Review Article

Recurrent Glomerulonephritis in the Kidney Allograft

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Abstract

Renal transplantation is the preferred form of renal replacement therapy in patients who develop end-stage kidney disease (ESKD). Among the diverse etiologies of ESKD, glomerulonephritis is the third most common cause, behind hypertensive and diabetic kidney disease. Although efforts to prolong graft survival have improved over time with the advent of novel immunosuppression, recurrent glomerulonephritis remains a major threat to renal allograft survival despite concomitant immunosuppression. As a result, clinical expertise, early diagnosis and intervention will help identify recurrent disease and facilitate prompt treatment, thus minimizing graft loss, resulting in improved outcomes. In this review, we highlight the clinicopathologcal characteristics of certain glomerular diseases that recur in the renal allograft.

Keywords: *Focal segmental glomerulosclerosis, glomerulonephritis, IgA nephropathy, kidney allograft, lupus nephritis, membranoproliferative, membranous nephropathy, monoclonal gammopathy*

Introduction

Glomerulonephritis (GN) is a significant cause of end-stage kidney disease (ESKD) world-wide and kidney transplantation is the optimal form of renal replacement therapy. Data from national registries and large publications from Australia, New Zealand, China, United States, and Saudi Arabia suggest that GN accounts for ESKD in 50%, 48%, 30%, and 21% of renal transplant recipients respectively.[1] In India, the true prevalence of GN as a cause for ESKD cannot be estimated in the absence of a national registry; however, primary glomerulonephritis accounted for 69.1% of renal disease in a 19 year retrospective, single-center study of biopsy proven renal disease in south India.[2] Recurrence of glomerulonephritis in the renal allograft is an important complication in those with native kidney GN, accounting for 14.3% (23 of 153) of death-censored graft losses in one study.[3] In fact with improved outcomes of renal allografts due to improved immunosuppressive strategies and decreased graft loss from rejection, recurrent and *de novo* glomerulonephritis is becoming an important cause of allograft loss.

The extent of recurrent glomerulonephritis is most likely underestimated for many reasons. First, several patients undergo transplantation without a biopsy diagnosis of the cause of ESKD and therefore, many recurrent GN are misdiagnosed as de-novo disease. Second, insufficient duration of follow-up and lack of established registries lowers reported rates of recurrence. Third, detection is missed in centers where follow-up is more remote to the transplant center and who pursue only for cause biopsies and finally, diagnosing recurrent GN is dependant on comprehensive biopsy evaluation with immunofluoresence (IF) and electron microscopy (EM), which is not routine practice in allograft biopsy evaluation.

In this review, we will focus on the clinicopathological characteristics of certain recurrent glomerular diseases: immunoglobulin A (IgA) nephropathy,[4,5] membranous nephropathy (MN),[5,6] focal segmental glomerulosclerosis (FSGS),[5] lupus nephritis, complement-mediated glomerulonephritis,[5] and some monoclonal gammopathy-related renal diseases.

IgA nephropathy

IgA nephropathy (IgAN) is a common cause of GN in Asia, accounting for approximately 7–16% of biopsy proven glomerular disease in the Indian population, with recent rates from South India reported at 13.2% of all

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native kidney biopsies peformed in Bangalore, Chennai, Hyderabad, and Kochi combined.[7] Although not the most common primary GN in this population, it appears to have a more severe phenotype in India and renal outcomes are poor.[8] Berger's original report described recurrence in as many as half of the patients who are transplanted.[9] Reported rates of recurrence of IgAN are highly variable, from 12% to 65%[10] and one restrospective study from India showed a recurrence rate of 25%,[11] which is attributed to high rates of subclinical detection in protocol biopsies, as opposed to those clinically indicated. IgA recurrence was seen in as many as 12.5% of protocol biopsies performed at 1 year and in 32% of protocol biopsies by 2 years[1,12] with routine IF increasing rates of recurrence detection to 46.4%.[13] The follow-up time influences the reported rates of recurrence, as IgAN is often seen later. Median time to recurrence is around 39.5 months (31–48) [Table 1]. Odum *et al*. demonstrated that the only predictor identified for recurrence of mesangial IgA deposits was length of time posttransplantation, with biopsy being studied at 45.9 ± 10.0 versus 15.3 ± 4.8 months ($P = 0.008$) posttransplantation, in patients with and without recurrent deposits, respectively.[14]

Clinical features at recurrence are similar to native disease with proteinuria, microscopic, and macroscopic hematuria. Marked mesangial proliferative histology and glomerulosclerosis are indicators of increased graft loss due to recurrent disease[15] [Figure 1]. Allograft survival survival was 66% in 36 patients with IgAN versus 57% in 363 with other renal diseases studied by Alamartine.[16] Soler *et al*. observed a 5-year graft survival of 81% in those with IgAN versus 78% without IgAN,[15] but differences were seen in patients with crescentic IgA/HSP glomerulonephritis diagnosed in the native biopsy with 5-year graft survival of 71% in contrast with 100% graft survival without crescentic lesions.[15] Crescentic IgAN accounts for 11% to 57% of native biopsy proven IgAN in a series reported from India,[17,18] suggesting the need for a more guarded prognosis and warranting closer monitoring of urinalysis and renal function in higher risk recipients.

