of IgAN may occur immediately after transplantation, but on average the diagnosis is made approximately 3 years after transplantation (7,9) and is usually heralded by hematuria and low-grade proteinuria. The results of renal transplantation in patients with IgAN have been differently estimated. Some investigators (10,11) reported a more favorable
outcome of the renal allograft in patients with IgAN than in other transplant recipients, but others found that graft survival in an IgAN group was similar to that of non-IgAN renal transplant recipients (12–14). An analysis of the Eurotransplant registry data reported the outcome of 1207 patients with IgAN and 7935 other renal transplant recipients. The 10-year death-censored graft survival was identical in the control group with and without the HLA-B8, DR3 haplotype (71.1% versus 70.2%) but significantly worse in IgAN patients carrying the HLA-B8, DR3 haplotype than in patients without it (52.5% versus 69.1%, \( P = 0.009 \)), suggesting that this HLA haplotype may represent a risk factor for transplant recipients with IgAN (15). The limit of this study rests on the large heterogeneity between patients with IgAN and the control population. A case-control study compared the long-term outcome of 106 patients transplanted because of IgAN with that of 212 non-IgAN patients transplanted in the same period and in the same center (16). After censoring the graft failures in the first 6 months, the 10-year graft survival probability was not significantly different between the two groups: 75% in patients with IgAN and 82% in controls. The regression coefficient of the reciprocal of plasma creatinine was also similar in the two groups. In a Cox proportional hazards model analysis, IgAN recurrence was not associated with an increased risk of graft failure. Other series reported that recurrence of IgA deposition has only a modest and inconsistent effect on graft survival. In the Australia-New Zealand registry, the long-term graft survival was not affected by the increased risk of recurrence in zero-haplotype kidneys (17). In two large Asian reports, the risk of graft loss due to recurrence ranged around 3% to 4% (18,19). However, in the very long term it is possible that recurrent IgAN may represent a substantial risk factor for graft failure. Rarely, a rapidly progressive renal failure caused by an underlying crescentic GN may occur (20,21).

Recurrence tends to occur more frequently in younger patients and in those with a rapid progression of the original disease (16,22,23). It is unclear if recurrence is (24,25) or is not (16,26) more frequent in transplants using related donors. A review of the data collected by the Australia-New Zealand registry reported that biopsy-proven IgAN recurrence was significantly more frequent in zero HLA-matched living donor grafts (17). However, these results should be interpreted with caution because several details are lacking in retrospective reviews of registry data. Most other pretransplant characteristics are not consistently predictive for recurrence, although some authors have suggested that latent IgA deposits in the donor kidney (in “zero” time biopsies of the transplanted kidney) are highly associated with a recurrence of disease (27), and underlying crescentic GN with rapid progression to ESRD may also predict a higher risk for recurrence (28). There is now general agreement that the type and intensity of posttransplant immunosuppression does not influence the risk of IgAN recurrence. However, Berthoux et al. (29) recently reported that the 10-year cumulative recurrence rate of IgAN was 9% (3 of 29) in patients who received induction with anti-thymocyte globulins versus 41% (21 of 52) in patients who did not receive such induction therapy. The authors hypothesized that the protective effect of anti-thymocyte globulins could be related to an augmented production of regulatory T cells.

The finding that some apparently normal donors (living or deceased) may have “hidden” IgA deposits in the kidney (9) may have important relevance for pathogenesis of the recurrent disease. It may be presumed that the circulating autoantibody to exposed N-acetylgalactosamine residues on galactose-deficient IgA1 in some subjects with IgAN could react with the “planted” IgA deposits (posited also to be deficient in galactose residues thus exposing the neo-N-acetylgalactosamine epitopes) in the allograft and thus promote an immunopathological recurrence (4,6,30,31). Whether this immunopathological recurrence would rise to the level of clinical detection would depend on the activation of accessory factors (e.g., complement and cytokines [32]). Circulating immune complexes composed of IgG or IgA autoantibodies to galactose-deficient IgA1, and the relevant autoantigen might theoretically participate in recurrent disease, especially if these immune complexes escape normal reticuloendothelial-dependent removal mechanisms (33).

