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REVIEW

De novo glomerular diseases after renal transplantation: How is it different from recurrent glomerular diseases?

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Abstract

The glomerular diseases after renal transplantation can occur *de novo*, *i.e.*, with no relation to the native kidney disease, or more frequently occur as a recurrence of the original disease in the native kidney. There may not be any difference in clinical features and histological pattern between *de novo* glomerular disease and recurrence of original glomerular disease. However, structural alterations in transplanted kidney add to dilemma in diagnosis. These changes in architecture of histopathology can happen due to: (1) exposure to the immunosuppression specifically the calcineurin inhibitors (CNI); (2) in vascular and tubulointerstitial alterations as a result of antibody mediated or cell-mediated immunological onslaught; (3) post-transplant viral infections; (4) ischemia-reperfusion injury; and (5) hyperfiltration injury. The pathogenesis of the *de novo* glomerular diseases differs with each type. Stimulation of B-cell clones with subsequent production of the monoclonal IgG, particularly IgG3 subtype that has higher affinity to the negatively charged glomerular tissue, is suggested to be included in PGNMID pathogenesis. *De novo* membranous nephropathy can

be seen after exposure to the cryptogenic podocyte antigens. The role of the toxic effects of CNI including tissue fibrosis and the hemodynamic alterations may be involved in the *de novo* FSGS pathophysiology. The well-known deleterious effects of HCV infection and its relation to MPGN disease are frequently reported. The new concepts have emerged that demonstrate the role of dysregulation of alternative complement pathway in evolution of MPGN that led to classifying into two subgroups, immune complex mediated MPGN and complement-mediated MPGN. The latter comprises of the dense deposit disease and the C3 GN disease. *De novo* C3 disease is rather rare. Prognosis of *de novo* diseases varies with each type and their management continues to be empirical to a large extent.

Key words: *De novo* glomerulonephritis; Renal transplantation; New concepts of therapy

Core tip: The role of post-transplant glomerulonephritis in affecting both patient and allograft survival is well documented. For decades recurrent glomerular diseases after renal transplantation have been thoroughly investigated. On the other hand a group of a newly classified *de novo* glomerular diseases attained an increasing interest. However, the paucity of data concerned with *de novo* glomerular diseases after renal transplantation have been shown to be a great obstacle necessitating more active cooperation between transplant centers. A thorough work up is clearly warranted to declare not only their pathogenesis, but also to draw the proper therapeutic plan.

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INTRODUCTION

De novo glomerular disease is a glomerular disease that damages the renal allograft and it is totally different from the native renal disease. The most common types of *de novo* glomerulonephritis (GN) are: Membranous nephropathy (MN), focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN) and TMA secondary to drug intake[1,2]. Since immunofluorescence technique (IF) and electron microscopy (EM) are not used that often when assessing histopathology of a biopsy specimen in early post-transplant period, and the possibility of a range of renal diseases of unknown etiology, make it difficult to evaluate the real prevalence of *de novo* GN diseases[3]. *De novo* GN disease is reportedly uncommon[4-9]. In this review we shall discuss the most common *de novo* GN after renal transplantation in addition to the recently presented *de novo* proliferative GN with monoclonal IgG deposits (PGNMID). The *de novo* GN disease presents late, usually one year after renal transplantation, on the other hand recurrent GN might present earlier, sometimes within the first few weeks of renal transplantation. Unfortunately, both types of patterns of GN, whether *de novo* or recurrent, do have a lower graft survival as compared to patients without glomerular involvement[3].

DE NOVO GLOMERULAR DISEASES AFTER RENAL TRANSPLANTATION

De novo MN

Definition: *De novo* MN, is rather uncommon etiology among causes of allograft failure, can be defined as a MN lesion that is developed in the renal allograft of a patient originally suffered from another renal disease in native kidney[10].

***De novo* or recurrent MN:** The type of IgG subclass deposition is different in recurrent MN when compared to *de novo* MN, where IF is of immense use. Kearney *et al*[11] (2011) reported that IgG4 was dominant in glomerular deposits of recurrent MN, IgG1 was the dominant subtype in *de novo* MN. Honda *et al*[12] (2011) and others reported a clear predominance of IgG4 in idiopathic MN in comparison with the *de novo* type[13]. Another vital difference is the lack of phospholipase A2 receptor (PLA2R) staining in *de novo* MN, in contrast to the *recurrent* MN that is characterized by positive glomerular PLA2R staining[14,15].

Incidence: Of 1000 allograft biopsy, 19 cases of *de novo* MN were reported in a large French series[16], while the incidence was 1.8% in another French study[17], which means that 2% of renal transplant recipients can develop *de novo* MN[14]. In United Kingdom, *de novo* MN is considered to be the second most common cause of nephrotic syndrome after kidney transplantation[18]. The disease was reported to be 9% in a pediatric series[19]. *De novo* MN can be associated with: Alport's syndrome, ureteral obstruction, newly diagnosed HCV and recurrent IgA[10].