Graft loss due to recurrent IgAN is variable, from as low as 0.9% to 17.2% and variability is due to, criteria for recurrence, the population and length of follow-up.[19] However, in a Chinese population who had posttransplant glomerulonephritis, IgA nephropathy accounted for 49% of those who had allograft loss due to recurrent GN.[20] In a single center experience from the Mayo Clinic, Merzkani *et al*. showed that among 137 patients with IgAN who were transplanted between 1999 and 2012, 54.7% demonstrated histological recurrence with 50.6% of those with clinical data (45/89) having a clinical recurrence. Twelve of 44 had allograft loss due to recurrent disease at 71.9 ± 43 (28–152) months from transplant. However, those with histological recurrence did not show an increased risk of graft loss, even when adjusted for donor type and age vs non-IgA, whereas those with clinical recurrence demonstrated increase risk of graft loss.[21] There are data supporting the ongoing use of steroids to reduce recurrence risk, although there are no standardized protocols for treatment of recurrent disease.[22] In addition, crescentic native disease, significant proteinuria, or patients with a rapidly progressive course, may require higher doses or longer duration of steroid therapy.[19]

Table 1: Median time to recurrence of Glomerulopnephritides after Transplantation

Native Disease	Median Time to Recurrence (IQR)	Increased Risk/Earlier Recurrence
IgA Nephropathy	39.5 months (31-48)[86,87]	Crescentic/rapidly progressive native disease. Lack of glucocorticoid use.
Focal Segmental Glomerulosclerosis (Primary)	2 days (1-70)[28]	Primary forms due to circulating factor. Genetic FSGS recurrence with APOL1 in donor. Secondary less likely to recur.
Membranous Nephropathy	8.5 months (3.0-22.9)[3,45,49,56]	High PLA2R antibody titer present at time of transplant
MPGN pattern: Immune Complex Mediated	1561 days (1-5591)[77]	Lupus anticoagulant or anti-phospholipid antibody[72,75]
Lupus Nephritis		Female, young age, Black, nonhispanic
MPGN pattern: Complement Mediated		
C3GN	21 months (14-28)[62,63]	Monoclonal protein Circulating Autoantibodies
DDD	9.0 months (2.9-15)[63,65]	Genetic Mutations
Monoclonal Gammopathy		
Amyloid	5.9 years (IQR 3.8-6.3)[80]	AL, AA, Afib amyloid types, Inadequate suppression of precursor protein.
MIDD	33.3 months (LCDD) (2-45)[88]	
PGNMID	4.7 months (3.8-5.5)[83,89]	

IQR – Interquartile range, MPGN – Membranoproliferative Glomerulonephritis, C3GN – C3 Glomerulonephritis, DDD – Dense Deposit Disease, PGNMID – Proliferative Glomerulonephritis wth Monoclonal IgG Deposits, MIDD – Monoclonal Immunoglobulin Deposition Disease. LCDD – light chain deposition disease.

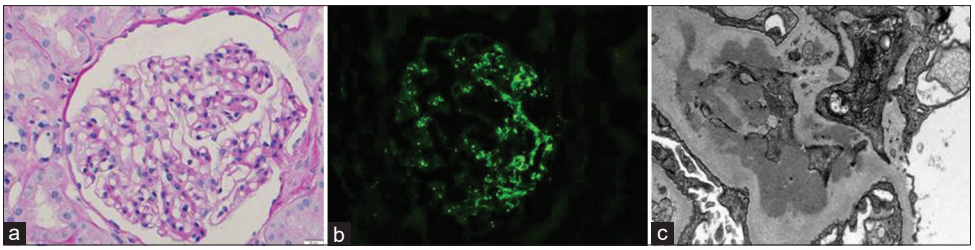

Figure 1: IgA nephropathy: The glomerulus demonstrates very mild mesangial hypercellularity (a: PAS; 400×). Immunofluorescence studies demonstrate bright granular staining of IgA (b; 400×). Electron dense deposits are identified in the mesangium (c; 20K×)

Focal segmental glomerulosclerosis

FSGS is a histological pattern of injury and can be seen in diverse etiologies and pathogenic mechanisms. It is best classified as primary, genetic, or secondary (structural and adaptive mechanisms that ensue from nephron loss, drugs, and viral toxins). Unfortunately, due to the variability in diagnostic criteria and bias in data collection, accurate estimation of recurrence of FSGS in the transplant is challenging.

