Recurrence of Secondary Glomerular Disease after Renal Transplantation

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Summary
The risk of a posttransplant recurrence of secondary glomerulonephritis (GN) is quite variable. Histologic recurrence is frequent in lupus nephritis, but the lesions are rarely severe and usually do not impair the long-term graft outcome. Patients with Henoch-Schönlein nephritis have graft survival similar to that of other renal diseases, although recurrent Henoch-Schönlein nephritis with extensive crescents has a poor prognosis. Amyloid light-chain amyloidosis recurs frequently in renal allografts but it rarely causes graft failure. Amyloidosis secondary to chronic inflammation may also recur, but this is extremely rare in patients with Behçet’s disease or in those with familial Mediterranean fever, when the latter are treated with colchicine. Double organ transplantation (liver/kidney; heart/kidney), chemotherapy, and autologous stem cell transplantation may be considered in particular cases of amyloidosis, such as hereditary amyloidosis or multiple myeloma. There is little experience with renal transplantation in light-chain deposition disease, fibrillary/immunotactoid GN, or mixed cryoglobulinemic nephritis but successful cases have been reported. Diabetic nephropathy often recurs but usually only after many years. Recurrence in patients with small vessel vasculitis is unpredictable but can cause graft failure. However, in spite of recurrence, patient and graft survival rates are similar in patients with small vessel vasculitis compared with those with other renal diseases. Many secondary forms of GN no longer represent a potential contraindication to renal transplantation. The main issues in transplantation of patients with secondary GN are the infectious, cardiovascular, or hepatic complications associated with the original disease or its treatment.


Introduction
The possibility of recurrence in a renal transplant of the original disease that lead to end-stage renal disease has been known for almost 50 years (1). We have recently reviewed the topic of recurrence of primary glomerular disease in renal grafts (2) and here we will review the topic of recurrence of secondary glomerular and vascular diseases, including lupus nephritis, Henoch-Schönlein nephritis, amyloidosis, light-chain deposition disease, fibrillary/immunotactoid glomerulonephritis cryoglobulinemic nephritis, diabetic nephropathy, and small vessel vasculitis. Emphasis will be placed on recent developments.

Lupus Nephritis
The reported risk of recurrence of lupus nephritis (LN) after renal transplantation has been quite variable. Some investigators found that the recurrence rate was quite low, <5% (3–9), whereas others reported that about 10% of patients with LN experienced recurrence (10–13). An additional group of investigators pointed out that the risk of recurrence was even higher, when diligently searched for, ranging between 30 and 54% (14–16). A number of reasons may account for these discrepancies: (1) The indication for renal allograft biopsy varies among transplant units; (2) some studies reported the results seen in single centers whereas others collected data through national or multinational registries; (3) the follow-up was short in many studies—an important point because recurrences may occur more than a decade after transplantation (11,17); (4) the risk of recurrence may vary in different ancestral groups (10,18); (5) a diagnosis of recurrence of LN requires a graft biopsy examined by light microscopy, immunofluorescence, and electron microscopy, which were not always routinely performed (19).

Clinically, recurrence of GN in the renal allograft may be heralded by mild proteinuria and microscopic hematuria, and is seldom accompanied by arthralgias or cutaneous rash. The histologic lesions of recurrent LN are usually mild, mostly consisting of mesangial lesions or atypical pauci-immune proliferative GN in those studies which adopted a policy of elective surveillance biopsy (14–16,19). However, patients of diffuse proliferative nephritis have been reported when the decision to undertake a renal biopsy was made on clinical grounds (6,10).

The effect of recurrent LN on graft survival is usually of minor significance. In a retrospective analysis (6) only 4 out of 97 patients with LN lost their graft because of recurrence. In a multicenter French study of 60 transplants in patients with LN, no graft was lost because of recurrence (7). A review of the United Network for Organ Sharing (UNOS) data reported that graft failure in patients with recurrent LN was...
attributable to recurrence in only 7% of patients, rejection being the main cause of graft failure (11). Single-center studies also pointed out that the main causes of graft failure in transplant patients with LN was either rejection (4,13,20,21) or chronic allograft nephropathy (16), rather than recurrence of LN.

Factors that tend to be associated with recurrent LN are black non-Hispanic ancestry, female gender, and young age (10,11). Patients with antiphospholipid (aPL) autoantibodies (13) and those receiving the kidney from living donors (16) also have a higher risk of recurrence.