Pathogenesis: The new autoimmune disease IgG-related lesions have been recently shown to affect the renal allograft in several ways including *de novo* MN[20]. A novel regulatory protein (named: Pdlim2) has been recognized, with an observed decline of this protein in the podocytes of MN patients. A possible role of this protein in *de novo* MN pathogenesis has been suggested[21]. Various types of injury, *e.g.*, viral, ischemic, immunological and mechanical can induce podocyte damage, exposing the hidden or cryptogenic antigens, which could be different from that of the idiopathic

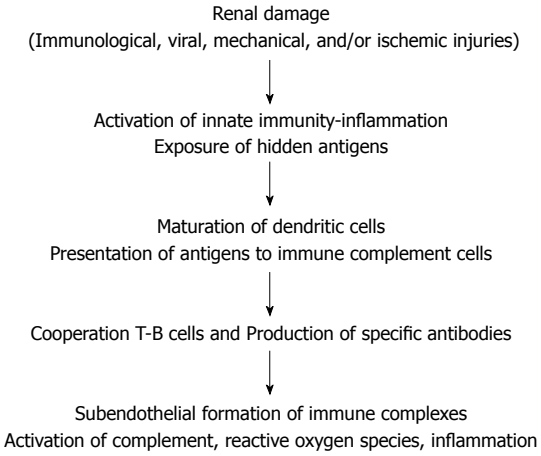

Figure 1 Any type of kidney injury can cause tissue damage. The danger signals released by the damaged tissue alert the recognition receptors, which activate the inflammatory cells and mediators of the innate immunity system. In this inflammatory environment, hidden podocyte antigens may be exposed, whereas dendritic cells become mature, migrate to lymphatic system, and present the antigen to immune competent cells. T cells cooperate with B cells favoring the production of antibodies directed against the exposed antigens planted in the subepithelium, with *in situ* formation of immune complexes, activation of complement, formation of free oxygen radicals, and inflammation. Adapted from: Ponticelli *et al*[10], 2012. *De novo* membranous nephropathy (MN) in kidney allografts. A peculiar form of all immune disease? With permission.

MN. This is quite evident, for example, in allogenic hematopoietic stem cell transplantation[22]. Consequently, these damaged cells will generate danger signals that intercepted by toll-like receptors and other receptors, which in turn initiate a cascade of signals activating transcription factors encoding the inflammatory gene[23]. Finally, the inflammatory cells of the innate system (PNLC, monocytes, macrophages and natural killers' cells) eventually release cytokines, inflammatory mediators and other mediators. Dendritic cells present the antigen to immunocompetent CD4 T cells that trigger B-cell induced antibody production. The end result is subepithelial immune complex deposition, complement activation and glomerular effector cell induced injury[24] (Figure 1).

No one single antigen can be "blamed" to be responsible of evolution of *de novo* MN, but rather a wide array of various antigens. An alloimmune response, viral infection and may be mechanical injury can create an environment that lead to release of various cryptogenic (hidden) autologous podocyte-antigen with subsequent production of auto- and alloantibodies (namely IgG1 subtype) that ultimately results in "*in situ*" immune complex formation, subepithelial deposits and eventually histological form of MN[10]. A thorough search for underlying malignancy and a hidden viral infection should be performed in view of the clear general association between MN and both cancer and infection[14]. Honda *et al*[12] (2011) reported frequent association of the AMR with *de novo* MN. El Kossi *et al*[25] (2008) suggested a possible evolutional role of DSA in development of *de novo* MN.

Role of HCV: HCV is a small RNA virus (30-38 nm) with lipid envelope and related to the *Flaviviridae* family. A robust relation to many glomerular (FSGS, immunotactoid, IgA, post-infectious and fibrillary GN)[26-31] and non-glomerular (tubulointerstitial and TMA) diseases has been reported[30,32]. Prevalence of HCV exceeds 8%-10% in many dialysis centers. HCV is known to be related to a range of renal diseases, such as MPGN Type Ⅰ associated type Ⅱ mixed cryoglobulinemia being the most common, other less common pathologies include MNGN and non-cryoglobulinemic MPGN[3]. Thereby, chronic HCV infection is a serious risk factor for development of *de novo* MN[27]. Another series reported an incidence of 3.6% in patients with positive HCV infection as compared to those with lack of HCV infection (0.36%)[13]. Genesis of *de novo* GN can be influenced by several factors on long-run including impact of immunosuppressive agents, HCV-induced modulation of lymphocyte response and the production of antibodies, so that an imbalance between antigens and antibodies will be created and the subjective allograft susceptibility of the allograft itself[33]. For patients with chronic HCV and post-transplant AMR, a particular focus of attention should be directed to *de novo* MN, with the IgG subtype staining being much helpful to differentiate recurrent from *de novo* MN[13].

The LM features of allograft biopsy of *de novo* lesions are similar to that in idiopathic MN, but with more foam cells in arterial intima and possibly with signs of AMR[34]. IF shows diffuse granular deposits of IgG in the subepithelial side of the glomerular basement membrane, with the IgG1 subclass being dominant in *de novo* MN, while the IgG4 is usually seen in *recurrent* type[11].

Clinical presentation: Clinical features vary much from no symptoms up to nephrotic range proteinuria[7,35,36], with some 25% of them would present with allograft dysfunction[19]. *De novo* MN usually presents a few years after renal transplantation[11,12,37,38].