Primary FSGS is assumed to be caused by a circulating factor which causes generalized injury to podocytes.[23] These patients present with new onset nephrotic syndrome (NS) and ultrastructural examination will demonstrate diffuse and extensive podocyte foot process effacement (FPE) as opposed to segmental FPE of secondary FSGS. Primary FSGS typically responds to corticosteroids, immunomodulatory agents, plasmapheresis, and is prone to recur posttransplantation with a recurrence rate of 25% to 50% in the first graft and an incremental risk of up to 80% in subsequent allografts.[24-26] The spectrum of severity at recurrence varies from primary nonfunction to chronic proteinuria with slowly declining renal function and is associated with reduced graft survival.[24-27] Unfortunately, data relevant to studies on recurrent FSGS are limited by including cases of nonprimary FSGS, due to poor definition of inclusion criterion. Hickson *et al.*, applied stringent diagnostic criteria for primary FSGS and from 5% of the transplant population labelled FSGS, only 2.4% fulfilled the biopsy criteria for primary FSGS and only 1.9% of these were classified as rapidly progressive. This study showed a recurrence rate of 46.7% in the high-risk group. Primary FSGS was more common in pediatric versus adult allograft recipients (8.2% vs. 1.5%, $P = 0.002$) and recurrence was more prevalent (86% vs. 35%, $P < 0.01$) in the pediatric group. Time from transplantation to diagnosis of FSGS recurrence was similar for adult and pediatric recipients and typically occurred within 24 to 48 h of transplantation. Recurrence was associated with worse allograft survival.[28]

The pathology of recurrent FSGS is not well studied. Although most publications report the presence of diffuse FPE at recurrence, in our personal experience, the extent of FPE is only mild to moderate in the earliest biopsies performed when earliest signs of increasing proteinuria trigger a renal allograft biopsy.[29-32] Given the high recurrence rates in FSGS, 5-year graft survival is worse with recurrent FSGS, with rates as high as 57%.[33] The need for meticulous monitoring is warranted, however, this can become a challenge especially in distinguishing between proteinuria from the native kidney versus the allograft. Goh *et al*. demonstrated the safety of bilateral native ureter ligation without nephrectomy as a safe option, making this technique useful in guiding post transplant recurrence monitoring.[34]

Using the current hypothesis for a circulating factor as the underlying cause of primary FSGS, therapeutic plasmapheresis (TPE) alone, or in combination with immunosuppression has been attempted in the setting of recurrence. Hickson *et al*. also showed that preemptive plasmapheresis was not associated with decreased frequency of recurrence and the outcome for those treated with TPE alone was poor. The use of rituximab in the pediatric group that had recurrent FSGS was associated with sustained remission and good graft function.[28] Overall, the reports on utility of rituximab are variable based on the initial response to steroid therapy. However, one small pediatric case series demonstrated complete remission in three of four patients treated with ofatumumab who previously had poor response to plasmapheresis and various immunosuppressive regimens including rituximab.[35]

Genetic FSGS

Genetic FSGS is caused by mutations to the genes encoding podocyte proteins, the slit diaphragm protein, actin cytoskeleton, and cell signaling apparatus. De Vriese *et al*. provide an exhaustive list of genes involved in familial FSGS.[36] Familial forms of FSGS are not expected to be associated with increased risk of recurrence in the allograft. Patients with a homozygous or complex mutation of NPHS2 had a lower risk of recurrence (<10%) unless the donor was also a carrier of NPHS2 mutations. Patients with heterozygous mutation/P20L variants of NPHS2 have increased rates of recurrence (>30%).[37] Specific "risk" variants of the APOL1 gene, G1 and G2, located on chromosome 22 are strongly associated with ESKD in African Americans. The risk of developing FSGS in individuals who carry two APOL1 risk alleles is very high. Kidneys from African Americans deceased donors expressing two APOL1 risk variants failed more rapidly after renal transplantation than those with zero or one risk

variants.[38] Importantly, the presence of APOL1 risk alleles in recipients does not adversely impact graft survival.[39] Additionally, as the understanding of the application of genetic testing in chronic kidney disease is becoming better understood, more patients will be diagnosed with genetic FSGS. In patients with FSGS with genetic etiologies, caution should be exercised when family members, or those with proven APOL1 risk variants are being evaluated for donation.