Some studies reported a higher risk of graft failure in LN (4,6,10), whereas others reported patient and graft survival in LN patients comparable to those seen in other renal diseases (22–25). The studies that compared the results of renal transplantation in LN patients with those of well-matched controls usually reported that patient and graft survival were similar in the two groups even in the long-term (3,6,7,12,13,21). Also, morbidity after transplantation was similar in patients with LN and in well-matched controls, with the exception of thrombotic events that were more frequent in LN (26). Several retrospective analyses of UNOS and United States Renal Data System (USRDS) reported no difference in patient and graft survival rates between adults with LN and other transplant recipients of living or deceased donor kidneys, after adjusting for confounding factors (10,11,27,28). Also a retrospective analysis of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) database found that the results of renal transplantation in young patients with LN were comparable to those seen in an age-, ancestry-, and gender-matched control group, in spite of an unexplained increase in recurrent rejections in the living donor LN patients (22).

The clinical condition of the patient at transplantation can markedly influence the outcome. In patients who have received vigorous immunosuppression or long-term glucocorticoid therapy for their disease before transplantation, it may be advisable to postpone transplantation for several months after initiating dialysis to minimize the possible contribution of prior therapy on the risk of infectious, cardiovascular, and other complications after transplantation (29). An issue also manifests itself when the aPL syndrome is present. This can be associated with vascular thrombosis and early graft failure (30,31). Anticoagulation with heparin can reduce the risk of vascular thrombosis (32). However, not all patients respond and bleeding complications remain a serious side effect of anticoagulation therapy (31).

The basic posttransplant immunosuppression for LN patients does not differ from that normally used in management. In patients with LN recurrence, an intensification of immunosuppression should be reserved for the exceptional cases showing a severe (life threatening) lupus flare-up because of the potential risks of serious or lethal infection.

In summary, LN may recur after renal transplantation but in most patients recurrence neither causes severe histologic lesions nor has a relevant clinical effect on the long-term outcome (29). The results of renal transplantation are at least as good in LN patients as in patients with other renal diseases. Pretransplantation screening for aPL antibodies in renal transplant candidates with LN is recommended as it may indicate which patients will benefit from anticoagulant therapy (30).

**Henoch-Schönlein Nephritis**

A review of the literature reported that histologic recurrence of IgA mesangial deposits occurred in 52 out of 67 (78%) renal allografts in patients with Henoch-Schönlein nephritis (HSN), whereas a clinical recurrence occurred in only 15 out of 67 (22%) patients at 5 years posttransplantation (33). However, after longer follow-up clinical recurrence may be evident in 29 to 42% of patients (34,35), more frequently in children (36). Henoch-Schönlein nephritis patients with circulating IgA-ANCA (ANCA, antineutrophil cytoplasm antibody) are particularly prone to recurrence after transplantation (37). Hematuria, sometimes macroscopic, moderate proteinuria, and hypertension are common in patients with clinical evidence of recurrence. Histologically, focal and segmental necrotizing GN with mesangial IgA deposits is observed.

Recurrence of HSN can lead to graft failure in about 10% of patients, the prognosis being more guarded in adults than in children (33). In a European survey, graft survival in patients with HSN recurrence was 57% at 2 years (38). Alternatively, in a small single-center study (39), the 5-year graft survival was 78%. In another small study, out of eight adults with recurrent HSN one patient died and four restarted dialysis in mean after 55 months after renal transplant (35). Therefore, recurrent HSN should not be regarded as a benign condition.

Recurrence is more frequent and severe in patients who had a rapidly progressive course and necrotizing/crescentic GN in the native kidneys (35,39). Living related donor transplantation also shows a trend of higher recurrence compared with those receiving unrelated grafts. However, the graft survival rate in related-donor recipients was not less than that found in unrelated-donor recipients (34).

A comparison of the graft outcome of kidney recipients with HSN with age-, sex-, and donor source-matched controls revealed an actuarial 15-year patient survival of 80% in 17 HSN patients and 82% in 34 controls. The death-censored graft survival was 64% in both of the two groups. The risks of rejection, chronic graft dysfunction, arterial hypertension, and infection were also similar in the two groups (35). In addition, in another study, 20 patients with HSN were compared with 40 patients with IgA nephropathy and 40 patients with other renal diseases. The 10-year graft survival was 88% in HSN, similar to that seen in the other two groups. Recurrence of HSN occurred in 29% of patients (34).