Prognosis: There are no established risk factors for poor prognosis. In pediatric patients, 60% of Antignac *et al*[19] (1988) patients, for example, lost their grafts in 6 years after diagnosis of *de novo* MN, despite 20% have no proteinuria. In another series, 4 of 7 patients who received a second transplant, developed *de novo* MN for the second time[11]. Prognosis of *de novo* MN in adults is different. *De novo* MN was reported to have no impact on allograft function in a large French series as well as in Schwarz *et al*[39] (1991) study that reported similar 5 year survival in 21 patients with *de novo* MN to other RTR. On the other hand, Monga *et al*[34] (1993) reported a progression of the pathological stage and deposit extension to more glomeruli in serial biopsies. Accelerated allograft loss was also reported by Dische *et al*[40] (1981). Of note, most cases with deleterious outcome showed signs of chronic rejection in allograft biopsy[10]. The observed poor prognosis of *de novo* MN may be attributed by some authors to the associated AMR[41]. The latter is responsible of 20%-30% of allograft losses

in the literature[37]. The impact of *de novo* MN on allograft survival continues to be debatable. While a higher rate of allograft loss associated with signs of chronic rejection was reported in some series[37], no impact on allograft survival has been shown by others[14,37].

Anti-vascular endothelial growth factor therapy related de novo PLA2R-negative membranous nephropathy

The role of vascular endothelial growth factor (VEGF) in angiogenesis is well documented[42,43]. Local (intravitreal) and systemic (IV) anti-VEGF therapy have been recently introduced in many diseases. Systemic (IV) therapy has been used in the management of advanced cancer therapy. Unfortunately, this type of therapy has been associated with several untoward effects, *e.g.*, hypertension, hemorrhage, proteinuria and thromboembolic events[44]. On the other hands, local (intravitreal) route is usually well tolerated[45], due to its low administrated dose and the localized nature of injection. However, clearance of these agents has individual variations that may be reflected as systemic insults[46].

Recently, Wisit Cheungpasitporn *et al*[46] (2015) reported two cases of allograft dysfunction that are related to the administration of intravitreal anti-VEGF therapy. First case developed MN with spherular deposits after one year of initiation of therapy[47]. Moreover, PLA2R antibodies were reported to be negative in biopsy and no anti-PLA2R antibodies were detected in serum[48,49], which favours the *de novo* nature of MN, as only one third of idiopathic MN can express the lack of anti-PLA2R antibodies[48,49]. The increased level of proteinuria was not due to MN, as no evidence of immune complex GN in subsequent biopsy (4 mo), which is in agreement with other reports[49,50]. The second case has long standing decline but stable renal function, it showed progressing proteinuria observed few months after initiation of therapy with a clear evidence of both acute and chronic AMR in allograft biopsy[51].

Relation to proteinuria: Appearance of proteinuria in anti-VEGF treated patients is reported to be related to the start of anti-VEGF therapy, a finding that is supported by allograft biopsy findings (microspherule substructure variant of MN) properly due to a new antibody formation or unmasking of already present anti-HLA antibodies. The appearance of proteinuria is clearly related to the systemic use of anti-VEGF in cancer patients[44]. An observation that can be explained by the well documented effect of VEGF on preserving the glomerular filtration barrier integrity[42,52]. Moreover, an altered VEGF activity has been proposed to be a potential aetiology of mTOR inhibitors-induced proteinuria[53]. On the other hand local (intravitreal) administration of anti-VEGF may lack this effect[45]. A given explanation may be due to its different formulation and the local route of administration. However, clearance of these agents is ultimately systemic[45]. Furthermore, a recent report recorded a precipitous decline of allograft function (GFR < 25 mL/min per 1.73 m^2) in a group of anti-VEGF treated patients[54].

Mechanism of renal injury: The following mechanisms have been postulated as a given explanations for allograft injury: (1) Disruption of the normal survival signals mediated by VEGF leading to creation of alloreactive antibodies or exaggerated renal allograft injury induced by the already present antibodies; (2) Loss of the mitigating effect exerted by VEGF on CyA toxicity[55]; (3) Unmasking action on the already present anti-HLA antibodies; (4) Renal allograft susceptibility to anti-VEGF-induced injury leading to an increased tissue marker expression, including HLA and non-HLA antibodies; and (5) Evolution of antibody-mediated rejection through anti-HLA antibodies production[46]. The exact role of anti-VEGF agents' interference in allograft biology is complex, necessitating more extensive investigations[56-58].

Recommendations: Two recommendations have been proposed in the context of anti-VEGF therapy: (1) RTR should be strictly monitored through at least monthly determination of urinary proteins; and (2) The threshold index for allograft biopsy should be lowered, with application of both IF and EM studies[46].

De novo MPGN

The recent classification of MPGN relies primarily on the immunofluorescence (IF) findings. While cases with only capillary and mesangial complement deposition with lack of the Ig deposits are categorized as C3 glomerulopathy (C3 GN or DDD) or complement-mediated GN (CGN)[14,59], other cases with Ig mesangial and capillary deposits can be classified as immune complex-mediated GN (ICGN) (Table 1) (monoclonal, oligoclonal and polyclonal). Recurrence of MPGN post renal transplantation is frequent (mostly ICGN)[59]. On the other hand, *de novo* C3 glomerulopathy has not been reported[14]. In regards to *de novo* IC-mediated MPGN, it can be seen, but not frequently after renal transplantation, usually in association with HCV infection in about 50% of patients[60].

