Recurrent glomerular disease in the kidney allograft

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1. ABSTRACT

Glomerulonephritis is responsible for nearly 15% of prevalent end-stage renal disease, and many of these patients will receive kidney transplants with the potential for a long duration of allograft survival. Recurrent glomerular disease, however, is not uncommon and can lead to both substantial morbidity and/or loss of the kidney allograft. The timing of recurrence after transplantation as well as the prevalence of recurrent disease vary by study, especially accounting for differences in protocol *versus* clinically-indicated biopsies, the use of immunofluorescence or electron microscopy in histopathological evaluation, and length of follow-up. Transplant immunosuppression alone may be sufficient to keep some recurrent disease in a subclinical form, whereas other recurrent glomerular diseases may be clinically evident and progress to threaten the allograft. This review highlights the epidemiology, diagnosis, and treatment of five common glomerular diseases that may recur in the transplant: focal and segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), membranoproliferative glomerulonephritis (MPGN), immunoglobulin A nephropathy (IgAN), and lupus nephritis (LN).

2. INTRODUCTION

Glomerulonephritis (GN) is responsible for 6.4% of incident and 14.5% of prevalent end-stage renal disease (ESRD), including transplants, in the United States (U.S. Renal Data System, USRDS 2012 Annual Data Report) and therefore represents a significant burden of disease. Other national registries worldwide report a 10-25% prevalence of GN as the cause of ESRD (1). Although many of these patients, often in a younger demographic group than those with other causes of ESRD, may transiently require dialysis, the ultimate goal for renal replacement therapy in the appropriate surgical candidate is kidney transplantation. Modern surgical techniques and immunosuppression regimens have extended the median half-life for the kidney allograft to 8.8 years for deceased donors and to nearly 12 years for living donors (2). However, recurrent disease in the allograft imposes the potential for early or late allograft loss, further morbidity, and the challenge of finding yet another renal transplant. It has been estimated that 10-20% of patients transplanted for GN will develop a recurrence, and that 50% of those with recurrence will ultimately lose their allograft in long-term follow-up (1). This article will review the major histopathological classes of GN that recur in the allograft, along with the epidemiology, risk factors, diagnostic tests, and therapeutic measures associated with each.

In order for a disease to be identified as recurrent in the allograft, there must be a defined diagnosis in both the native kidney and the allograft. There are a number of patients who initially present with advanced chronic kidney disease (CKD) whose biopsies are non-diagnostic or are never performed. Global glomerulosclerosis, tubular atrophy, and interstitial fibrosis can be end-stage features of a variety of GNs and are therefore non-diagnostic. Although less of a problem, the frequent omission of immunofluorescence (IF) or electron microscopy (EM) studies in routine allograft biopsies may also occasionally overlook early recurrent disease. *De novo* disease represents GN that appears in the allograft but is a distinct disease from that which caused ESRD in the native kidneys. The diagnosis of *de novo* disease also rests upon a clear diagnosis in the native kidney.

Rates of recurrence for a particular glomerular disease often vary widely from study to study. One important reason involves the distinction between clinically evident disease and histopathologically-defined recurrence, which can be diagnosed at an earlier time point and in the presence of only mild clinical or subclinical symptoms. Those centers which perform protocol biopsies in all patients tend to pick up recurrent disease early, whereas other centers which perform transplant biopsies according to clinical indication diagnose recurrent disease at later time points. Because each particular subtype of GN is rare, and due to these differences in methodology, it is often a challenge to determine true recurrence rates for each type of GN. Other potential reasons for the discrepancies in rates include differences in data collection (single center studies compared to national or multinational registries); short follow-up period, as many diseases may not recur for years after transplantation; and for certain diseases, the diagnostic criteria used to define recurrence. It must be kept in mind that the 'disease' categories as presented below are often only histopathological descriptors, with many potential underlying etiologies. The ability of each specific etiological cause to recur in the allograft is likely to be different.

In a transplant patient who is not scheduled to receive protocol biopsies, disease should be suspected and allograft biopsy considered whenever there is the appearance of urinary abnormalities or change in renal function not easily attributable to hemodynamic factors or doses of calcineurin inhibitors. The origin of proteinuria post-transplantation is not always straightforward (3). Patients with ESRD may have variable amounts of proteinuria prior to transplantation depending on the amount of residual renal function, although the time to normalization of proteinuria after transplantation is on average 3-5 weeks (4, 5). Therefore, proteinuria that is increasing after the first month post-transplant should be assumed to be coming from the transplant. Proteinuria *per se* does not immediately implicate recurrent disease, as it can also be caused by acute or chronic rejection, sirolimus toxicity, or transplant glomerulopathy. Cellular elements such as red and white blood cells may also signify recurrent GN, but rejection or infection also needs to be carefully considered and ruled out by biopsy and other appropriate measures.

3. INDIVIDUAL DISEASES RECURRENT IN THE KIDNEY ALLOGRAFT

3.1. Focal and segmental glomerulosclerosis

Focal and segmental glomerulosclerosis (FSGS) is not a single disease, but merely a

catch-all pathological descriptor describing segmental scarring in a minority of the glomeruli. It may be primary, genetic, adaptive, or due to exposures such as viral infection or certain medications. In an attempt to better classify the disease, several histopathological variants have been described: collapsing, tip-lesion, cellular, perihilar, and FSGS not-otherwise-specified (6).

It is the primary form of FSGS that is most likely to recur in the kidney allograft. The precise pathogenesis of primary FSGS remains unknown, but there is strong evidence for a circulating "permeability factor" that brings about changes in the structure and function of the glomerular podocyte. The existence of a soluble circulating factor that is freely filtered and acts globally on podocytes explains the nearly complete effacement of podocyte foot processes, virtually identical to the ultrastructural changes seen in minimal change disease. The existence of such a circulating permeability factor also seems to explain why a newly-transplanted kidney can become proteinuric within hours in its new host. Several candidate molecules have been proposed, such as cardiotrophin-like factor (7) and soluble urokinase receptor (8).

3.1.1. Epidemiology of recurrent FSGS

FSGS may recur in approximately 30-40% of patients who have been transplanted due to primary FSGS. When limited to those studies focusing on primary FSGS alone or on pediatric populations, the incidence of recurrent FSGS may be as high as 50% (1). Due to the aggressiveness of the primary disease and the young age at which ESRD and the need for transplantation may occur, the burden of recurrent disease is quite large in this population and may occur in sequential allografts in the same patient. If the first kidney allograft is lost to recurrent FSGS, the risk of recurrence in the second graft is on the order of 80-100%. Risk factors are mainly those of severe disease, such as childhood onset, rapid progression from diagnosis to ESRD, heavy proteinuria prior to transplantation, or recurrence of FSGS in a previous allograft.

3.1.2. Diagnosis of recurrent FSGS

The hallmark of recurrent FSGS is the rapid onset of heavy proteinuria, averaging two weeks post-transplantation in children, and 7.5 months in adults. In one study that investigated 42 recurrences in 77 pediatric and adult subjects transplanted for primary FSGS, 76% demonstrated evidence of recurrence within 48 hours (9). Early histopathology will show a minimal change-like pattern, with diffuse foot process effacement but few changes on light microscopy (LM) or IF (9, 10). The lesions of FSGS appear to develop over the course of weeks and months of persistent proteinuria, and are more likely to be seen in 3- and 12-month biopsies. Podocyte foot process effacement in post-reperfusion biopsies can be seen within minutes and correlates with early recurrence (11). Later biopsies taken during active recurrent disease will show actual FSGS lesions, suggesting that there is a time course needed for the initial cytoskeletal changes to lead to overt glomerulosclerosis. Recurrence may take the form of the initial variant in approximately 80% of cases, especially for the collapsing and cellular variant of FSGS (10). However, other authors have not seen such as correlation between variant types in the native and transplanted kidney (9).