Patients with recurrent HSN and extensive crescents in the transplant biopsy have a decidedly poor prognosis. Methyl prednisolone pulses (MPP), antiplatelet agents, or cytotoxic drugs have been used without any notable benefits (33–35). In a single patient proteinuria resolved and renal biopsy demonstrated marked reduction in mesangial IgA deposition after 4 cycles of plasmapheresis (40).

In summary, HSN recurs more frequently in children but the outcome after recurrence is more severe in adults and in patients with extensive crescentic GN. In spite of recurrence, the cumulative long-term graft survival in pa-
patients with HSN is similar to that seen in patients with other renal diseases.

Amyloidosis

Previous studies have shown that amyloid light-chain (AL) amyloidosis and hereditary amyloidosis regularly recur after kidney transplantation, but only a few have been reported in the literature (41–43). However, a successful renal transplant without recurrence of amyloidosis after 9 years was described in a patient with familial apolipoprotein II amyloidosis (44) and a recent series of 22 renal transplant recipients with AL amyloidosis reported that no renal graft failed because of recurrent amyloidosis after a mean follow-up of 48 months. The patient survival was 95% at 1 year and 67% at 5 years (45).

The risk of recurrence for secondary AA amyloidosis depends on the type and the activity of original disease. Up to 26% of patients with amyloidosis secondary to chronic inflammation (such as rheumatoid arthritis) may develop a renal recurrence (46) whereas no case of recurrent renal amyloidosis has yet been reported in patients with amyloidosis secondary to Behcet’s disease (47–49). Amyloidosis may also recur after transplantation in patients with familial Mediterranean fever, but the early administration of colchicine, 1 to 2 mg/d indefinitely, can prevent the deposition of amyloid in the transplanted kidney (50).

Recurrence of renal amyloidosis is often associated with various degrees of proteinuria. When present, nephrotic proteinuria heralds the relentless progression to graft failure. The graft survival in patients with amyloidosis has improved with time and with better immunosuppression. In a series of 105 renal transplants in 96 patients with amyloidosis (primary amyloidosis in 5 patients and secondary amyloidosis in the other 91 patients), graft survival was comparable to that seen in transplant patients with diabetes (51). The Collaborative Transplant Study (CTS) reported that the patient and renal graft survival at 5 years were inferior in patients with secondary amyloidosis than in patients with GN or polycystic kidney disease, but adequate enough to justify kidney transplantation (52). Two main issues with renal transplantation in amyloidosis are life-threatening infections and cardiovascular complications (53,54), particularly when cardiac involvement is present.

In summary, patients with renal amyloidosis without other organ involvement (especially cardiac) may undergo kidney transplantation. However, in view of the increased risk of postoperative complications, a preoperative cardiovascular evaluation is mandatory even in asymptomatic patients. Specific treatment should be considered for particular forms of amyloidosis, that is, chemotherapy and autologous stem cell transplantation followed by kidney transplantation in progressive primary AL amyloidosis (55), a dual liver and kidney transplantation in hereditary amyloidosis and multisystemic involvement (42,43,56), a dual heart and kidney transplantation in severe and irreversible cardiac and renal involvement (57). Patients with familial Mediterranean fever should be treated regularly with colchicine (58,59).

Light-Chain Deposition Disease

Patients with light-chain deposition disease (LCDD) have a very high risk of recurrence of the monoclonal κ or λ chain deposition in the graft (60–67). Recurrence of LCDD developed in 5 out of 7 renal transplant patients after a mean period of 33 months (64).

The prognosis is poor in patients with recurrence of LCDD. Four of the 5 patients with recurrence quoted above died and the fifth patient entered dialysis (64). Of the other two patients one died from multiple myeloma and another was still alive with graft functioning 13 years posttransplantation. However, a review of the ERA/EDTA registry reported that the mean survival in 35 transplanted patients with LCDD was 9.6 years (65).

In spite of a high risk of recurrence and death, renal transplantation may be offered to patients with LCDD who respond satisfactorily to chemotherapy, as demonstrated by serum-free light-chain assays. Preliminary results have shown the possibility of preventing an early recurrence of LCDD with the proteasome inhibitor bortezomib (66) or with rituximab (67). The best current therapeutic approach is chemotherapy and autologous stem cell transplantation followed by kidney transplantation in case of good hematologic response (68). We suggest that renal transplantation should not be performed until after the light-chain production has been curtailed with appropriate chemotherapy and documented with serum-free light-chain assays repeated every 3 months until transplantation.