Incidence: In a large French study, only 13 of 399 (3.25%) patients develop *de novo* MPGN[60]. According to Ponticelli *et al*[14] (2014), *de novo* C3 glomerulopathy (CGN) subtype has not been reported, however, some case reports appear thereafter (see below section "VI").

Allograft biopsy: Typical pattern of hypercellularity with broad capillary loops due to reduplication of the glomerular basement membrane. In IF study, mesangial and subendothelial deposition of Ig as well as complement glomerular subendothelial electronic dense deposits (EDD), while fibrillary pattern is usually seen with cryoglobulinemia, most probably as a result of the associated HCV infection[61]. The impact of the associated systemic diseases is usually responsible of

Table 1 Prevalence of the *de novo vs* recurrent membranoproliferative glomerulonephritis according to the new membranoproliferative glomerulonephritis pathological classification depending on the mechanism of glomerular injury instead of deposits distribution[14,59]

No.	MPGN subtype	Pathological criteria	Recurrent MPGN	*De novo* MPGN
1	ICGN (immune complex-mediated GN)	Contains immune complexes + complement compounds	More common (most of the recurrent cases are ICGN)	Reported (3.25%)
2	CGN (complement-mediated GN)	Contains complement compounds only	Less prevalent (change from one type to another)	Not reported (Ponticelli *et al*[14], 2014)

MPGN: Membranoproliferative glomerulonephritis; ICGN: Immune complex mediated glomerulonephritis; CGN: Complement-mediated glomerulonephritis.

Table 2 Case reports in the literatures on *de novo* proliferative glomerulonephritis with monoclonal IgG deposits in renal allografts

Case	Age at diagnosis	Gender	Onset time (mo)	Type of IgG deposits	C1q deposition	Native kidney disease	Pattern of glomerular injury	Monoclonal gammopathy	Ref.
1	24	M	43	IgG3κ	N/A	T1DM	MPGN	None	Albawardi *et al*[64] (2011)
2	68	F	156	IgG1κ	N/A	PKD	MPGN	None	Albawardi *et al*[64] (2011)
3	38	F	72	IgG3κ	1+	T1DM	MesGN or EC	N/A	Hussain *et al*[72] (2017)
4	61	F	98	IgG3κ	C1q	MPGN	EC	None	Al-Rabadi *et al*[73] (2015)
5	40	F	132	IgG3κ	N/A	MPGN	MPGN	None	Al-Rabadi *et al*[73] (2015)
6	46	M	49	IgG1κ	1+	FSGS	MesGN	N/A	Li *et al*[77] (2017)
7	69	M	6	IgG3κ	1+	Obesity (FSGS?)	MPGN	N/A	Merhi *et al*[75] (2017)

EPGN: Endocapillary proliferative glomerulonephritis; FSGS: Focal segmental glomerulosclerosis; MesGN: Mesangioproliferaitve glomerulonephritis; MPGN: Membranoproliferative glomerulonephritis; N/A: Not available; PGNMID: Proliferative glomerulonephritis with monoclonal IgG deposits; PKD: Polycystic kidney disease; T1DM: Type 1 diabetes mellitus; EC: Endocapillary proliferative; M: Male; F: Female.

the *de novo* pattern of allograft biopsy[14].

Pathogenesis: The pathogenesis is not completely understood. However, the glomerular deposits of the hepatitis C virus as well as the anti-HCV antibodies may be responsible of the histological patterns in HCV positive patients[60]. Presence of cryoglobulin is seen in some patients[62]. Evolution of the clinical and histological pattern associated with *de novo* MPGN may be also triggered by the stress of rejection, calcineurin inhibitors (CNI) toxicity as well as viral infection[14].

Clinical features: Nearly, about 50% of cases presents with nephrotic syndrome, but the majority usually show non-nephrotic range proteinuria (*i.e.*, < one gram). Presence of signs of thrombotic microangiopathy in allograft biopsy is usually associated with the clinical and laboratory manifestations of hemolytic uremic syndrome. Some patients with normal kidney function and non-nephrotic range proteinuria usually experience a slow and silent course, while in others the evolution of *de novo* MPGN can trigger rapid graft loss[33].

De novo proliferative GN with monoclonal IgG deposits

De novo proliferative GN with monoclonal IgG deposits (PGNMID) is an extremely rare disease[63-68]. PGNMID is a unique type of GN that was first presented in the literature for the first time in 2004[69], 5 years later the largest series (37 case) was presented in 2009[70]. PGNMID is a proteinuria/hematuria syndrome with a reported incidence of only 0.17%, usually with a normal workup for paraproteinemia[70]. While the recurrent PGNMID presents early (within the initial two years after renal transplantation), *de novo* PGNMID appears several years later[63,64]. A handful of cases of *de novo* PGNMID have been reported in the literature (Table 2), since Nasr *et al*[70] (2009) presented his largest series of the native PGNMID. After a 30 mo follow up of these patients, 38% had complete or partial recovery, 22% developed ESRF, and (38%) of these patients experienced persistent allograft dysfunction. Only 10% of patients expressed low complement level. No M protein bands were detected, which indicates that PGNMID disease should not be considered a precursor for multiple myeloma development[9]. However, Batal *et al*[68] (2014) reported that 18% of their patient with native PGNMID disease showed an evidence of low grade lymphoma. Moreover, Barbour *et al*[71] (2011) and others also reported two patients with native PGNMID kidney disease with evidence of chronic lymphocytic lymphoma.