It is important to understand that other, non-primary forms of FSGS are less likely to recur after transplantation (12). The adaptive form of FSGS due to hyperfiltration-induced injury due to decreased nephron mass relative to body size is unlikely to recur. Inherited forms of FSGS, such as those due to podocin (*NPHS2*) mutations which appear to cause intrinsic podocyte damage are much less likely to recur after transplantation, as the allograft would not be expected to express the same mutant phenotype (13, 14).

3.1.3. Treatment of recurrent FSGS

Despite the fact that FSGS is a leading cause of pediatric kidney failure and that recurrence frequently occurs in the allograft, there is still not a well validated scheme for treatment. Plasmapheresis, to remove immune mediators and the putative permeability factor, has been the mainstay of many treatment regimens, and appears to induce complete or partial remission in 75-85% of cases if performed in the first month after transplantation (13, 15, 16). Remissions may require 8 to 12 pheresis sessions, and a proportion of adult patients with recurrent FSGS may require long term therapy (16). Some investigators have advocated prophylactic plasmapheresis prior to transplantation, while others have not seen a benefit. Immunoadsorption using protein A columns as well as high-dose cyclosporine have also been used effectively (17, 18). Rituximab, often as adjunctive therapy to plasmapheresis, is currently being investigated as a promising therapeutic agent, and has shown benefit in several

case series (19). Pre-emptive treatment with rituximab may also be considered prior to a planned living-donor transplant (19).

3.2. Membranous nephropathy

Membranous nephropathy (MN) occurs as primary disease in the majority of cases diagnosed in the native kidney. MN may also be secondary to a number of systemic disease processes or exposures, such as systemic lupus erythematosus (SLE), hepatitis B infection, malignancy, and use of nonsteroidal anti-inflammatory agents. Only the primary form of recurrent disease will be discussed here; the recurrence of lupus-associated MN will be briefly discussed in the section on recurrent LN.

Prior to discussion of recurrent MN, it is important to highlight the recent findings in primary MN in the native kidney. The long-sought target antigen in adult primary MN was recently identified as the M-type phospholipase A2 receptor (PLA2R), a 180 kDa transmembrane glycoprotein expressed by the glomerular podocyte (20). Autoantibodies to this protein (anti-PLA2R antibodies) can be found in approximately 80% of patients with active disease; the relevant antigen/autoantibody system in the remaining 20% is not currently known. PLA2R-associated MN can also be diagnosed by the enhanced expression of the PLA2R antigen within the immune deposits on biopsy (21-23). Anti-PLA2R is associated with active disease; it is found in the nephrotic state and at relapse, but not during remission. Several studies have shown that changes in anti-PLA2R precede clinical changes as reflected by proteinuria of clinical remission, which hints at the pathogenicity of anti-PLA2R as opposed to its being merely a biomarker.

The natural history of MN in the native kidney is such that one third of patients who undergo spontaneous remission, another third with persistent proteinuria, and a final third who progress to end-stage renal disease. It is not clear if the underlying pathophysiology differs among these groups, and if those who develop ESRD are necessarily more predisposed to an aggressive disease course.

3.2.1. Epidemiology of recurrent MN

Clinically, MN may recur in 10-30% of allografts. However, a recurrence rate as high as 42% has been demonstrated with early surveillance biopsies (24) that have detected the disease in its earliest stages (25). It is not clear that all of these would have led to clinical disease if not treated,

although one study shows similarly high recurrence rates in those with protocol biopsies, whose recurrent disease was detected at a median of 4 months after transplantation, and those with clinical evidence of recurrence, who are detected much later at a median of 83 months after transplantation (26). The potential for a very rapid recurrence of MN following transplantation (within the first week) suggests the presence of a circulating factor that may be present at the time of transplantation (27). A leading candidate is the autoantibody to PLA2R described above. Anti-PLA2R has been reported in patients with recurrent MN (28, 29) and its presence at the time of transplantation may increase the risk of developing disease recurrence (30). Other autoantibodies that have been described in primary MN of the native kidney, such as antibodies to superoxide dismutase or aldose reductase (31), have not yet been reported in recurrent MN.

Similar to other GN, it had initially been suggested that patients receiving living-related kidney transplants are at higher risk of recurrence than those who received deceased-donor allografts (32). However, this has not been confirmed by larger, more recent studies, and no additional risk factors for recurrence have been identified (24, 27, 33).

3.2.2. Diagnosis of recurrent MN

Although indications for biopsy vary among transplant centers, it is reasonable to biopsy any transplant recipient with a history of MN who develops a persistent increase in proteinuria. Diagnosis, as in native disease, is made by the finding of GBM thickening, often with spikes and craters on Jones' stain, with a fine granular capillary loop pattern of IgG and C3 staining. When EM is performed on the allograft biopsy, there may or may not be electron dense subepithelial deposits. Examining protocol biopsies, Rodriguez and colleagues have described stage 0 deposits – absent or miniscule electron dense deposits in the presence of IgG staining on IF (25). An additional tool that may help distinguish recurrent MN from *de novo* disease (often associated with chronic humoral rejection) is the presence of PLA2R within the immune deposits (29, 34). One group found that the presence of PLA2R within deposits has a sensitivity of 83% and specificity of 92% for recurrent MN (34).

Clinical manifestations of recurrent MN are most often observed 13-15 months after transplantation although they may be observed much earlier (within weeks) (24, 27, 35). The most common

clinical manifestation is proteinuria, the degree of which may vary on presentation between only minimally elevated to fully nephrotic-range. Protein excretion is often lower among those with recurrent MN detected by protocol biopsy and without overt signs or symptoms of disease (24, 27). In one study, proteinuria was 0.3 g/d when disease was detected by protocol biopsy at a median of 4 months after transplantation *vs.* 4.4 g/d when detected clinically at a median of 83 months after transplantation (26). Progression of proteinuria is common even among patients with mild or no proteinuria on presentation. GFR is typically normal at presentation but often decreases with progression of disease.

3.2.3. Treatment of recurrent MN

Recurrent disease can lead to loss of the allograft (36, 37), emphasizing the need to identify and potentially treat patients early in their disease course. In the largest study to date, including 81 renal transplant recipients with MN on biopsy of their native kidney, the incidence of allograft loss at 10 years due to recurrent disease was 12.5% (37). Patients with recurrent MN may have intrinsically more aggressive disease since they already represent the minority of MN patients whose disease in the native kidney has led to ESRD, and since their disease has recurred in spite of transplant immunosuppression. Initial therapy should be supportive, with the use of renin-angiotensin-aldosterone system (RAAS) inhibitors, optimization of blood pressure control, and diuretics if necessary. This may be all that is necessary for mild proteinuria, although frequent reassessment is necessary, since proteinuria may increase with duration of active disease (25).

For those with heavy proteinuria and/or worsening renal function from recurrent MN, rituximab is currently considered the first line agent. The standard doses of cyclosporine, tacrolimus, and mycophenolate mofetil (MMF) used for immunosuppression after transplantation do not seem to protect against or change the course of recurrent disease (38, 39). There are no large clinical trials to guide therapy in recurrent MN and therefore much of the clinical experience with rituximab is anecdotal. In one series, eight patients with recurrent MN and nephrotic range proteinuria were treated with two 1g doses of rituximab (24). Six had entered remission by 12 months, although one had relapsed by 24 months. Post-treatment biopsies showed evidence of partial resolution of the disease process, with resorption of electron dense immune deposits and negative staining for C3 and IgG in a number of the biopsies. Rituximab has also stabilized or reduced proteinuria in two other small series of recurrent MN (26, 27).