Membranous nephropathy

MN is becoming increasingly prevalent in Asia and the most common cause of NS in elderly Chinese. Among patients with NS, one Japanese study showed a prevalence of 36.8%, whereas in Saudi Arabia and Bangladesh, studies show a prevalence of 9.9% and 7.4%, respectively.[40] The occurrence of MN in the allograft can be due to recurrence of the initial nephropathy or to new disease called *de novo* MN that develops in the transplant showing a histologic pattern indistinguishable from recurrent MN. Currently, MN in the native kidney is classified as antiphospholipase A2 receptor antibody (PLA2R) associated MN (70% of cases),[41] as well as thrombospondin type-1 domain-containing 7A antibody (THSD7A) associated MN (3-5%).[42] Additional antigens have been recently discovered by Sethi *et al*. who describes the exostosin 1/exostosin 2–association with the autoimmune phenotype of MN[43] and neural tissue encoding protein with EGF-like repeats (NELL-1) associated MN, both in the absence of PLA2R and THSD7A antibodies.[44] Other forms are considered secondary to etiologies, such as systemic lupus erthyematosus, hepatitis infection, malignancy, and medications. Primary MN has variably reported rates of recurrence ranging from 7 to 57% of allografts.[45-48] The variability again is likely dependant on detection by protocol biopsy versus clinically indicated biopsies for proteinuria, length of follow-up, and living versus deceased donors. The clinical presentation and severity of recurence is variable, ranging from a subclinical finding apparent only on protocol kidney biopsy to a severe disease manifesting by heavy proteinuria and a high risk of allograft failure.[3]

Histological recurrence is usually noted by 1 year [median 8.5 months (3.0–22.9)] [Table 1] and sometimes as early as 2 weeks posttransplant.[45,49] Rodriguez *et al*. evaluated recurrence of MN as early as 4 months posttransplant and found that recurrent MN, like in native biopsies, is associated with granular peripheral capillary wall deposits of IgG, kappa, and lambda light chains but differ from native disease due to absent/weak staining with C3, possibly representing a difference in regulation of complement in the transplant compared with native kidney [Figure 2]. Interestingly C4d shows bright granular peripheral capillary wall staining in glomeruli with recurrent MN in contrast to the weak nonspecific glomerular staining in allograft glomeruli, postulated to be related to mannose binding lectin in MN. Additionally, recurrence at 4 months was discovered often due to IF findings (MN by IF) and lack of significant subepithelial deposits was noted in early recurrence. *De novo* MN is diagnosed when MN occurs in the allograft void of any prior history of MN, but in the etiology of *de novo* MN it has been suggested that donor specific antibodies and antibody-mediated rejection are involved.[50] Clinically, as the time from transplant progresses, it is important to distinguish late recurrence from *de novo* MN. Recurrence can occur as late as 5 years, and one case series detected de novo MN at 54 months from transplant.[47]

IgG subtypes in transplant-related MN is IgG4 dominant in recurrent MN regardless of association with PLA2R or THSD7A antibody status. There was no temporal variation in IgG subtype noted in recurrent MN, unlike the class switch from IgG1 to IgG4 appreciated in native MN.[51] IgG1, IgG2, and IgG3 are seen in secondary MN (lupus, malignancy) and IgG1 is noted in 75% of denovo MN.[52] PLA2R staining, also plays a key role as it was found to be 83% sensitive and 92% specific for recurrent MN, while it was only positive in 1 of 12 cases of *de novo* MN.[53] Recently, HLA-DQA1 and PLA2R1 risk alleles have been associated with primary MN.[54] Although this study was done in a Caucasian population, Ramachandran R, *et al*. demonstrated that these risk alleles were also noted in the South Indian population[55] and this finding becomes a key consideration when considering living-related donors for transplation in patients with PLA2R associated MN.

With rates of recurrence ranging from 34%[56] to 58%, graft loss attributable to recurrence is variable as low as 12.5% in one study,[57] whereas others have demonstrated 5 year survival rates of 59%.[33] Rituximab has been used in recurrent MN, and in one case series of 12 patients with biopsy proven recurrence, 8 patients had progressively worsening proteinuria warranting additional immunosuppressive treatment and received rituximab with follow up at 1 year, 75% had partial or complete remission, whereas at 2 years only 1 patient of the 8 had a relapse.[3] Kattah *et al*. demonstrated in a cohort of patients with PLA2R associated MN who had anti-PLA2R antibodies titers followed posttransplant, the positive predictive value of anti-PLA2R was 83% and the negative predictive value was estimated to be 42%.[48] There was heterogeneity in the kinetics and titers of anti-PLA2R antibodies as some patients had early recurrence, whereas others were delayed and yet others, despite pretransplant elevation of serum anti-PLA2R antibodies had no recurrence.[47] In those with disappearance of anti-PLA2R antibodies with standard transplant immunosuppression, serial measurements of serum antibody levels by ELISA should be performed as they provide utility as a noninvasive tool which can provide evidence of early recurrence.