No specific therapy for recurrent IgAN is currently available. A review of the U.S. Renal Data System examined the effect of immunosuppressive medication on allograft failure due to recurrent GN. After adjusting for important covariates, the use of cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, sirolimus, or prednisone was not associated with graft failure due to recurrent GN for any type of GN, including IgAN (34). Angiotensin converting enzyme inhibitors (ACEIs) may be prescribed because a study showed that their use could reduce proteinuria and blood pressure in transplant recipients with IgAN (35). However, in using these drugs one should take into account that the use of ACEIs or angiotensin receptor blocker (ARBs) in renal transplant recipients may be associated not only with reduction in proteinuria but also with significant decreases in GFR and hematocrit (36). Tonsillectomy has been suggested to be of benefit by Japanese investigators. Sixteen of 28 transplant patients with biopsy-proven recurrence of IgAN and persistent proteinuria underwent tonsillectomy alone, whereas the remaining 12 patients did not receive tonsillectomy. Proteinuria decreased significantly in all of the tonsillectomized patients but in none of the other group. The reduction in proteinuria after tonsillectomy was especially marked in patients with mild mesangial changes on renal biopsy (37). Long-term outcomes were not examined in this study. In the rare cases of recurrent IgAN associated with a rapidly progressive course and crescents at biopsy, a trial with high-dose corticosteroids, cyclophosphamide, and plasmapheresis may be attempted, although the results are usually poor.

**FSGS**

Idiopathic FSGS is often associated with a fully developed nephrotic syndrome (NS) and may affect children and adults. In the absence of a treatment-induced remission, FSGS commonly progresses to ESRD. Approximately 30% of patients develop recurrence of FSGS in the first kidney allograft (38). The risk of recurrence with a second graft in patients who lost a first graft because of recurrence may approach 100% (39). Two patterns of clinical presentations of recurrent FSGS after trans-
plantation are recognized: (1) an early recurrence (the most frequent) characterized by a massive proteinuria within hours to days after implantation of the new kidney, and (2) a late recurrence that develops insidiously several months or years after transplantation.

The graft survival in patients with FSGS is lower for children than adults, particularly if the patient is white or Hispanic (40,41), and is lower in children with FSGS than in those with other renal diseases (42,43). The renal prognosis is strongly influenced by recurrence because the relative risk of graft failure is 2.25 times higher in patients with recurrent FSGS as compared with patients without recurrence (2). Graft loss caused by recurrent FSGS is significantly higher in children receiving living donor transplants compared with deceased donor transplants in children (44). Only few single-center studies reported data on graft survival in adults with FSGS. Pardon et al. (45) reported a graft survival rate of 73% at 5 years in 33 transplanted adults with FSGS, with a significant difference between the patients with (57%) or without (82%) recurrence. No comparison with a control group was made. Moroni et al. (46) compared the long-term outcomes of 52 renal transplants performed in adults with FSGS with those of 104 matched controls. At 15 years, graft survival was not significantly different: 56% in FSGS and 64% in controls. Recurrence of FSGS occurred in 12 patients (23%) and led to graft failure in 7 within 10 months (median). In the other five patients, proteinuria remitted and grafts were functioning 106 months (median) after transplantation. In the long term, patient and renal allograft survivals of adults with FSGS were comparable to those of controls.

Several clinical factors have been reported to be associated with an increased risk of recurrence, including young age, mesangial proliferation in the native kidneys, a rapid progression to ESRD, a pretransplant bilateral nephrectomy, white ethnicity, and specific aspects of genetic background (47). The histologic variant type of FSGS observed in the native kidneys does not seem to reliably predict either recurrence or type of FSGS seen on the allograft (48). There is a higher risk of recurrence in living donor transplant pediatric recipients (49); however, the reduced risk of rejection and a lower immunosuppression in living-related transplants may overcome the deleterious effect of recurrent GN. A review of the U.S. Renal Data System data reported that, after correction for other factors, living donor transplants had no association with graft loss from recurrent FSGS; rather, a living donor transplant was associated with superior overall graft survival (50). Cibrik and co-workers (51) also found that the risk of death-censored graft loss was 1% per year in adults with FSGS who received a zero HLA mismatch kidney from living donors versus a 4.4% loss per year for patients with FSGS who received a zero HLA mismatch kidney from deceased donors. Another issue concerns the living-related kidney donation to a subject affected by familial FSGS. Until recently the current opinion was that patients with familial FSGS caused by mutations of NPHS2, the gene encoding podocin, did not run any risk of recurrence after transplantation. However, there is now evidence that the risk of recurrence in patients with the NPHS2 mutation is low (but not zero) at approximately 8% (52). Therefore, caution should be observed in transplanting patients with NPHS2 mutations using the kidney of their parents who are obligate carriers of the NPHS2 mutation (53). It is also possible to speculate that in patients with genetic FSGS the transplant of a normal kidney may evoke an alloimmune response to slit diaphragm proteins.