The optimal dose of rituximab for recurrent MN is not known, as dosing regimens used for native MN (two doses of 1g given two weeks apart or 4 weekly doses of 375 mg/m^2) may cause significant immunosuppression or other toxic effects among patients who are already on transplant immunosuppression (40). Lower doses of rituximab may be equally effective at depleting B cells in this transplant population, but no studies have examined such low-dose therapy for the treatment of recurrent MN. All other transplant immunosuppressive agents are continued and in general dose reduction is not necessary. The clinical response to rituximab may be delayed for months, especially if the patient has already developed nephrotic-range proteinuria and well-established subepithelial deposits by electron microscopy. With the availability of clinical testing for anti-PLA2R, serological monitoring of anti-PLA2R levels may represent an earlier biomarker of immunological response in those patients with PLA2R-associated recurrent MN (41).

Among transplanted patients who do not respond to rituximab, cytotoxic agents such as cyclophosphamide may be cautiously used for the treatment of recurrent MN. If such therapy is considered, antimetabolic agents such as MMF or azathioprine should be discontinued and patients should be followed closely for bone marrow suppression, infection, and malignancy. There are no rigorous studies that have examined the effect of cyclophosphamide or chlorambucil in recurrent MN (35).

3.3. Membranoproliferative glomerulonephritis

Just like FSGS and MN, MPGN represents a histopathologic pattern of injury rather than a specific diagnosis. The classification of subtypes of MPGN have recently been updated to better emphasize underlying cause (42), although much of the literature on recurrence is based on the older classification scheme, which was defined by the ultrastructural location of the immune deposits. MPGN-I had primarily subendothelial deposits, MPGN-II (now known as dense-deposit disease; DDD) had very electron dense intramembranous deposits, and the rarer entity of MPGN-III had evidence of both subendothelial and subepithelial deposits. The

current classification relies on IF microscopy to assess the presence of immunoglobulin (Ig) and the complement component C3. Cases associated with chronic infection, autoimmune disease, monoclonal gammopathies or paraproteinemias typically exhibit an Ig+ C3+ pattern, whereas MPGN involving dysregulation of the complement system (such as DDD and C3 GN) lack Ig by IF (Ig- C3+). Other forms of MPGN such as that due to endothelial injury from malignant hypertension or calcineurin inhibitors may lack both Ig and C3. We will focus on the primary or idiopathic forms of MPGN and DDD in this review; other forms of MPGN may recur in the transplant, such as that due to lupus (see below), infection with hepatitis C, monoclonal gammopathies, or various causes of thrombotic microangiopathy (35).

3.3.1. Epidemiology of recurrent MPGN

The specific etiologic cause of MPGN likely influences the likelihood of recurrence, and therefore estimates of recurrence rates are unreliable, as various subtypes have been lumped together in previous reports on recurrence as well as treatment. The 5-year allograft survival in the broad category of MPGN is poorer than in other high-risk glomerular disorders (43), but may vary somewhat depending on the subtype of disease. Patients with type I MPGN and DDD have a younger median age at transplantation than for many other glomerular disorders, and thus recurrent disease assumes a larger magnitude of disease burden, similar to recurrent FSGS (44). In this cohort, recurrent disease was found to be the cause of allograft failure in 14.5% of type I MPGN, but 29.5% cases of DDD. The 5-year allograft survival in the setting of recurrent DDD is only 50% (45). Others have found a similar overall 5-year allograft survival of 50% in a cohort of 75 pediatric patients (46), although only a proportion were felt to have lost their allograft due to recurrent disease.

Although the specific underlying etiology of MPGN / DDD appears to affect the recurrence rate, the severity of the disease in native kidney is also another important predictor; crescentic disease tends to have a higher recurrence rate in the allograft (47). Moroni and colleagues (48) found that both long-term patient and graft survival were similar in patients who were transplanted for ESRD due to MPGN *vs*. other causes of kidney failure. However, recurrent MPGN, which occurred in approximately one quarter of the patients, was associated with graft loss in 56%. Patients with recurrence were younger at the onset of disease in their native kidneys, and tended to have low C3 after transplantation.

3.3.2. Diagnosis of recurrent MPGN

Due to a high rate of recurrence and its associated morbidity, especially for DDD, transplant recipients should be followed closely for manifestations of recurrent disease, which presents as hematuria with sub-nephrotic or nephrotic proteinuria in the first year after transplantation (49), often with worsened allograft function. Biopsy will show the MPGN lesion, although there is lack of specificity, since an MPGN pattern can also be seen due to established transplant glomerulopathy or a chronic thrombotic microangiopathy due to transplant medications (1). IF and EM analysis is necessary to look for evidence of discrete electron dense deposits consisting of immunoglobulin and/ or complement factors. Endothelial injury, mesangial interposition, and duplication of the GBM may be seen in all forms of recurrent and *de novo* MPGN, and thus are not as specific in the allograft biopsy.

3.3.3. Treatment of recurrent MPGN

Little data exists as to whether intensification of existing transplant immunosuppression or provision of adjuvant therapy will alter the course of recurrent MPGN. Studies are limited by the disparate etiologies of underlying disease, and thus transplant nephrologists must individualize treatment based on current understanding of disease pathophysiology. Anecdotal reports suggest that recurrent primary MPGN may respond to cyclophosphamide or high dose mycophenolate but overall results are disappointing (35). Plasmapheresis is of equivocal benefit as well. Rituximab has been tried in several cases to inhibit production of C3 nephritic factor, but often without avail. Eculizumab, a humanized monoclonal antibody that inhibits the terminal complement pathway, has stabilized the disease process in several reports, but cannot be withdrawn without re-exacerbating the disease process (50, 51).

3.4. Immunoglobulin A nephropathy

IgA nephropathy (IgAN) is the most common primary GN worldwide. It is characterized histopathologically by diffuse mesangial deposits consisting of IgA associated with mesangial hypercellularity. Recent research has shown that these deposits often consist of IgA1 molecules that carry galactose-deficient O-linked glycan chains in their hinge region (52). The deposits may also contain autoantibodies (which can be IgG, IgA, or IgM) to this abnormally glycosylated IgA1 molecule, in addition to C3 and properdin (35, 52). Biopsy-proven IgAN may lead to ESRD in 30-50% of patients after 25 years of follow up, although this is likely

a significant overestimate, as many patients with subclinical, mild disease are never biopsied. In some Asian populations, the disease is so common that a significant proportion of donor kidneys will have evidence of pre-existing IgAN (53). For patients that require renal replacement therapy, transplantation is the treatment of choice (35, 52).

3.4.1. Epidemiology of recurrent IgAN

Similar to other recurrent GN, rates of recurrent IgAN differ according to whether biopsies are performed by protocol or by clinical indication. Fifty to sixty percent of patients will experience a histologic recurrence of the disease if protocol biopsies are obtained (54, 55) but many of these may never have come to clinical attention. Recurrent IgAN was initially thought to be a relatively benign disease, but this view has changed more recently as longer follow-up data have become available. A review of 11 retrospective studies that included 1200 patients with an average follow up of 5 years (55) revealed that 13% of the patients had some graft dysfunction related to disease recurrence, and only 5% lost their graft. During the first years after transplantation, graft and patient survival in IgAN appears to be superior to other glomerular diseases as well as other transplant patients and other causes for allograft nephropathy (55).

In another contemporary review (39) that summarized data from 16 different studies (including Asian populations with potentially more aggressive clinical disease), recurrence rates ranged from 13%-50%, with a 2-16% risk of graft loss 5-10 years post-transplant. Others have documented a 10 year graft survival in patients with recurrent IgAN that was similar when compared to that in other renal diseases (56). However, there is a significant amount of evidence showing that with even longer follow up, graft survival in patients with recurrence of IgAN might in fact be worse, ranging from 9.7%-13% graft loss after 10 years of follow up (37, 57, 58). A recent single center Italian study compared 190 transplanted IgAN patients to 380 non-diabetic control transplant recipients and demonstrated a 10% lower graft survival in the IgAN patients after 15 years of follow-up (59). The risk of recurrence in a second allograft in patients with prior graft loss due to IgAN is significant with high reported rates of graft loss (25%-60%) (39, 55, 60). However, a recently-published retrospective review of 33 patients with second transplant due to primary disease recurrence, 75% of the patients with IgAN had no significant graft dysfunction more than ten years following their second transplant (61). This may

suggest that patients with graft loss due to recurrent IgAN should be still considered for re-transplantation.