Fibrillary/Immunotactoid Glomerulonephritis

The high risk of early graft failure due to recurrent fibrillary/immunotactoid glomerulonephritis (F/ITGN) (69,70) was considered as a contraindication to renal transplant in the past. However, Samaniego et al. (71) reported 14 cases of F/ITGN in which, in spite of histologic recurrence in 6 cases, the allografts functioned in four patients for 4, 5, 11, and 13 years whereas a fifth patient died with stable graft function 7 years posttransplantation. Rosenstock et al. (72) reported two other cases of renal transplant in patients with FGN. One patient had normal serum creatinine, no proteinuria, and no signs of recurrence 8 years posttransplantation. The other patient died from colon cancer 4 years after transplantation with a stable serum creatinine of 2.2 mg/dl. In a third series, five patients with F/ITGN were followed in mean for 52 months posttransplantation (73). Only one patient lost the graft (because of thrombo-embolism). Thus, in spite of an increased risk of recurrence, renal transplantation may be considered as a viable option for patients with F/ITGN.

Mixed Cryoglobulinemic Nephritis

Up to 40% of patients, particularly those who are HCV-positive, may develop mixed IgG/IgM cryoglobulinemia and eventually a membranous or a membranoproliferative GN after renal transplantation (74). However, only 13 patients with mixed cryoglobulinemic nephritis (MCN) who submitted to renal transplantation have been reported in the literature (75–80). In all patients cryoglobulinemia was detected after transplantation and 7 (54%) showed a recurrence of MCN, characterized by proteinuria and hematu-
ria. Histology usually showed a membranoproliferative-type GN with extensive monocyte and polymorphonuclear leukocyte accumulation in capillary loops and small cellular crescents. Immunofluorescence showed C3, IgG, and IgM deposition in a mesangial and capillary wall pattern in all cases.

It is unclear whether the recurrence of MCN will interfere with the long-term survival of the transplanted kidney; as in reported cases graft failure was usually caused by rejection whereas some patients showed good graft function for 4 to 10 years in spite of histologic recurrence (78,80). Rituximab has proven to be an effective treatment for de novo MCN in transplant patients (81) but in some transplant patients rituximab may cause life-threatening infections (82).

Because chronic hepatitis (with cirrhosis), cardiovascular disease, and infection are the main causes of death in patients with MCN (83,84), we recommend that the clinical condition of the potential recipient should be carefully evaluated before a patient can be considered a suitable candidate for renal transplantation.

**Diabetic Nephropathy**

It is difficult to estimate the actual rate of recurrence of diabetic nephropathy (DN) in renal allografts because about 20% of transplant patients may develop de novo onset of diabetes posttransplantation (PTDM), which can also eventually lead to de novo DN (85). Recurrence of DN accounted for only 1.8% of graft losses in one of the largest series of renal transplants in diabetic recipients (86). This low risk may depend on the short duration of follow-up because the mean interval between the onset of insulin-dependent diabetes and the development of overt nephropathy in renal transplant recipients requires several years (87). A more recent series demonstrated a histologic recurrence in almost 40% of diabetic patients in a mean of 6.7 years after transplantation (88). Cases of recurrent DN have also been reported in patients with type 1 diabetes who were receiving a simultaneous pancreas and kidney transplantation (89). Vendrame et al. (90) demonstrated that recurrence of diabetes was associated with autoantibodies and reappearance of CD4 T cells capable of mediating β cell destruction. Microalbuminuria heralds the presence of DN, whereas overt proteinuria and nephrotic syndrome develop later, preceding the onset of progressive renal failure. In transplanted patients with DM who develop overt proteinuria and renal insufficiency, the typical nodular intercapillary glomerulosclerosis (Kimmelstiel-Wilson lesion) is infrequent, whereas vascular changes are prominent (87). The progression of histologic, diabetes-related lesions in the transplanted kidney is slow, but more rapid than in the original disease, perhaps because of the lower nephron mass, the use of nephrotoxic calcineurin inhibitors, and glucocorticoid therapy, and the frequency of concomitant hypertension. Thus, recurrent DN has little effect on graft function in the short term but can eventually contribute to graft loss in the long term.

A number of single-center series reported that, with modern immunosuppression, the patient and renal graft survival were similar in patients who had diabetes (type 1 or 2) to those who did not have diabetes, at least up to 2 to 5 years (91–93). A major problem for patients with diabetes remains—the high incidence of coronary artery disease and peripheral vascular events that can impair the survival and quality of life.