The frequent occurrence of a rapid relapse of proteinuria after transplantation led to a postulate that a circulating factor, perhaps secreted by an abnormal clone of T cells, may induce redistribution and loss of nephrin and podocin, two critical components of the glomerular slit-diaphragm of podocytes, thereby reducing the efficiency of the glomerular barrier to proteins. However, despite intensive research by different groups of investigators (54–58), the biochemical nature of the posited circulating permeability factor(s) remains unknown, and we still lack a reliable chemical or immunoassay for its presence and quantitation.

The management of patients with recurrent FSGS and NS is difficult, controversial, and none of the multiple approaches currently available has been shown to be consistently beneficial. Perhaps more targeted approaches will emerge based on our improving knowledge of podocyte biology and function. An amelioration of proteinuria has been reported in children treated with intravenous cyclosporine at high doses (59–62). This anti-proteinuric effect of cyclosporine may be attributed to suppression of T cells and inhibited production of their cytokines and to the inhibition of calcineurin-mediated dephosphorylation of synaptopodin, a protein critical for stabilizing the actin cytoskeleton in kidney podocytes (63). Cyclosporine and other calcineurin inhibitors thus have systemic immunoregulatory and local podocyte modulatory actions: Either one or both can be responsible for their anti-proteinuric effects in recurrent FSGS. However, the long-term efficacy and tolerance of such a therapy remains to be established. The most commonly used therapeutic approach is the use of plasma exchange (PE) or immunoabsorption with protein A (59,64–66). A review of the literature reported that 70% of children and 63% of adults with recurrent FSGS who received PE entered complete or partial remission of proteinuria (47). However, all studies were retrospective, uncontrolled, and most of them had only short-term follow-ups. In a pilot trial, 10 adults with FSGS recurrence received concomitantly high-dose steroids, intravenous cyclosporine for 14 days followed by oral cyclosporine therapy, and an intensive and prolonged course of PE. Complete, rapid, and sustained remission was obtained in 9 of 10 patients. At month 3 and month 12, proteinuria was 0.16 and 0.19 g/d, respectively. PE was stopped at month 9 in all patients except for one patient who remained PE dependent (64). A protective role of prophylactic PE before transplantation has also been reported (65,66). Several single-case reports pointed out the benefit of rituximab when given alone or in combination with PE (67–72), but failures were also reported (73–76). Currently, PE combined with high-dose calcineurin inhibitors with or without rituximab seems to be the most promising approach, but further controlled trials are needed to define the optimal therapeutic regimens to treat recurrence of FSGS (77). Despite the risk of recurrence, patients with FSGS should not
be excluded from transplantation. In the case of living donation, the possibility of recurrence and its consequences should be clearly explained to the donor and the recipient and preemptive PE should be planned in advance of transplantation. An early and aggressive treatment should be provided if proteinuria develops.

**IMN**

IMN is characterized histologically by uniform thickening of the glomerular capillary due to immune-complex deposits in the outer or subepithelial aspect of the glomerular basement membrane. IMN is a frequent cause of NS in adults and may lead in 40% to 50% of patients to ESRD in the long term (78,79). A recurrence of IMN after renal transplantation is probably more frequent than generally estimated. Up to now, almost 300 cases of recurrent MN have been reported in renal transplant patients (80–108), most cases occurring in adults. However, the true proportion of recurrence is difficult to assess because the indications for graft biopsy are extremely variable among transplant centers. Moreover a de novo form of secondary MN may develop in transplanted kidneys showing a histologic pattern indistinguishable from recurrent IMN. This de novo MN may occur even more frequently than the recurrent MN. In a study with protocol biopsies, 6 of 17 cases of MN were identified; of them 6 (35%) were considered to be recurrent IMN and 11 (65%) de novo MN (108). With these difficulties in mind, the rate of IMN recurrence has been estimated to range between 30% and 44% (96,108).