Multiple risk factors for IgAN recurrence in the allograft have been identified over the years. The current consensus in the literature is that younger recipient age and rapid progression of native disease increase the risk for recurrence, whereas the presence of proteinuria and elevated creatinine are associated with shortened graft survival (35, 55, 56, 62, 63). The presence of crescents and/or fibrinoid necrosis on allograft biopsy has also been shown to negatively impact graft survival (59, 63). In an Asian population with a relatively high proportion of subclinical IgAN in the general population, Moriyama and colleagues studied the role of latent IgA deposits from the donor kidney as a risk factor for IgA recurrence (53). This study demonstrated a significantly higher prevalence of latent deposits in the recurrent IgAN group (38.5%) than in the non-recurrent group (9.1%) as well as an increased incidence of graft loss in those patients (53). Data from more than 1200 IgAN transplanted patients in the Eurotransplant registry demonstrated a worse 10 year graft survival in IgAN patients carrying the HLA-B8, DR3 haplotype (64). A Japanese study (62) failed to show a correlation between HLA haplotype and IgAN recurrence *per se*, but similar to the previous report, also demonstrated a worse 10 year graft survival in patients carrying the HLA-B8 and DR3 haplotype. The role of HLA haplotype as a risk factor for recurrent IgAN remains controversial at this point.

The relationship between the risk of IgA recurrence and the donor type (living related *vs*. non-related) also remains unresolved in the literature. Although the impact of living related donor was previously reported as having a negative effect on graft survival (65), most of the studies failed to demonstrate a significant difference (35, 39, 55, 57, 59, 63). However, since familial IgA nephropathy carries a significantly increased risk for end stage renal disease, even minor urinary abnormality in a related donor should be evaluated by kidney biopsy prior to transplant.

3.4.2. Diagnosis of recurrent IgAN

Recurrent IgA nephropathy usually manifests itself clinically as persistent microscopic hematuria as well as proteinuria that can exceed 0.5 g/day but will more often remain below this level. Histologic recurrence of IgAN requires not only mesangial deposits of IgA, but also evidence of a mesangioproliferative GN. Occasionally, recurrent

IgAN can present as a crescentic GN, which carries a significantly worse prognosis in terms of allograft survival (35, 52, 55, 59). The diagnostic or prognostic role of glycan-specific IgG and IgA antibodies that recognize the undergalactosylated IgA1 molecule remains untested in recurrent IgAN.

3.4.3. Treatment of recurrent IgAN

There is currently no effective therapy for the prevention and/or treatment of recurrent IgAN (35, 39). Although initially promising, some of the newer agents for transplant immunosuppression such as MMF, originally thought to slow progression to graft failure in recurrent IgAN, have failed to demonstrate any significant benefit (39, 55). Induction with anti-thymocyte globulin has been associated with a significant decrease in the recurrence rate of IgAN in one study (66) and the use of steroids in the transplant immunosuppression regimen has also been strongly associated with decreased risk of recurrence (67). Based on previous reports of the efficacy of tonsillectomy in conjunction with steroids in native disease (68), a randomized trial demonstrated that tonsillectomy alone was an effective treatment for persistent proteinuria in patients with recurrent IgA nephropathy (69). Such a strategy remains controversial, especially in a US population. RAAS blockade with ACE inhibitors or angiotensin receptor blockers, a well-established treatment for reducing proteinuria and controlling blood pressure in patients with native IgAN, is a reasonable therapeutic approach for IgAN recurrence in the allograft (35, 52, 70).

3.5. Lupus nephritis

Despite the significant improvement in management of LN for the last few decades, 10-30% of patients with severe LN will progress to ESRD, with renal injury being one of the most significant predictors of mortality in patients with SLE (71). In the early era of renal transplantation, LN patients that developed ESRD were managed on chronic dialysis and renal transplantation was avoided, mainly for the concern of rapid destruction of the renal allograft by the immune complex depositions. This approach changed significantly followed by the publication of the Renal Transplant Registry Report (72) that documented similar graft survival rates in renal transplant recipients with SLE compared to other non-diabetic causes of ESRD.

3.5.1. Epidemiology of recurrent LN

The frequency and clinical significance of recurrent LN in the kidney allograft varies considerably. An early review of the literature reported a recurrence rate of 2.7-3.8% in a total of 366 allografts transplanted at multiple centers (73). Only 5.7% of the patients experienced clinical symptoms of extra-renal lupus, and 11.1% had positive serologies. Other studies reported similarly low recurrence rates of 2-3% (74, 75), whereas some have demonstrated much higher rates (76-80). Some of this discrepancy is due to the increased use of IF and EM, in addition to light microscopy, for analysis of the transplant biopsy, as studies using these modalities to detect recurrent disease report rates in the 20-50% range (78-80). All types of LN may recur in the allograft, including class V (membranous) LN, although the milder mesangioproliferative forms tend to predominate (76, 79).

Most cases of recurrent LN will not result in loss of the allograft, with only 4-9.1% of graft failure attributed to recurrence of LN (74, 75, 80-82). Cohorts that include a higher percentage of class IV LN in the native kidney appear to have higher overall relative risks for allograft failure (75), although only 7% of these were considered due to recurrent LN and most were due to rejection. Both recurrent LN and chronic rejection are clearly major risk factors for allograft loss in this population (76). Factors identified as risk factors for recurrent disease are female gender, black non-Hispanic race, and age less than 33 years (75, 76). Patients with anti-phospholipid antibodies are at increased risk of thrombotic complications, graft loss, as well as higher rates of recurrent LN (77, 78, 83-85).

3.5.2. Diagnosis of recurrent LN

Recurrent LN tends to be a relatively benign disease, often clinically apparent only as mild proteinuria and microscopic hematuria, and rarely with systemic manifestations such as arthritis or cutaneous lesions (78, 81). There is minimal evidence to support positive serologies as diagnostic of recurrent LN (74, 79, 83). Anti-nuclear and anti-double stranded DNA antibodies may be positive post-transplantation but do not necessarily indicate recurrent LN (77, 79, 83).

The histologic features of recurrent LN are predominantly mesangial deposits (class I or II LN) that can develop at any time from 6 days to one decade post-transplant (74, 76, 79, 80). IF of the allograft biopsy will usually demonstrate polyclonal staining for IgG, IgM, C1q and C3, with evidence of subendothelial and mesangial deposits by EM, similar to the findings typical of LN in the native kidney (73, 79, 80).

3.5.3. Treatment of recurrent LN

The recommended immunosuppressive treatment for patients transplanted for LN does not differ from the standard transplant immunosuppression protocols. Azathioprine, MMF, and calcineurin inhibitors have been successfully used to treat LN (81, 85, 86). The favorable response to treatment of recurrent LN with pulse steroid therapy as well as increased doses of MMF is consistent with the fact that most of the cases of recurrent disease are mild (80). Of note, Burgos and colleagues have demonstrated a protective effect of azathioprine, as well as negative effect of tacrolimus, with regard to the development of recurrent LN (76), although no effect on allograft or patient survival was shown.