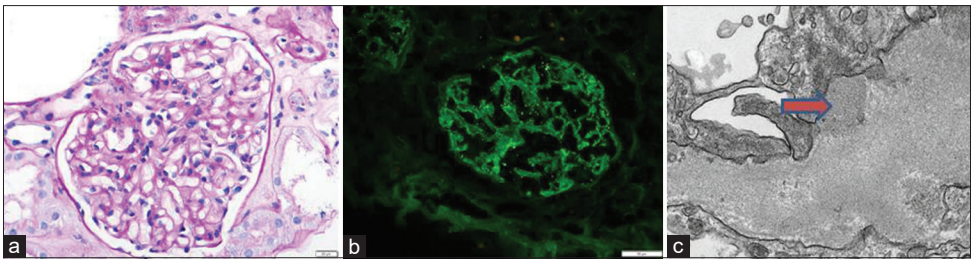

Figure 2: Membranous nephropathy: The glomerulus shows no remarkable pathology. Specifically, the glomerular basement membranes appear to be of normal thickness without spikes or craters (a; PAS; 400×). Immunofluorescence studies demonstrate bright granular peripheral capillary wall deposits of IgG (b; 400×) along with kappa and lambda light chain. C3 staining was minimal. Small subepithelial deposits (arrow) are identified on ultrastructural studies (c; 20K×)

Recurrent glomerulonephritis with a membranoproliferative pattern

Membranoproliferative glomerulonephritis (MPGN) is a pattern of injury common to a heterogeneous group of etiologies and comprises 7–10% of native biopsy proven glomerulonephritis. Until recently MPGN was classified into types I–III based on ultrastructural characteristics. Recurrence rates of MPGN, based on this original classification, range from 19–65%[58] Briganti *et al*. observed that MPGN accounted for 19% of all allografts lost due to recurrent glomerulonephritis, with MPGN type I accounting for 90% of those losses.[57] The challenges with the older classification of MPGN was that it was viewed as a single disease entity and did not allow evaluation of its etiological factors that influenced rate of recurrence as well as graft loss in glomerular disease. The more recent classification of MPGN provides an etiological classification: immune complex mediated or complement mediated. The immune complex-mediated pattern of injury includes infections, autoimmune diseases, and monoclonal gammopathies. The complement mediated MPGN includes C3 glomerulonephritis (C3GN) and dense deposit disease (DDD), collectively referred to as C3 glomerulopathy (C3G).[59] In India, immune complex-mediated MPGN accounts for 89% of cases.[60] Complement-mediated MPGN accounted for 12% of native renal disease with MPGN pattern of injury in one series.[58] Single-center data from the United States showed that 78% of adult kidney transplant candidates with a diagnosis of MPGN had immune complex-mediated MPGN (polyclonal and monoclonal immune complex deposits in 39% each). C3GN accounted for 19% and DDD accounted for 3%.[1] The risk of recurrence and graft loss due to recurrent disease was different in these groups. MPGN with monoclonal deposits had a recurrence rate of 66% with 50% of these grafts being lost secondary to monoclonal deposits. Although MPGN with polyclonal deposits had recurrence in up to 35% of cases and only 10% lost their grafts due to recurrence. MPGN secondary to complement mediated disease processes have recurrence rates that exceed 70% regardless of whether it was due to C3GN or DDD; however, graft loss is higher in C3GN (50%) than in DDD (25%). Since the etiological factors rather than histological patterns of injury influence rates of recurrence and allograft loss, C3 glomerulopathies, renal diseases with monoclonal deposits, and infection-related glomerular diseases are discussed below.

Complement mediated glomerulonephritis with an MPGN pattern

Complement-mediated glomerular diseases, which encompass C3GN and DDD, are caused by dysregulation of the alternate complement pathway. Histologically, these diseases are defined by C3 dominance with minimal or absent immunoglobulin deposition on IF staining.[61] The two entities, DDD and C3GN, are distinguished based on the presence or absence of intramembranous highly electron dense deposits on EM. Both diseases are characterized by progression to ESKD in 50%. Recurrence in the transplant has been evaluated in a few series as well as case reports.[62-65] C3GN is associated with a high rate of recurrence ranging from 60 to 86%.[62-64] In one series, the median time from transplantation to recurrence of disease was 28 months (ranging from 9 days to over 11 years, mean = 46 months). Graft loss occurred in 30 to 50% of those with recurrent disease.[62,63] While diagnosis of recurrence might be made on protocol biopsies, clinical indications for allograft biopsy included proteinuria, hematuria and worsening renal function. Zand *et al*. observed that those who had clinical indications for renal biopsy had poorer graft outcome than those where a diagnosis of recurrent C3GN was made on protocol biopsies.[62] Monoclonal proteins were identified in the serum of 21% of patients with recurrent C3GN. The presence of monoclonal protein in the serum was associated with a faster rate of recurrence (3.6 months versus 43.3 months). Abnormalities of the alternate complement pathway identified in those with recurrent C3GN included C3nef, C5nef, and CD46 mutations.[63] At recurrence, a mesangioproliferative pattern of injury was the most common histological pattern, although membranoproliferative was observed, likely due to the earlier stage of detection than native biopsies. C3 dominance or exclusive C3 staining was noted and EM showed mesangial and capillary wall deposits.[62]