Case reports of *de novo* PGNMID in the literature: A detailed summary of the case reports of the *de novo* PGNMID in the literature, as regard age, gender, time elapsed since kidney transplantation, type of the deposited IgG, presence of C1q, native kidney disease, pattern of glomerular injury as well as presence of monoclonal gammopathy have been shown in Table 2[64,72-75].

Clinical presentation: Like recurrent PGNMID, *de novo* PGNMID usually manifests with allograft dysfunction associated with a variable degrees of proteinuria with or without hematuria in a white female patient, the disease generally can be seen in adults above 50 years of age[72,73].

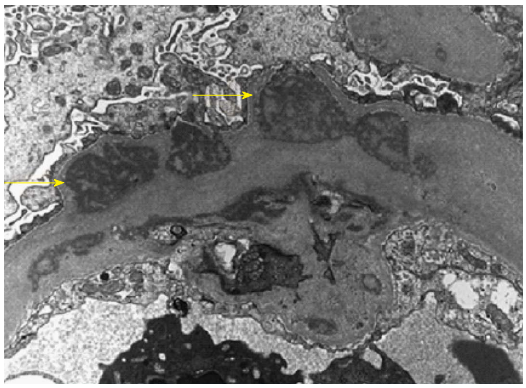

Figure 2 Glomerular capillaries are greatly distorted and thickened by the presence of numerous, sometimes large and/or confluent subendothelial electron-dense deposits (arrows). The electron-dense deposits have a variegated ("two-toned") appearance and are finely granular, but they do not show organized substructures. Adapted from: Al-Rabadi *et al*[73] (2015) (open access).

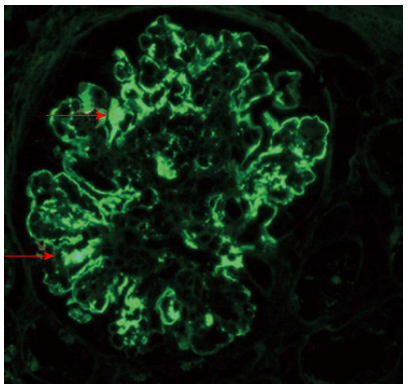

Figure 3 Diffuse irregular granular and pseudo linear deposition of IgG (3+/4+) (arrows). No staining is found in Bowman's capsule or the tubular BM. Adapted from: Al-Rabadi *et al*[73] (2015) (open access).

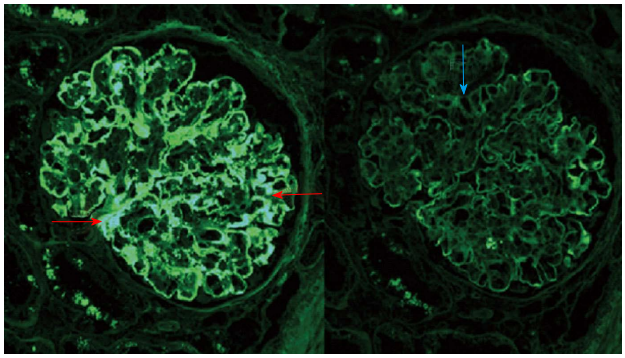

Figure 4 Kappa light chains stain strongly positive (3+/4+) (Rt side, red arrows) along the peripheral capillary walls and mesangial areas. Lambda light chains are negative in the deposits (Lt side, blue arrow). Adapted from: Al-Rabadi *et al*[73] (2015) (open access).

Pathogenesis: Pathogenesis of PGNMID is not clear. However, the reported recurrence of this disease suggests the presence of a circulating factor in RTR[72]. Other reports suggest deposition of a circulating non-deleted monoclonal IgG in the glomeruli, followed by complement fixation with outburst of inflammatory mediators[69]. A variety of intrinsic and extrinsic antigens would cause glomerular injury through stimulation of B-cell clones with subsequent production of the monoclonal IgG, particularly IgG3 subtype (8% of the total IgG). The latter is rapidly absorbed by the glomeruli so that it cannot be detected by immunofixation. Three criteria have been postulated to increase the avidity of IgG3 to glomerular deposition: (1) Positively charged nature; (2) The heaviest molecular weight; and (3) The greatest complement fixing capacity. So, these criteria would augment the affinity of IgG3 to the negatively charged glomerular elements, making it highly nephritogenic[63].

Histopathology: LM usually shows mesangioproliferative or endocapillary GN. EM shows prominent granular mesangial and subendothelial electron dense deposits (EDD) (Figure 2)[73]. Finally, IF study could ultimately establish the PGNMID diagnosis. A positive staining of one of the monoclonal IgG subtypes, with IgG3 being the most common and either *kappa* (most common) or the less common *lambda* subtype, strictly and exclusively in the glomerular constituents. C1q and complement 3 may be positive denoting complement activation (Figures 3 and 4)[73].