Recurrence of IMN is usually diagnosed between the 2nd and 3rd year after transplantation, but earlier and later cases have been described. So far, no clinical or histologic factor seems to reliably predict the risk of recurrence. In one series (89) posttransplant recurrence occurred earlier in recipients of a living-donor allograft (mean 9.3 months after transplantation) than in deceased donor transplant recipients (18.2 months). However, a study from Hong Kong reported that MN (including recurrent IMN and de novo MN) occurred later, at a mean of 45 months after transplantation (98). The initial clinical manifestations of recurrent IMN may be mild or absent, and in several patients recurrence could be detected only by protocol renal biopsies (101). However, many patients show a progressive increase in proteinuria over time and can eventually develop a full-blown NS. Proteinuria may spontaneously improve or even disappear only rarely (94,102).

The results of renal transplantation in patients with IMN are not different than those observed in patients with other renal diseases, including primary GN. The Australian registry reported that the actuarial renal allograft survival at 10 years was similar in patients transplanted because of IMN and in 1505 transplanted patients with other renal diseases (3). The outcome of recurrent IMN may be as variable as in the original native disease and its effect on graft survival has been differentially estimated. Some studies have reported that 60% to 65% of patients with recurrent IMN progressed to ESRD in a mean of 4 years after diagnosis (89,95). However, in many patients the graft failure was caused by rejection rather than recurrence of IMN. Other investigators reported that there was not any significant difference in death, graft failures, or serum creatinine between IMN with recurrent disease and those without recurrence after mean follow-ups of 73 and 57 months, respectively (108).

The mechanisms leading to IMN recurrence are still far from being elucidated. There is now evidence that MN is triggered by autoantibodies directed against podocyte proteins. Debiec et al. (109) identified in newborns from mothers deficient in these podocyte proteins circulating specific antibodies (IgG4 and IgG1) against neutral endopeptidase. This is an example of an allo-immune reaction causing MN and may be more akin to the pathogenesis of de novo MN. Recently, circulating autoantibodies directed against other podocyte enzymes, such as M-type phospholipase-2 receptors (110) and aldose reductase and manganese superoxide dismutase (111), have been detected in adults with IMN and are uniformly absent in secondary forms of MN. The expression of these autoantigens in podocytes can trigger the production of specific antibodies (mainly IgG4 and IgG1) and in situ deposits of immune complexes on the epithelial side of the glomerular basement membrane, with consequent activation of complement, oxygen radicals, and other components of the inflammatory response. As far as the pathogenesis of recurrent IMN is concerned, it is possible to hypothesize that recurrent disease is due to the reaction of autoantibodies (anti-phospholipase A2 receptor) from the circulation with conformational epitopes exposed or genetically determined in the donor kidney. This possibility has been recently confirmed by clinical observations (112).

Symptomatic treatment with diuretics, ACEIs, ARBs, hypolipemic drugs, and anticoagulants may help in reducing the signs and symptoms related to the NS in recurrent IMN. No convincing evidence exists that corticosteroids, cytotoxic drugs, or other immunosuppressive agents are of benefit in recurrent IMN. Rituximab has shown very promising effects in patients with IMN in native kidneys (113,114) and has also been used successfully in anecdotal cases of posttransplant IMN recurrence (100,103,104). In a recent study, eight patients with recurrent IMN and a mean proteinuria of 4.5 g/d were given two separate doses of intravenous rituximab (1000 mg each) 2 weeks apart. Twelve months later, 35% of patients had a complete remission and another 40% had a partial remission. After 24 months, one patient had relapsed. Post-treatment biopsies showed reabsorption of electron-dense immune deposits in six of seven patients (107). In another series, four patients with recurrent IMN and severe proteinuria were given rituximab, either at a weekly dose of 375 mg/m² for 4 weeks, or at a dose of 100 mg repeated 2 weeks later. Two patients responded to the first course and the other two patients received a second course of rituximab. Mean proteinuria decreased from 4.0 to 1.8 g per day, and serum creatinine remained stable at approximately 1.5 mg/dl (108).