DDD has a high recurrence rate in the transplant ranging from 55 to 86%.[63-65] Graft failure occurs in over 80%

of those with recurrence disease.[63,65] Time to recurrence in one series ranged from 2 to 32 months and time to allograft failure ranged from 4 to 71 months. As in C3GN, the pathogenesis is due to abnormalities of the alternate complement pathway. In the series from Columbia University, USA, abnormalities of the alternate complement pathway testing were frequently noted. C3Nef was the most common abnormality and other abnormalities included antibodies to CFH, CFI deficiency, heterozygous CFI mutation, and homozygous CFHR5 deletion. Seven patients were treated with eculizumab (C5 inhibitor) therapy but five of these had allograft failure.[63] There are poor outcomes associated with recurrence of C3G and the need for improved therapeutic options and clinical trials are needed.

Immune complex-mediated glomerulonephritis with an MPGN pattern

This comprises three main etiologies; infection related, monoclonal gammopathy related, and autoimmune disease, of which the main entity is systemic lupus erythematosus.

Infection-related MPGN

Chronic viral infections, such as hepatitis B, hepatitis C, with or without cryoglobulins, chronic bacterial infections, such as endocarditis, abscesses, as well as fungal and parasitic infections in the developing world are the most common infectious causes of an MPGN pattern of injury. Recurrence rates of infection-related MPGN are not well documented and mainly limited to case reports with their associated outcomes. In the setting of chronic bacterial, fungal, or parasitic infections, care must be taken to ensure the underlying infection is thoroughly treated as the introduction of immunosuppression can trigger recurrence of the infection and the resulting disease. In a case series looking at patients with recurrent MPGN, none of those with MPGN secondary to hepatitis B or C recurred in the allograft.[66] However, in one case series of recurrent MPGN type 1 using the old classification, 7 of 16 patients with recurrent MPGN had hepatitis C as the initial etiology[67] suggesting varying rates of recurrence. With the advent of new treatments for hepatitis C, a decrease in the rates of recurrent hepatitis C-related MPGN may be seen.

Recurrent lupus nephritis

The most common secondary glomerular disease in India is lupus nephritis.[2,5,18] Up to 30% of patients affected by lupus nephritis progress to ESKD.[68] Race and ethnicity are key considerations for prognostication, with those of African, Hispanic, and Asian descent having increased frequency and worse outcomes, excepting Asian patients who have similar outcomes to Caucasians.[69] The histological lesions can be diverse, but separated into six histological classes based on the International Society of Nephrology and Renal pathology society (ISN/RPS) criteria.[70] In a study of 46 patients with lupus nephritis from a single tertiary care hospital in South India, class IV (37.1%) and class III (21.7%) were the most common patterns identified, with class I and VI the least common (2.2% each).[71] Interestingly, despite class III and IV being the most likely patterns to progress to ESKD, mesangial proliferative (class II) is the most common pattern identified in recurrent lupus nephritis, followed by class III and V.[72]

In a single-center study from Eastern India, 86 patients with class III/IV lupus nephritis were followed to evaluate prognostic factors and outcomes. Cyclophosphamide was used as induction in 90.7% of patients with the remainder receiving mycophenolate mofetil. At 6 months, 44% of patients had complete or partial remission of proteinuria, increasing to 64% at 1 year. Of note, compared to Caucasians and Africans, patients with lupus nephritis in Eastern India presented with lower eGFR and proteinuria but higher chronicity scores.[69]

When lupus nephritis progresses to ESKD, transplantation has been shown to have a lower overall mortality rate compare to dialysis making it a favorable option.[73] However, while the native disease has frequent relapses, recurrence in the allograft can occur but is less common, likely due to ongoing immunosuppression. Additonally, recurrence rates and presentations vary, with reports ranging from 0 to 44%,[74] and dependant on protocol vs for indication biopsies. The incidence of clinically significant recurrent lupus nephritis has been reported at around 2–11%.[74] In one cross-sectional surveillance biopsy study of 41 patients, 54% of patients were found to have histological evidence (class I/II) of lupus nephritis, with the majority of cases being subclinical. Factors associated with recurrence were presence of lupus anticoagulant and higher proteinuria.[72] Consistent with this is a study by Golebiewska that emphasized an increase risk of graft loss with the presence of anti-phospholipid antibodies. In that study of 19 patients with lupus nephritis where all but one patient received deceased donor kidneys, only 1 patient developed recurrent disease treated with increasing doses of immunosuppression.[75]