Differential diagnosis: PGNMID should be differentiated from other entities, *e.g.*, Type I cryoglobulinemic GN, transplant glomerulopathy, primary MPGN, post infectious GN, immunotactoid and fibrillary GN. In comparison to Type I cryoglobulinemic GN, PGNMID lacks the serologic evidence of cryoglobulinemia, and also the annular-tubular as well as the fibrillary substructure by EM are absent. The microtubules of 30-40 nm in EM that characterizing immunotactoid are missed, so did the negative Congo red randomly organized fibrils of 16-24 nm diameter of the fibrillary GN. Lack of IF and EM studies can lead to a suspicion of transplant glomerulopathy, but the absence of monoclonality and the faint staining of the IgG can differentiate it from PGNMID[64]. PGNMID may simulate LHCDD in many aspects, but the pathogenesis is not alike[73]. While the heavy and the light chains deposition involve the glomerular as well as the tubular basement membrane in LHCDD, deposition of the intact monoclonal Ig is usually confined to the glomerular constituents in PGNMID. Also, the EDD are of granular nature in PGNMID as opposed to the powdery nature of LCDD deposits[73].

In the last few years, PGNMID disease attained a particular entity. Given the lack of monoclonal bands either in urine or serum, with normal appearance of bone marrow biopsy, this entity should be differentiated from other diseases with similar presentation, a challenging insight during RTR preparation[73]. Once the features of MPGN have been observed in the LM of allograft kidney biopsy, PGNMID disease should be considered

among differential diagnoses. Long term monitoring of PGNMID is recommended to look for occult hematological malignancy[71].

De novo non-collapsing FSGS

De novo FSGS was reported to be the commonest form of *de novo* GN in some Canadian series[76]. While the recurrent FSGS can develop early post renal transplantation, usually in the form of nephrotic syndrome, *de novo* FSGS usually presents more than 12 mo after renal transplantation.

Clinically: *De novo* FSGS presents with a variable amounts of proteinuria up to nephrotic syndrome. Hypertension and progressive decline in allograft function can be seen[14].

Pathogenesis: The size discrepancy between the recipient's body mass and the nephron mass of his allograft as a single kidney will induce compensatory hyperfiltration of the residual nephrons. DM, hypertension, BK polyomavirus[77], or parvovirus B19[78] can be also included in the pathogenesis of FSGS in addition to any pathological event that results in nephron loss. CNI toxicity can result in development of *de novo* FSGS months after transplant procedures in the form of proteinuria, hypertension and progressive decline in allograft function. The robust vasoconstrictor effect in addition to the typical microvascular lesions induced by CNI could ultimately induce arteriolar ischemic changes with subsequent characteristic histopathological lesions. A pivotal role of transforming growth factor-β (TGF-β), the multipotent protein responsible of cell growth regulation, differentiation and matrix formation can be observed. CNI can augment the expression of the podocyte TGF-β[79], leading to podocyte apoptosis and detachment from the glomerular basement membrane with synechia and glomerulosclerosis[14].

Allograft biopsy: Focal and/or global glomerular sclerosis in addition to arteriolar occlusion, tubular atrophy, interstitial nephritis and striped interstitial fibrosis could be seen. On the other hand, RTR who converted their immunosuppression protocol from CNI to a high dose of sirolimus (SRL) have developed *de novo* FSGS with proteinuria and similar lesion to that seen in the classic FSGS. The immunohistochemical studies show decreased or lack of expression of the podocyte-specific epitopes synaptopodin p57 with acquired expression of cytokeratin and PAX2, which reflects an immature fetal phenotype[80]. This pattern reflects a state of podocyte dysregulation, which was confirmed in human by exposure of human podocytes to sirolimus. Decreased VEGF and protein kinase B phosphorylation have been also observed. Dose-dependent decline in Wilms' tumor 1, a transcription factor responsible of podocyte integrity was also observed[81]. *De novo* non-collapsing FSGS usually presents months or year after renal transplantation, with expected poor prognosis. The 5 years graft survival is only 40% after disease diagnosis in cases associated with CAN findings[82,83].

De novo collapsing FSGS

Collapsing FSGS (CG) is a distinct clinical and pathological variant from FSGS[14]. The reported incidence of *de novo* collapsing FSGS is about 0.6%[84]. *De novo* CG usually present 4-5 years after renal transplantation with heavy proteinuria and rapid decline of allograft function. Allograft biopsy usually shows segmental and/or global collapse of the glomerular capillary tuft. Prominent podocytes occupying the Bowman's capsule with marked tubulointerstitial damage as well as obliterative vascular disease are usually seen[85]. Pathogenesis is not clear, but these histological changes could be seen with acute rejection, diabetic nephropathy and immune complex GN disease. Altered hemodynamic stability may be included in the *de novo* CG behavior. Certain infections, *e.g.*, CMV and parvovirus B19 may be also associated with *de novo* CG disease[86,87]. Post-transplant antibody to angiotensin Ⅱ Type Ⅰ receptors, have been implicated in development of AMR[88].