4. SUMMARY AND PERSPECTIVES

Recurrent glomerular disease may occur any time from days to years after transplantation, and is often associated with worse outcome in terms of allograft survival. Recurrent primary FSGS, type I MPGN, and DDD appear to have the most aggressive course, followed by recurrent MN, IgAN, and LN. Although not discussed here, small vessel vasculitis and anti-GBM nephritis may also recur in the allograft in a small proportion of cases. Transplant nephrologists need to be aware of the potential of recurrence, early or late, in those with known or suspected glomerular disease that led to ESRD in the native kidney. Future research into the pathogenesis of specific glomerular disorders as well as related biomarkers will have an important impact on the diagnosis and prognosis of recurrent disease. It is hoped that a future emphasis on disease-specific therapy, rather than on generalized immunosuppression, will allow the precise targeting of recurrent glomerular disease without negatively impacting infection risk or alloimmunity to the transplanted organ.

5. ACKNOWLEDGEMENTS

6. REFERENCES

1. W. A. Golgert, G. B. Appel and S. Hariharan: Recurrent glomerulonephritis after renal transplantation: an unsolved problem. Clin J Am Soc Nephrol, 3(3), 800-7 (2008)
DOI: 10.2215/CJN.04050907

2. K. E. Lamb, S. Lodhi and H. U. Meier-Kriesche: Long-term renal allograft survival in the United States: a critical reappraisal. Am J Transplant, 11(3), 450-62 (2011)
DOI: 10.1111/j.1600-6143.2010.03283.x

3. M. K. Shamseddin and G. A. Knoll: Posttransplantation proteinuria: an approach to diagnosis and management. Clin J Am Soc Nephrol, 6(7), 1786-93 (2011)
DOI: 10.2215/CJN.01310211

4. P. T. D'Cunha, R. Parasuraman and K. K. Venkat: Rapid resolution of proteinuria of native kidney origin following live donor renal transplantation. Am J Transplant, 5(2), 351-5 (2005)
DOI: 10.1111/j.1600-6143.2004.00665.x

5. M. Myslak, H. Amer, P. Morales, M. E. Fidler, J. M. Gloor, T. S. Larson, M. D. Stegall and F. G. Cosio: Interpreting post-transplant proteinuria in patients with proteinuria pre-transplant. Am J Transplant, 6(7), 1660-5 (2006)
DOI: 10.1111/j.1600-6143.2006.01361.x

6. V. D. D'Agati, A. B. Fogo, J. A. Bruijn and J. C. Jennette: Pathologic classification of focal segmental glomerulosclerosis: a working proposal. Am J Kidney Dis, 43(2), 368-82 (2004)
DOI: 10.1053/j.ajkd.2003.10.024

7. E. T. McCarthy, M. Sharma and V. J. Savin: Circulating permeability factors in idiopathic nephrotic syndrome and focal segmental glomerulosclerosis. Clin J Am Soc Nephrol, 5(11), 2115-21 (2010)
DOI: 10.2215/CJN.03800609

8. C. Wei, S. El Hindi, J. Li, A. Fornoni, N. Goes, J. Sageshima, D. Maiguel, S. A. Karumanchi, H. K. Yap, M. Saleem, Q. Zhang, B. Nikolic, A. Chaudhuri, P. Daftarian, E. Salido, A. Torres, M. Salifu, M. M. Sarwal, F. Schaefer, C. Morath, V. Schwenger, M. Zeier, V. Gupta, D. Roth, M. P. Rastaldi, G. Burke, P. Ruiz and J. Reiser: Circulating urokinase

receptor as a cause of focal segmental glomerulosclerosis. Nat Med, 17(8), 952-60 (2011)
DOI: 10.1038/nm.2411

9. G. Canaud, D. Dion, J. Zuber, M. C. Gubler, R. Sberro, E. Thervet, R. Snanoudj, M. Charbit, R. Salomon, F. Martinez, C. Legendre, L. H. Noel and P. Niaudet: Recurrence of nephrotic syndrome after transplantation in a mixed population of children and adults: course of glomerular lesions and value of the Columbia classification of histological variants of focal and segmental glomerulosclerosis (FSGS). Nephrol Dial Transplant, 25(4), 1321-8 (2010)
DOI: 10.1093/ndt/gfp500

10. D. H. IJpelaar, A. B. Farris, N. Goemaere, K. Amann, R. Goldschmeding, T. Q. Nguyen, E. Farkash, M. C. van den Heuvel, E. de Heer, J. A. Bruijn, R. B. Colvin and I. M. Bajema: Fidelity and evolution of recurrent FSGS in renal allografts. J Am Soc Nephrol, 19(11), 2219-24 (2008)
DOI: 10.1681/ASN.2007121365

11. J. W. Chang, V. Pardo, J. Sageshima, L. Chen, H. L. Tsai, J. Reiser, C. Wei, G. Ciancio, G. W. Burke and A. Fornoni: Podocyte foot process effacement in postreperfusion allograft biopsies correlates with early recurrence of proteinuria in focal segmental glomerulosclerosis. Transplantation, 93(12), 1238-44 (2012)
DOI: 10.1097/TP.0b013e318250234a

12. L. J. Hickson, M. Gera, H. Amer, C. W. Iqbal, T. B. Moore, D. S. Milliner, F. G. Cosio, T. S. Larson, M. D. Stegall, M. B. Ishitani, J. M. Gloor and M. D. Griffin: Kidney transplantation for primary focal segmental glomerulosclerosis: outcomes and response to therapy for recurrence. Transplantation, 87(8), 1232-9 (2009)
DOI: 10.1097/TP.0b013e31819f12be

13. M. E. Schachter, M. Monahan, J. Radhakrishnan, J. Crew, M. Pollak, L. Ratner, A. M. Valeri, M. B. Stokes and G. B. Appel: Recurrent focal segmental glomerulosclerosis in the renal allograft: single center experience in the era of modern immunosuppression. Clin Nephrol, 74(3), 173-81 (2010)
DOI: 10.5414/CNP74173

14. T. C. Jungraithmayr, K. Hofer, P. Cochat, G. Chernin, G. Cortina, S. Fargue, P. Grimm, T. Knueppel, A. Kowarsch, T. Neuhaus, P. Pagel, K. P. Pfeiffer, F. Schäfer, U. Schönermarck, T. Seeman, B. Toenshoff, S. Weber, M. P. Winn, J. Zschocke and L. B. Zimmerhackl: Screening for NPHS2 mutations may help predict FSGS recurrence after transplantation. J Am Soc Nephrol, 22(3), 579-85 (2011)
DOI: 10.1681/ASN.2010010029

15. J. K. Deegens, M. B. Andresdottir, S. Croockewit and J. F. Wetzels: Plasma exchange improves graft survival in patients with recurrent focal glomerulosclerosis after renal transplant. Transpl Int, 17(3), 151-7 (2004)
DOI: 10.1111/j.1432-2277.2004.tb00420.x

16. M. Vinai, P. Waber and M. G. Seikaly: Recurrence of focal segmental glomerulosclerosis in renal allograft: an in-depth review. Pediatr Transplant, 14(3), 314-25 (2010)
DOI: 10.1111/j.1399-3046.2009.01261.x

17. V. L. Esnault, D. Besnier, A. Testa, P. Coville, P. Simon, J. F. Subra and M. A. Audrain: Effect of protein A immunoadsorption in nephrotic syndrome of various etiologies. J Am Soc Nephrol, 10(9), 2014-7 (1999)

18. G. Canaud, F. Martinez, L. H. Noël, M. F. Mamzer, P. Niaudet and C. Legendre: Therapeutic approach to focal and segmental glomerulosclerosis recurrence in kidney transplant recipients. Transplant Rev (Orlando), 24(3), 121-8 (2010)
DOI: 10.1016/j.trre.2010.04.001

19. A. Sinha and A. Bagga: Rituximab therapy in nephrotic syndrome: implications for patients' management. Nat Rev Nephrol, 9(3), 154-69 (2013)