Time to recurrence of lupus nephritis can also vary considerably and is also dictated by the use of surveillance vs for indication biopsies. Goral *et al*. showed early recurrence at 6 days posttransplant,[76] whereas Contreras *et al*. showed late recurrence at 16 years with the majority of recurrence occurring within 10 years.[77] The latter study was one of the largest cohorts of patients who underwent transplantation for lupus nephritis with 167 of 6850 patients experiencing recurrent lupus nephritis betweent 1987 to 2006 with a median time to rejection of 4.3 years. Of note, despite a fourfold increased risk of graft loss in those with recurrent disease, only 7% of these were deemed due to recurrence with the majority having chronic rejection.[77]

These studies highlight the importance of the patient's demographics, indication for biopsy, as well as studies

available, such as LM, IF, and EM in evaluating for recurrent disease. Many of the recurrent disease identified in studies were subclinical in nature and the impact of recurrence on graft loss seems to be low. Management of recurrent lupus nephritis is variable and patient dependant with no protocolized studies. Cyclophosphamide, steroids, mycophenolate, and even plasma exchange have been used with varying results.[78] Overall, despite the risk of recurrence, transplantion for lupus nephritis remains the best option for long term patient outcomes.

Recurrent glomerular diseases due to monoclonal gammopathy or monoclonal deposits in the kidney

Monoclonal gammopathy refers to the overproduction of monoclonal immunoglobulin due to clonal proliferation of immunoglobulin producing plasma cells or B- cells. The monoclonal proteins can be produced by pre-malignant states, in the absence of definite hematological disease, namely myeloma or lymphoproliferative disease. The monoclonal proteins based on their unique physicochemical properties can cause renal disease. The various diseases that are included in this category include amyloidosis, monoclonal immunoglobulin deposition disease (MIDD), proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID, fibrillary glomerulonephritis (FGN), and immunotactoid glomerulopathy.

Amyloid

Amyloidosis is a systemic disease which is known for extracellular deposition of protein fibrils in the form of β-pleated sheets.[79] There are various subtypes of amyloidosis; the most common forms being AL amyloidosis (monoclonal Immunoglobulin light chain fibrils), AA amyloidosis (serum amyoid protein fibrils), Afib (hereditary fibrinogen A-chain fibrils), apolipoprotein A-I, A-II and lysozyme amyloidosis. Mass spectrometry has significantly improved the ability to determine the type of amyloidosis and is a useful adjunct to renal biopsy.[80] Renal involvement is common with varying rates of prevelance in India from 3.7%[81] to 8%. Histologically, renal amyloid depositis are weak positive for periodic acid Schiff staining, distinguishing it from the collagenous composition of the basement membrane. Renal amyloid deposition is Congo red positive and has an apple-green birefringence with polarized light. On EM, amyloid deposits are identified as fibrils 7 to 10 nm in diameter with a haphazard orientation.[79]

Renal transplantation for amyloidosis requires extensive pretransplant evaluation, as there is often concomitant involvement of other organs, immunosuppression resulting in increased risk of malignancy and the risk of recurrent disease. Graft survival and recurrence appears to depend on the type of amyloid involvement. Median time to recurrence is estimated at 5.9 years (interquartile range 3.8–6.3) [Table 1]. In a case series of 104 patients from the United Kingdom, median graft survival for apolipoprotein A-I and hereditary lysozyme amyloidosis was 13.1 years as opposed to 10.3 years in AA amyloid, 5.8 years in AL amyloid, and 7.3 years in fibrinogen amyloid. They also demonstrated variable recurrence rates from 18.8 to 33.3% based on the type of amyloid. One key finding was that among those with AL amyloidosis, if at least a partial clonal response was achieved with chemotherapy, graft survival was 8.9 years vs 5.2 years among those with no response.[80] As such, amyloidosis is a heterogenous disease with various types and associated outcomes. A comprehensive evaluation and treatment of systemic diseases or clonal proliferation is key prior to transplantation to minimize risk of recurrence in the allograft.