A deleterious impact to the glomerular visceral and parietal epithelial cells integrity leading to cellular dedifferentiation with loss of glomerular filtration barrier function has been suggested[89-91]. Mitochondrial function disturbance has also been postulated as a deleterious mechanism in CG pathogenesis[92]. Ten cases of CG have been reported in serial biopsies in Mayo Clinic performed between 1994 and 2003[93]. CG is found to be prevalent in deceased donor kidney, presented usually with heavy proteinuria, higher serum creatinine level and poor response to plasmapheresis and ultimately allograft loss[94].

Prognosis: Outcomes of *de novo* CG is ultimately poor. All cases reported by Swaminathan *et al*[93] (2006), for example, lost their allograft within three years.

De novo C3 glomerulopathy

C3GN is a recently presented rare GN disease, characterized by predominant C3 glomerular deposits with similar morphology to that seen in DDD. However, in C3 GN there is lack of the ribbon-like intramembranous EDD. Recurrence of C3GN is reported, however, *de novo* C3GN disease is very rare[95].

In 2012, Sethi *et al*[96] (2012) presented the first two cases of recurrent C3GN, with subsequently reported 14 cases more in the next two years[97]. On the other hand, in 2008, Boyer *et al*[98] (2008) present two cases of *de novo* C3GN, however, these cases were presented as an aHUS or complement H deficiency. Furthermore, Nahm *et al*[95] (2016), reported a case of *de novo* C3 GN in a patient with no past history of alternative complement pathway abnormality, family history of renal disease or any symptoms related to glomerular disease. Tests related to complement factor H, complement factor H-related protein 5 genes and C3 nephritic factors were all negative[95]. They postulated an acquired complement

Table 3 Main characteristics of the more frequent *de novo* glomerulonephritis after transplantation (minimal change disease, nephrotic syndrome, membranous nephropathy, membranoproliferative glomerulonephritis, hepatitis C virus, IgAN)

Disease	Presentation	Time of onset	Difference with native GN	Treatment	Prognosis
MN	Proteinuria sometimes in nephrotic range	Late after transplant	Associated with trans-plant complications; IgG1 deposits instead of IgG4	No specific treatment	Slowly progressive
MPGN	Proteinuria, hematuria, NS, nephritic sediment	Months or years after transplant	Often associated with HCV, or with other diseases	Steroids + cytotoxic drugs if crescentic GN (?)	Slowly progressive; poor with many crescents.
FSGS	Proteinuria, rarely in nephrotic range	Months or years after transplant	NS is rare; signs of rejection or CNI toxicity at biopsy	Removal of associated events	Usually poor, particularly in collapsing GN
MCD	NS	Early after transplant	Mild mesangial sclerosis, hypercellularity	Steroids	Good

Adapted from: Ponticelli *et al*[14] (2014). *De novo* Glomerular Diseases after Renal Transplantation. *Clin J Am Soc Nephrol* 2014; 9: 1479-1487, with permission. MCD: Minimal change disease; NS: Nephrotic syndrome; MN: Membranous nephropathy; MPGN: Membranoproliferative GN; HCV: Hepatitis C virus.

abnormality after renal transplantation.

Histopathology: The C3GN early pathological changes usually show minimal mesangial expansion which may progress later to mesangial proliferation. EDD initially located in the mesangium, extend later to the subepithelial and subendothelial areas[97]. The EDD that present early in tubular basement membrane and in Bowman's capsule may change to band-like simulating that present in dense deposition disease (DDD) that is characterizing and specified to its diagnosis[99]. However, C3 GN showed segmental tubular basement membrane deposits[100]. The DDD disease may experience phenotypical transformation to C3GN in the native kidney[101]. However, DDD usually shows more profound MP features as well as more intense complement abnormalities as compared to C3 GN[102]. The presence of an overlap may justify using the term "C3 glomerulopathy" instead of exerting to separate the two pathological identities, DDD and C3 GN[95]. *De novo* C3GN is a rare subtype of post renal transplantation GN diseases. The fundamental role observed through both IF and E/M studies in diagnosis and serial follow up is quite mandatory[95]. Of note that despite the observed decline in C3 deposition, renal function as well as histopathological changes continue to progress.

De novo minimal change disease

De novo minimal change disease (MCD) is a rarely reported disease in RTR. Fulfilled criteria of MCD diagnosis is not always present in some cases, which suggests a misdiagnosis of FSGS disease. While Markowitz *et al*[103] (1998) succeeded to report eight cases with full criteria of MCD, Truong and his associates (2002) added five more cases[104]. Furthermore, *de novo* MCD have been reported in incompatible ABO transplants[105]. With evolution of *de novo* MCD, a nephrotic range proteinuria developed rapidly after renal transplantation, however, some cases reported eight years after transplantation[106].

Histopathology: LM show typically normal appearance of the glomeruli. Some cases show hypercellularity and IgM/C3 deposition[103,105].

Pathogenesis: The pathogenesis of *de novo* MCD still uncertain. An activation of the innate and/or the adaptive immunity with T cell dysfunction and cytokines release, *e.g*., cardiotrophin-like cytokine-1[107] or the soluble urokinase-plasminogen receptor[108], leading to alteration of the glomerular capillary wall permeability has been suggested. The initial culprit agent is unknown, but certain viral-induced activity has been postulated. Another suggested factor, the costimulatory molecule B7-1 (CD80) in podocytes, has an additional impact on glomerular permselectivity. This agent [B7-1 (CD80)] has been proved to have a role in inducing an experimental nephrotic syndrome[109]. The role of this factor in inducing foot process fusion and proteinuria in the renal allograft is to be determined. The reported development of *de novo* MCD in a patient was on SRL therapy with clearance of the disease with drug withdrawal, has suggested a possible role of certain drugs in *de novo* MCD pathogenesis[110].