DOI: 10.1038/nrneph.2012.289

20. L. H. Beck, Jr., R. G. Bonegio, G. Lambeau, D. M. Beck, D. W. Powell, T. D. Cummins, J. B. Klein and D. J. Salant: M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med, 361(1), 11-21 (2009)
DOI: 10.1056/NEJMoa0810457

21. H. Debiec and P. Ronco: PLA2R autoantibodies and PLA2R glomerular deposits in membranous nephropathy. N Engl J Med, 364(7), 689-90 (2011)
DOI: 10.1056/NEJMc1011678

22. E. Hoxha, U. Kneißler, G. Stege, G. Zahner, I. Thiele, U. Panzer, S. Harendza, U. M. Helmchen and R. A. Stahl: Enhanced expression of the M-type phospholipase A2 receptor in glomeruli correlates with serum receptor antibodies in primary membranous nephropathy. Kidney Int, 82(7), 797-804 (2012)
DOI: 10.1038/ki.2012.209

23. C. P. Larsen, N. C. Messias, F. G. Silva, E. Messias and P. D. Walker: Determination of primary versus secondary membranous glomerulopathy utilizing phospholipase A2 receptor staining in renal biopsies. Mod Pathol, 26(5), 709-15 (2013)
DOI: 10.1038/modpathol.2012.207

24. T. S. Dabade, J. P. Grande, S. M. Norby, F. C. Fervenza and F. G. Cosio: Recurrent idiopathic membranous nephropathy after kidney transplantation: a surveillance biopsy study. Am J Transplant, 8(6), 1318-22 (2008)
DOI: 10.1111/j.1600-6143.2008.02237.x

25. E. F. Rodriguez, F. G. Cosio, S. H. Nasr, S. Sethi, M. E. Fidler, M. D. Stegall, J. P. Grande, F. C. Fervenza and L. D. Cornell: The pathology and clinical features of early recurrent membranous glomerulonephritis. Am J Transplant, 12(4), 1029-38 (2012)
DOI: 10.1111/j.1600-6143.2011.03903.x

26. Z. M. El-Zoghby, J. P. Grande, M. G. Fraile, S. M. Norby, F. C. Fervenza and F. G. Cosio: Recurrent Idiopathic Membranous Nephropathy: Early Diagnosis by Protocol Biopsies and Treatment with Anti-CD20 Monoclonal Antibodies. Am J Transplant, 9(12), 2800-7 (2009)
DOI: 10.1111/j.1600-6143.2009.02851.x

27. B. Sprangers, G. I. Lefkowitz, S. D. Cohen, M. B. Stokes, A. Valeri, G. B. Appel and C. L. Kunis: Beneficial effect of rituximab in the treatment of recurrent idiopathic membranous nephropathy after kidney transplantation. Clin J Am Soc Nephrol, 5(5), 790-7 (2010)
DOI: 10.2215/CJN.04120609

28. R. Stahl, E. Hoxha and K. Fechner: PLA2R autoantibodies and recurrent membranous nephropathy after transplantation. N Engl J Med, 363(5), 496-8 (2010)
DOI: 10.1056/NEJMc1003066

29. H. Debiec, L. Martin, C. Jouanneau, G. Dautin, L. Mesnard, E. Rondeau, C. Mousson and P. Ronco: Autoantibodies specific for the phospholipase A2 receptor in recurrent and De Novo membranous nephropathy. Am J Transplant, 11(10), 2144-52 (2011)
DOI: 10.1111/j.1600-6143.2011.03643.x

30. R. Ayalon, L. H. Beck, F. C. Fervenza, F. G. Cosio, D. C. Brennan and D. J. Salant: Do Anti-Phospholipase A2 Receptor Antibodies Predict Recurrence of Membranous Nephropathy after Transplantation? J Am Soc Nephrol, 23, 64A (2012)

31. C. Murtas, M. Bruschi, G. Candiano, G. Moroni, R. Magistroni, A. Magnano, F. Bruno, A. Radice, L. Furci, L. Argentiero, M. L. Carnevali, P. Messa, F. Scolari, R. A. Sinico, L. Gesualdo, F. C. Fervenza, L. Allegri, P. Ravani and G. M. Ghiggeri: Coexistence of Different Circulating Anti-Podocyte Antibodies in Membranous Nephropathy. Clin J Am Soc Nephrol, 7(9), 1394-1400 (2012)
DOI: 10.2215/CJN.02170312

32. B. E. Berger, F. Vincenti, C. Biava, W. J.

Amend, N. Feduska and O. Salvatierra: De novo and recurrent membranous glomerulopathy following kidney transplantation. Transplantation, 35(4), 315-9 (1983)
DOI: 10.1097/00007890-198304000-00010

33. G. Moroni, B. Gallelli, S. Quaglini, A. Leoni, G. Banfi, P. Passerini, G. Montagnino and P. Messa: Long-term outcome of renal transplantation in patients with idiopathic membranous glomerulonephritis (MN). Nephrol Dial Transplant, 25(10), 3408-15 (2010)
DOI: 10.1093/ndt/gfq223

34. C. P. Larsen and P. D. Walker: Phospholipase A2 Receptor (PLA2R) Staining Is Useful in the Determination of De Novo Versus Recurrent Membranous Glomerulopathy. Transplantation, 95 (10), 1259-62 (2013)
DOI: 10.1097/TP.0b013e31828a947b

35. C. Ponticelli and R. J. Glassock: Posttransplant recurrence of primary glomerulonephritis. Clin J Am Soc Nephrol, 5(12), 2363-72 (2010)
DOI: 10.2215/CJN.06720810

36. J. P. Cosyns, C. Couchoud, C. Pouteil-Noble, J. P. Squifflet and Y. Pirson: Recurrence of membranous nephropathy after renal transplantation: probability, outcome and risk factors. Clin Nephrol, 50(3), 144-53 (1998)

37. E. M. Briganti, G. R. Russ, J. J. McNeil, R. C. Atkins and S. J. Chadban: Risk of renal allograft loss from recurrent glomerulonephritis. N Engl J Med, 347(2), 103-9 (2002)
DOI: 10.1056/NEJMoa013036

38. M. A. Josephson, B. Spargo, D. Hollandsworth and J. R. Thistlethwaite: The recurrence of recurrent membranous glomerulopathy in a renal transplant recipient: case report and literature review. Am J Kidney Dis, 24(5), 873-8 (1994)
DOI: 10.1016/S0272-6386(12)80685-8

39. B. Y. Choy, T. M. Chan and K. N. Lai: Recurrent glomerulonephritis after kidney transplantation. Am J Transplant, 6(11), 2535-42 (2006)
DOI: 10.1111/j.1600-6143.2006.01502.x

40. P. Cravedi, P. Ruggenenti and G. Remuzzi: Low-dose rituximab for posttransplant recurrent membranous nephropathy. Am J Transplant, 10(5), 1336 (2010)
DOI: 10.1111/j.1600-6143.2010.03029.x

41. L. H. Beck, Jr., F. C. Fervenza, D. M. Beck, R. G. Bonegio, F. A. Malik, S. B. Erickson, F. G. Cosio, D. C. Cattran and D. J. Salant: Rituximab-induced depletion of anti-PLA2R autoantibodies predicts response in membranous nephropathy. J Am Soc Nephrol, 22(8), 1543-50 (2011)
DOI: 10.1681/ASN.2010111125

42. S. Sethi and F. C. Fervenza: Membranoproliferative glomerulonephritis -a new look at an old entity. N Engl J Med, 366(12), 1119-31 (2012)
DOI: 10.1056/NEJMra1108178

43. K. J. Van Stralen, E. Verrina, M. Belingheri, J. Dudley, J. Dusek, R. Grenda, M. A. Macher, Z. Puretic, J. Rubic, S. Rudaitis, C. Rudin, F. Schaefer, K. J. Jager and E. E.-E. Registry: Impact of graft loss among kidney diseases with a high risk of post-transplant recurrence in the paediatric population. Nephrol Dial Transplant, 28(4), 1031-8 (2013)
DOI: 10.1093/ndt/gfs549