**MPGN Types I and II (Dense Deposit Disease)**

MPGN is “pattern of injury” rather than a disease (115). It is now known to have a very diverse array of underlying causes, and the group designated as ‘idiopathic’ MPGN has corre-
spondingly declined in size (115). Nevertheless, MPGN is common cause of recurrent GN in allografts. The reported rate of recurrence of MPGN has been quite variable (27% to 65%) (116). MPGN has previously been divided into subtypes (types I, II, III, etc.) on the basis of ultrastructural features. Type I MPGN characteristically has subendothelial electron-dense deposits containing IgG and C3, which presumably represent immune complexes. Type II MPGN (also known as dense deposit disease [DDD]) shows an electron-dense transformation of the glomerular basement membrane and deposition of C3 (and other complement components without IgG deposition). In previous series, types I and II MPGN (DDD) were considered together, whereas the current trend is to separate DDD as a unique clinicopathologic entity having a higher risk of recurrence than typical type I MPGN (117). Differences in recurrence rates between type I MPGN and DDD may relate more to the superimposition of crescents than to the underlying ultrastructural features (118). Risk of recurrence may be marginally higher in living related donors. The most important aspect of recurrent MPGN or DDD is the identification of the processes responsible for the original native disease. Recurrent MPGN due to lupus nephritis, monoclonal gammopathies, thrombotic microangiopathies, and more frequently HCV infection (119) do occur, but they are beyond the scope of this review.

Recurrent MPGN type I can have significant deleterious effects on graft survival, especially when superimposed extensive crescentic disease is present (118), and thus should be prevented in so far as is possible by careful pretransplant evaluation.

Intensification of immunosuppressive therapy in recurrent MPGN can be hazardous because it may lead to overimmunosuppression and has little documented effect on the outcome of the recurrence, except perhaps when extensive crescentic disease is present. Occasional anecdotes and small series have suggested that improvement may be seen in recurrent MPGN type I with cyclophosphamide (120) or high-dose mycophenolate mofetil (121), but no controlled trial has yet confirmed the efficacy or safety of these approaches. Treatment of truly “idiopathic” recurrent MPGN is generally very disappointing and graft loss due to recurrence is common (116).

DDD

This disease has a very high risk of recurrence (approaching 100%). Most patients have low serum C3 levels, and 70% to 80% also have a circulating autoantibody to C3b known as C3 nephritic factor (C3Nef). Some patients with DDD may also have an abnormality in complement cascade regulation such as deficiencies of factor H) (122). Thus, hypocomplementemia and/or isolated C3 deposits suggesting DDD in a native kidney biopsy showing a pattern of MPGN is a feature highly associated with risk for recurrence (115,116). When ultrastructural analysis of the native kidney biopsy reveals DDD an evaluation for complement dysregulation (factor H, I, or membrane cofactor protein levels) seems appropriate. Serum C3 nephritic factor levels do not reliably predict the risk of recurrence of DDD in the renal allograft. Subtle monoclonal Ig deposition diseases such as light-chain deposition disease can also mimic idiopathic MPGN and contribute to recurrent disease (115,116), frequently appearing within a few months after transplantation (116). Finally, a newly described entity, known as “GN C3,” may also have clinical features similar to DDD and type I MPGN, but it lacks the ultrastructural features of typical DDD and fails to show any immune complex deposits characteristically found in type I MPGN. Only C3 without IgG deposits are observed. Deficiencies of complement factor H, I, or membrane cofactor protein are frequently noted. The risk of recurrence of GN C3 in the allograft is not well known but would be presumed to be elevated if abnormalities in complement dysregulation are found.

The successful treatment of an established recurrence of DDD is problematical, so prevention and anticipatory management based on precise assessment of the underlying mechanism responsible for the MPGN is very important. Patients with complement dysregulation (e.g., factor H deficiency) should receive replacement infusions (fresh frozen plasma) and/or rituximab might also be helpful in patients with a neutralizing autoantibody to factor H. Eculizumab (a monoclonal antibody to C5a) may also be beneficial, but this has not been yet been shown in a randomized trial (123). Patients with genetic causes for factor H or I deficiency may require combined liver and kidney transplantation to avoid recurrences (125), but this is mainly derived from experience with hereditary forms of atypical hemolytic uremic syndrome associated with factor H deficiency (126). Patients with documented underlying monoclonal gammopathies should receive appropriate aggressive chemotherapy and/or autologous stem cell transplantation before kidney grafting so as to minimize the risk of recurrence.

Conclusions

Although recurrent GN is relatively frequent and may worsen the outcome of renal allograft in some patients, its effect on the fate of a renal allograft is diluted by several other risk factors, including death with functioning graft, the quality of the donated kidney, rejection, drug nephrotoxicity, infections, and other renal and extrarenal complications such as hypertension, diabetes, coronary artery disease, liver disease, and cancer. These factors may have a greater effect than recurrent GN on long-term graft survival, as demonstrated by large series showing that overall long-term graft survival is similar in recipients with many forms of primary GN and in those with other renal diseases (2,127).

Disclosures

None.

References

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