Monocloncal immunoglobulin deposition disease

MIDD is a rare disease due to monoclonal Ig deposition in the basement membrane. It is differentiated from amyloid as deposits have no distinct fibrillary structure and are Congo-red negative. Of the three subtypes, light chain deposition disease (LCDD) is most common, with Kappa light chains the dominant isotype. Light and heavy chain deposition disease (LHCDD) and heavy chain deposition disease (HCDD) are the other two types with gamma light chains the dominant isotype in HCDD. Histologically, LM shows a nodular sclerosing pattern, with diagnostic findings on IF of diffuse linear GBM and TBM positivity based on the type of light chain present. Additionally, EM provides the findings of a "powdery" electron dense deposits in the GBM and TBM. Outcomes are related to treatment of the underlying monoclonal disorder. Median time to recurrence in one series of patients with LCDD only was 33.3 months (2–45) [Table 1]. In one of the largest series to date, Kourelis *et al*. described the outcomes of 88 patients with MIDD of which nine underwent renal transplantation.[82] Six of these nine patients had progression of their hematological conditions, treated with plasma cell directed therapy resulting in ample response without renal disease progression. The other three patients had relapse at 33 months, 7 years, and progression to ESRD at 9 years. This study demonstrated the need for proper clonal directed therapy prior to transplantation to minimize the risk of recurrence.

Proliferative glomerulonephritis with monoclonal immunoglobulin deposits

Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is rare and its prevalence in native biopsies range from 0.2% to 3.7%. Despite the hallmark of the disease being the deposition of intact monoclonal IgG in the glomeruli, monoclonal Ig in the serum is detected in only 20–30% of patients. The name of this entity accurately describes its histological pattern; LM findings of endocapillary or membranoproliferative proliferative glomerulonephritis with IF revealing IgG3 Kappa light chain and IgG subclass restriction. Electron

dense granular deposits can be identified in the mesangium, subendothelial and/or subepithelial zone [Figure 3].[83] Progression to ESRD is common and quite rapid and as such many patients undergo kidney transplantation.

There have been many case reports and small case series looking at recurrent or *de novo* PGNMID in the allograft; however, the largest case series describes 26 patients who underwent transplantation for ESRD secondary to PGNMID with an 89% recurrence rate. Median time to recurrence is estimated to be 4.7 months (3.8-5.5) [Table 1]. The most common pattern of injury was mesangial proliferative GN, IgG3 subtype restriciton on IF with 11 of 25 patients having graft loss due to recurrence at a mean time of 36 months from diagnosis, having had 86% of patients diagnosed within 4 months after transplantation,[83] supporting the need for increased surveillance and protocol biopsies in higher risk recipients.[84,85]

Conclusion

In summary, recurrent glomerulonephritis is of great relevance in the prognosis and management of the renal allograft. Earlier detection is possible with the routine use of close surveillance and urinary protein and hematuria monitoring, as well as protocol biopsies in high risk recipients. While some centers follow this practice, it is not routinely performed in most countries and transplant centers. Evaluation by LM remains a valuable component of allograft biopsy work up, however, including IF and EM evaluation makes a significant clinical impact in identifying recurrent and *de novo* disease in the allograft. At a minimum, ancillary testing where available, should be performed in biopsies done for clinical indications, such as hematuria, proteinuria, or worsening renal function. Recognizing that histological changes in the allograft will be different from native biopsies is important to avoid misdiagnoses. Early detection allows rapid and timely diagnosis – and entry into clinical trials to provide effective evidence of treatment for this growing number of rare diseases which collectively respresent a significant risk to allograft survival.

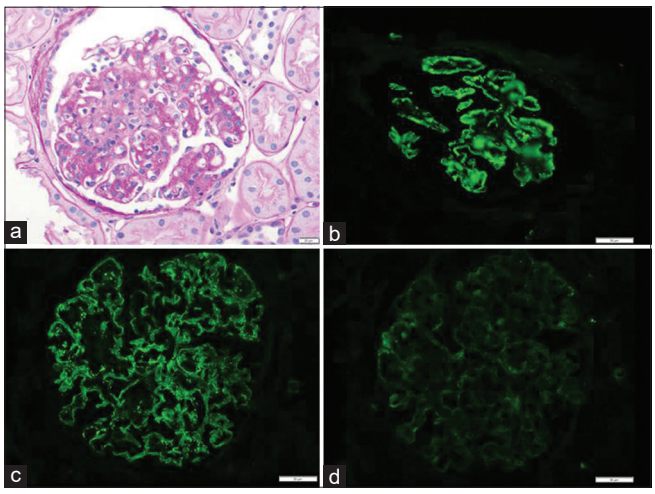

Figure 3: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits: The glomerulus shows a mesangioproliferative pattern of injury with a small segmental scar (a; PAS 400×). The immunofluorescence studies are characteristic with bright granular peripheral capillary wall staining with IgG. The IgG subtype studies demonstrated IgG3 restricted staining (b; 200×). The glomeruli demonstrate kappa light chain restriction (c; 400×) without lambda light chain (d; 400×)

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Conflicts of interest

There are no conflicts of interest.

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