44. J. R. Angelo, C. S. Bell and M. C. Braun: Allograft failure in kidney transplant recipients with membranoproliferative glomerulonephritis. Am J Kidney Dis, 57(2), 291-9 (2011)
DOI: 10.1053/j.ajkd.2010.09.021

45. R. J. Smith, J. Alexander, P. N. Barlow, M. Botto, T. L. Cassavant, H. T. Cook, S. R. de Córdoba, G. S. Hageman, T. S. Jokiranta, W. J. Kimberling, J. D. Lambris, L. D. Lanning, V. Levidiotis, C. Licht, H. U. Lutz, S. Meri, M. C. Pickering, R. J. Quigg, A. L. Rops, D. J. Salant, S. Sethi, J. M. Thurman, H. F. Tully, S. P. Tully, J. van der Vlag, P. D. Walker, R. Würzner, P. F. Zipfel

and D. D. D. F. Group: New approaches to the treatment of dense deposit disease. J Am Soc Nephrol, 18(9), 2447-56 (2007)
DOI: 10.1681/ASN.2007030356

46. M. C. Braun, D. M. Stablein, L. A. Hamiwka, L. Bell, S. M. Bartosh and C. F. Strife: Recurrence of membranoproliferative glomerulonephritis type II in renal allografts: The North American Pediatric Renal Transplant Cooperative Study experience. J Am Soc Nephrol, 16(7), 2225-33 (2005)
DOI: 10.1681/ASN.2005020175

47. M. A. Little, P. Dupont, E. Campbell, A. Dorman and J. J. Walshe: Severity of primary MPGN, rather than MPGN type, determines renal survival and post-transplantation recurrence risk. Kidney Int, 69(3), 504-11 (2006)
DOI: 10.1038/sj.ki.5000084

48. G. Moroni, C. Casati, S. Quaglini, B. Gallelli, G. Banfi, G. Montagnino and P. Messa: Membranoproliferative glomerulonephritis type I in renal transplantation patients: a single-center study of a cohort of 68 renal transplants followed up for 11 years. Transplantation, 91(11), 1233-9 (2011)
DOI: 10.1097/TP.0b013e318218e94e

49. B. Ivanyi: A primer on recurrent and de novo glomerulonephritis in renal allografts. Nat Clin Pract Nephrol, 4(8), 446-57 (2008)
DOI: 10.1038/ncpneph0854

50. J. A. McCaughan, D. M. O'Rourke and A. E. Courtney: Recurrent dense deposit disease after renal transplantation: an emerging role for complementary therapies. Am J Transplant, 12(4), 1046-51 (2012)
DOI: 10.1111/j.1600-6143.2011.03923.x

51. A. S. Bomback, R. J. Smith, G. R. Barile, Y. Zhang, E. C. Heher, L. Herlitz, M. B. Stokes, G. S. Markowitz, V. D. D'Agati, P. A. Canetta, J. Radhakrishnan and G. B. Appel: Eculizumab for dense deposit disease and C3 glomerulonephritis. Clin

J Am Soc Nephrol, 7(5), 748-56 (2012)
DOI: 10.2215/CJN.12901211

52. R. J. Wyatt and B. A. Julian: IgA nephropathy. N Engl J Med, 368(25), 2402-14 (2013)
DOI: 10.1056/NEJMra1206793

53. T. Moriyama, K. Nitta, K. Suzuki, K. Honda, S. Horita, K. Uchida, W. Yumura, K. Tanabe, H. Toma, H. Nihei and Y. Yamaguchi: Latent IgA deposition from donor kidney is the major risk factor for recurrent IgA nephropathy in renal transplantation. Clin Transplant, 19 Suppl 14, 41-8 (2005)
DOI: 10.1111/j.1399-0012.2005.00403.x

54. J. Odum, C. A. Peh, A. R. Clarkson, K. M. Bannister, A. E. Seymour, D. Gillis, A. C. Thomas, T. H. Mathew and A. J. Woodroffe: Recurrent mesangial IgA nephritis following renal transplantation. Nephrol Dial Transplant, 9(3), 309-12 (1994)

55. J. Floege: Recurrent IgA nephropathy after renal transplantation. Semin Nephrol, 24(3), 287-91 (2004)
DOI: 10.1016/j.semnephrol.2004.01.008

56. C. Ponticelli, L. Traversi, A. Feliciani, B. M. Cesana, G. Banfi and A. Tarantino: Kidney transplantation in patients with IgA mesangial glomerulonephritis. Kidney Int, 60(5), 1948-54 (2001)
DOI: 10.1046/j.1523-1755.2001.00006.x

57. B. Y. Choy, T. M. Chan, S. K. Lo, W. K. Lo and K. N. Lai: Renal transplantation in patients with primary immunoglobulin A nephropathy. Nephrol Dial Transplant, 18(11), 2399-404 (2003)
DOI: 10.1093/ndt/gfg373

58. A. Kamal Aziz, C. Mousson, F. Berthoux, D. Ducloux and J. M. Chalopin: Renal transplantation outcome in selected recipients with IgA nephropathy as native disease: a bicentric study. Ann Transplant, 17(3), 45-51 (2012)
DOI: 10.12659/AOT.883457

59. G. Moroni, S. Longhi, S. Quaglini, B. Gallelli, G. Banfi, G. Montagnino and P.

Messa: The long-term outcome of renal transplantation of IgA nephropathy and the impact of recurrence on graft survival. Nephrol Dial Transplant, 28(5), 1305-14 (2013)
DOI: 10.1093/ndt/gfs472

60. C. Ohmacht, V. Kliem, M. Burg, B. Nashan, H. J. Schlitt, R. Brunkhorst, K. M. Koch and J. Floege: Recurrent immunoglobulin A nephropathy after renal transplantation: a significant contributor to graft loss. Transplantation, 64(10), 1493-6 (1997)
DOI:10.1097/00007890-199711270-00024

61. C. Kennedy, A. Obilana, F. O'Brien, P. O'Kelly, A. Dorman, M. Denton, C. Magee and P. Conlon: Glomerular disease recurrence in second and subsequent kidney transplants. Clin Nephrol, 79(1), 31-6 (2013)
DOI: 10.5414/CN107653

62. K. Sato, H. Ishida, K. Uchida, K. Nitta and K. Tanabe: Risk factors for recurrence of immunoglobulin a nephropathy after renal transplantation: single center study. Ther Apher Dial, 17(2), 213-20 (2013)
DOI: 10.1111/j.1744-9987.2012.01139.x

63. K. Kiattisunthorn, N. Premasathian, A. Wongwiwatana, P. Parichatikanond, B. Cheunsuchon and S. Vasuvattakul: Evaluating the clinical course and prognostic factors of posttransplantation immunoglobulin A nephropathy. Transplant Proc, 40(7), 2349-54 (2008)
DOI: 10.1016/j.transproceed.2008.07.008

64. M. B. Andresdottir, G. W. Haasnoot, G. G. Persijn and F. H. Claas: HLA-B8, DR3: a new risk factor for graft failure after renal transplantation in patients with underlying immunoglobulin A nephropathy. Clin Transplant, 23(5), 660-5 (2009)
DOI: 10.1111/j.1399-0012.2009.01059.x

65. A. Y. Wang, F. M. Lai, A. W. Yu, P. K. Lam, K. M. Chow, P. C. Choi, S. F. Lui and P. K. Li: Recurrent IgA nephropathy in renal transplant allografts. Am J Kidney Dis, 38(3), 588-96 (2001)
DOI: 10.1053/ajkd.2001.26885