Present day, DN is not considered a contraindication to renal transplantation. However, measures are recommended to prevent the development of DN and other diabetes-related complications, including strict glycemic control (94), early use of ACE inhibitors and/or angiotensin receptor antagonists (95,96), a preemptive kidney transplantation in patients with type 2 diabetes (97), and a double pancreas and kidney transplantation in selected patients with type 1 diabetes (98).

**Small Vessel Vasculitis**

The risk of small vessel vasculitis (SVV) recurrence on renal graft is approximately 6% (99–100). The number of relapses of SVV per patients per year varied in three different studies, being respectively 0.02 (107), 0.076 (108), and 0.10 patients per year (101). Recurrence may develop within a few weeks after renal transplantation or many years later, with an average time from transplantation to recurrence of 31 months (105). Around 60% of recurrences involved the graft alone or in association with other organs, whereas the other 40% were primarily extrarenal (104,105). Microscopic hematuria and proteinuria are the heralding signs for renal recurrences of SVV. These are generally associated with or followed by the deterioration of graft function. The histologic picture is characterized by focal or diffuse pauci-immune extracapillary necrotizing glomerulonephritis.

The ANCA pattern or titers at time of transplantation, the duration of the original disease, the duration of dialysis, treatment with cyclosporine, and the source of donors do not influence the risk of recurrence (105,107–109), nor are clinical parameters very useful in predicting the risk of recurrence of SVV (108,109). No differences in the rate of recurrence after transplantation was observed between Wegener granulomatosis, microscopic polyarteritis, or renal limited vasculitis (105,108–110).

An Australian registry reported a graft loss of only 7.7% at 10 years caused by recurrence of SVV in transplant patients (111). By reviewing the data of single centers, we found that 7 of 323 (2%) SVV transplant patients lost their graft because of recurrence, but the risk of graft loss was 35% for patients who had clinical recurrence of SVV (14,100–110).

Patient and graft survival are quite similar in SVV and in the general transplant population. The UNOS registry reported a 3-year graft survival rate of 78% for deceased donor transplants, and 84% for living donor transplants in 114 recipients with Wegener granulomatosis (112). The ERA-EDTA registry reported a 70% graft survival at 3 years in 115 patients with SVV (38). In an abstract, the CTS (113) reported a 10-year patient survival of 80% and a graft survival of 65% for renal transplant recipients with Wegener granulomatosis. Relapses of SVV seldom occur after renal transplantation (101,102,109,110), perhaps because of concomitant immunosuppression.

The optimal timing for renal transplant in patients with SVV remains an unresolved question. Because clinical re-
mission of SVV for <1 year is associated with a high mortality rate (103,110). SVV candidates for renal transplantation should be in stable clinical remission at the time of transplantation. Prolonged immunosuppression may also expose patients to the risk of life-threatening infections after transplantation (114); thus, we believe that transplantation should be delayed for several months after starting dialysis in patients who have received a prolonged or intense period of immunosuppression for treatment of their underlying disease (108).

Despite the unpredictable potential for recurrence, transplantation is an acceptable option for patients with SVV. Persistent positivity of ANCA tests should not preclude transplantation (100,110). A careful monitoring of the urinary sediment during the first few years after transplantation may help in making a prompt diagnosis and treatment of a recurrence or relapse of SVV. Treatment of relapses is mainly based on MPP, cyclophosphamide, and plasmapheresis or possibly rituximab (14,108,115).

Summary and Conclusions
Glomerulonephritis (GN) secondary to systemic diseases may recur after transplantation, although the risk of recurrence and its effect on short- and long-term graft outcome depend on the type of the original disease as well as on the timeliness of diagnosis and treatment. In spite of the risk of recurrence, the long-term patient and graft survival rates in transplanted patients with LN, HSN, or SVV are similar to those reported patients with other kidney diseases undergoing renal transplantation. A recurrence of AA amyloidosis may be prevented by a careful management of the underlying disease. New management protocols or combined organ transplants are now available for treating the recurrence of AL amyloidosis. Diabetic nephropathy does not represent a contraindication to renal transplantation; the main risks for diabetic transplant recipients rests on cardiovascular disease not on recurrence of DN. Sporadic, successful cases of renal transplantation have been reported in diseases such as LCDD, IT/FGN, and MCN that may be prevented by careful management of the underlying disease.

Disclosures
None.

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