66. F. Berthoux, S. El Deeb, C. Mariat, E. Diconne, B. Laurent and L. Thibaudin: Antithymocyte globulin (ATG) induction therapy and disease recurrence in renal transplant recipients with primary IgA nephropathy. Transplantation, 85(10), 1505-7 (2008)
DOI: 10.1097/TP.0b013e3181705ad4

67. P. Clayton, S. McDonald and S. Chadban: Steroids and recurrent IgA nephropathy after kidney transplantation. Am J Transplant, 11(8), 1645-9 (2011)
DOI: 10.1111/j.1600-6143.2011.03667.x

68. O. Hotta, M. Miyazaki, T. Furuta, S. Tomioka, S. Chiba, I. Horigome, K. Abe and Y. Taguma: Tonsillectomy and steroid pulse therapy significantly impact on clinical remission in patients with IgA nephropathy. Am J Kidney Dis, 38(4), 736-43 (2001)
DOI: 10.1053/ajkd.2001.27690

69. T. Kennoki, H. Ishida, Y. Yamaguchi and K. Tanabe: Proteinuria-reducing effects of tonsillectomy alone in IgA nephropathy recurring after kidney transplantation. Transplantation, 88(7), 935-41 (2009)
DOI: 10.1097/TP.0b013e3181b75374

70. K. Oka, E. Imai, T. Moriyama, Y. Akagi, A. Ando, M. Hori, A. Okuyama, K. Toki, M. Kyo, Y. Kokado and S. Takahara: A clinicopathological study of IgA nephropathy in renal transplant recipients: beneficial effect of angiotensin-converting enzyme inhibitor. Nephrol Dial Transplant, 15(5), 689-95 (2000)
DOI: 10.1093/ndt/15.5.689

71. N. Maroz and M. S. Segal: Lupus Nephritis and End-Stage Kidney Disease. Am J Med Sci, 346(4), 319-23 (2013)
DOI: 10.1097/MAJ.0b013e31827f4ee3

72. Renal transplantation in congenital and metabolic diseases. A report from the ASC/NIH renal transplant registry. JAMA, 232(2), 148-53 (1975)
DOI: 10.1001/jama.1975.03250020022018

73. C. F. Mojcik and J. H. Klippel: End-stage renal disease and systemic lupus

erythematosus. Am J Med, 101(1), 100-7 (1996)
DOI: 10.1016/S0002-9343(96)00074-5

74. J. H. Stone, W. J. Amend and L. A. Criswell: Outcome of renal transplantation in systemic lupus erythematosus. Semin Arthritis Rheum, 27(1), 17-26 (1997)
DOI: 10.1016/S0049-0172(97)80033-9

75. G. Contreras, A. Mattiazzi, G. Guerra, L. M. Ortega, E. C. Tozman, H. Li, L. Tamariz, C. Carvalho, W. Kupin, M. Ladino, B. LeClercq, I. Jaraba, D. Carvalho, E. Carles and D. Roth: Recurrence of lupus nephritis after kidney transplantation. J Am Soc Nephrol, 21(7), 1200-7 (2010)
DOI: 10.1681/ASN.2009101093

76. P. I. Burgos, E. L. Perkins, G. J. Pons-Estel, S. A. Kendrick, J. M. Liu, W. T. Kendrick, W. J. Cook, B. A. Julian, G. S. Alarcón and C. E. Kew: Risk factors and impact of recurrent lupus nephritis in patients with systemic lupus erythematosus undergoing renal transplantation: data from a single US institution. Arthritis Rheum, 60(9), 2757-66 (2009)
DOI: 10.1002/art.24776

77. G. Moroni, F. Tantardini, B. Gallelli, S. Quaglini, G. Banfi, F. Poli, G. Montagnino, P. Meroni, P. Messa and C. Ponticelli: The long-term prognosis of renal transplantation in patients with lupus nephritis. Am J Kidney Dis, 45(5), 903-11 (2005)
DOI: 10.1053/j.ajkd.2005.01.038

78. G. E. Norby, E. H. Strøm, K. Midtvedt, A. Hartmann, I. M. Gilboe, T. Leivestad, J. Stenstrøm and H. Holdaas: Recurrent lupus nephritis after kidney transplantation: a surveillance biopsy study. Ann Rheum Dis, 69(8), 1484-7 (2010)
DOI: 10.1136/ard.2009.122796

79. S. Goral, C. Ynares, S. B. Shappell, S. Snyder, I. D. Feurer, R. Kazancioglu, A. B. Fogo and J. H. Helderman: Recurrent lupus nephritis in renal transplant recipients revisited: it is not rare. Transplantation, 75(5), 651-6 (2003)

DOI: 10.1097/01.TP.0000053750.59630.83

80. T. M. Yu, M. C. Wen, C. Y. Li, C. H. Cheng, M. J. Wu, C. H. Chen, Y. H. Chen, H. C. Ho and K. H. Shu: Impact of recurrent lupus nephritis on lupus kidney transplantation: a 20-year single center experience. Clin Rheumatol, 31(4), 705-10 (2012)
DOI: 10.1007/s10067-011-1931-y

81. C. Ponticelli, G. Moroni and R. J. Glassock: Recurrence of secondary glomerular disease after renal transplantation. Clin J Am Soc Nephrol, 6(5), 1214-21 (2011)
DOI: 10.2215/CJN.09381010

82. P. Grimbert, J. Frappier, J. Bedrossian, C. Legendre, C. Antoine, C. Hiesse, M. O. Bitker, J. D. Sraer and P. Lang: Long-term outcome of kidney transplantation in patients with systemic lupus erythematosus: a multicenter study. Groupe Cooperatif de Transplantation d'île de France. Transplantation, 66(8), 1000-3 (1998)
DOI: 10.1097/00007890-199810270-00006

83. J. A. Goss, B. R. Cole, M. D. Jendrisak, C. S. McCullough, S. K. So, D. W. Windus and D. W. Hanto: Renal transplantation for systemic lupus erythematosus and recurrent lupus nephritis. A single-center experience and a review of the literature. Transplantation, 52(5), 805-10 (1991)
DOI: 10.1097/00007890-199111000-00009

84. J. H. Stone, W. J. Amend and L. A. Criswell: Antiphospholipid antibody syndrome in renal transplantation: occurrence of clinical events in 96 consecutive patients with systemic lupus erythematosus. Am J Kidney Dis, 34(6), 1040-7 (1999)
DOI: 10.1016/S0272-6386(99)70009-0

85. C. Ponticelli and G. Moroni: Renal transplantation in lupus nephritis. Lupus, 14(1), 95-8 (2005)
DOI: 10.1191/0961203305lu2067oa

86. G. Dong, F. Panaro, D. Bogetti, C. Sammartino, D. Rondelli, H. Sankary, G. Testa and E. Benedetti: Standard chronic immunosuppression after kidney transplantation for systemic lupus

erythematosus eliminates recurrence of disease. Clin Transplant, 19(1), 56-60 (2005)
DOI: 10.1111/j.1399-0012.2004.00297.x

Abbreviations: FSGS: focal and segmental glomerulosclerosis; MN: membranous nephropathy; MPGN: membranoproliferative glomerulonephritis; IgAN: immunoglobulin A nephropathy; LN: lupus nephritis; GN: glomerulonephritis; ESRD: end-stage renal disease; CKD: chronic kidney disease; IF: immunofluorescence; EM: electron microscopy; LM: light microscopy; SLE: systemic lupus erythematosus; PLA2R: phospholipase A2 receptor; GBM: glomerular basement membrane; GFR: glomerular filtration rate; RAAS: renin-angiotensin-aldosterone system; MMF: mycophenolate mofetil; DDD: dense deposit disease; ACE: angiotensin converting enzyme

Key Words: Kidney transplant, Recurrent glomerulonephritis, Focal and segmental glomerulosclerosis, Membranous nephropathy, Membranoproliferative glomerulonephritis, IgA nephropathy, Lupus nephritis, Review

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