Prognosis: *De novo* MCD has a favorable prognosis in most cases[14]. Owing to its potential reversibility, *de novo* MCD has no deleterious impact on allograft survival on the long run. However, this disease is possibly still underestimated as a pivotal cause of nephrotic syndrome in the renal allograft (Table 3).

De novo IgAN

IgAN has been one of the most common GN worldwide. Graft loss has been frequently reported with *recurrent* IgAN[8]. On the other hand, this fate is rarely reported with *de novo* IgAN[111].

Incidence: *De novo* IgAN has been reported to be less common than recurrent IgAN[112]. Considering the high frequency of asymptomatic IgAN, some authors argue that *de novo* IgAN might be considered as "transmitted disease", which means that recipient received an allograft that already had a "latent" form of IgAN[14], this argument is supported by the finding that a considerable percentage of mesangial IgA deposition (16.1%) has been reported in 0-hour protocol biopsy performed by a

Table 4 The risk of recurrence of *de novo* glomerulonephritis after retransplantation is unknown

Disease	Indications to retransplant
MN	In view of the slow progression, there is no contraindication to retransplant
MPGN	The risk of recurrence is high in carriers of HCV, active autoimmune disease, or monoclonal gammopathy. These risk factors should be removed or inactivated before retransplant
FSGS	If FSGS was caused by calcineurin inhibitor or mTOR inhibitor toxicity, there is no contraindication to retransplant, but the dosage of the offending drug should be minimized. If FSGS was associated with AMR, the risk of recurrence is increased. Circulating antibodies should be removed before retransplant
Collapsing nephropathy	Risk of recurrence is probably high. Antiviral and/or removal of circulating AB before retransplant are recommended according to the possible role played by virus infection or AMR in the 1st transplant
MCD	In view of the favorable prognosis, there is no contraindication to retransplant
IgAN	No contraindication to retransplant

Adapted from: Ponticelli *et al*[14] (2014), De Novo Glomerular Diseases after Renal Transplantation. *Clin J Am Soc Nephrol* 2014; 9: 1479-1487. Published online 2014, with permission. MCD: Minimal change disease; NS: Nephrotic syndrome; MN: Membranous nephropathy; MPGN: Membranoproliferative GN; HCV: Hepatitis C virus; FSGS: Focal segmental glomerulosclerosis.

Japanese study[113].

Histopathology: Intracapillary proliferation with a possibility of crescent formation can be observed in many biopsies. IgA and C3 granular deposits in the glomerular capillary wall and mesangium are frequently seen in IF studies.

Clinical features: despite the presence of frequent IgA deposition, *de novo* IgA is frequently asymptomatic especially in Asian population that may be discovered only in protocol biopsy.

Course and prognosis: In case of presence of crescent formation in allograft biopsy, prognosis of *de novo* IgA is ultimately poor, otherwise course and prognosis is quiescent with mild mesangial hypercellularity[8]. For example, Robles *et al*[4] (1991) reported a case of *de novo* IgAN with progressive proteinuria, microscopic hematuria and rapid deterioration of allograft function after renal transplantation in a patient with ESRD due to MPGN. On the other hand, *de novo* Henoch-Schönlein purpura has been described post renal transplantation with a rapid graft loss[114,115].

THERAPY OF *DE NOVO* GN DISEASES

Treatment of de novo MN

Options of *de novo* MN therapy are variable, including rituximab, bortezomib, PE, and intravenous Ig[116-118]. Unfortunately, absence of randomized control prospective studies and the high cost would be an obvious obstacles[13]. Therapy of *de novo* MN is still unclear. There is no enough data to support the use of rituximab in *de novo* MN therapy and there no clear base supporting the introduction of cytotoxic therapy or the intensified immunosuppressive agents would be efficacious[37,119].

Indications for retransplantation: MN is a slowly progressive disease, there is no contraindication to retransplant (Table 4).

Treatment of de novo MPGN

Therapy of *de novo* MPGN is still elusive. Trial of intensification of immunosuppression and the use of steroids generally showed poor and unstable results. Re-transplantation, however, is not contraindicated as long as the HCV infection as well as other risk factors have been eliminated. In this instance, the newly introduced oral anti-HCV agents, *e.g*., protease inhibitors and/or RNA polymerase inhibitors, should be considered before attempting renal transplantation[14].

Indications for retransplantation: The risk of recurrence is high in HCV carriers, active autoimmune disease, or in monoclonal gammopathy. Risk factors should be eliminated before retransplantation (Table 4).

Treatment of de novo PGNMID GN

There is no established therapy for *de novo* PGNMID[68]. However, a trial of rituximab, cyclophosphamide, plasmapheresis and high dose steroids have been introduced[63,65-67]. An observed reasonable response to rituximab and cyclophosphamide was reported with the recurrent disease, which was attributed by the authors to an early application of the protocol biopsy[63]. Multiple protocols have been tried by others including: High-dose steroids, RAS blocking agents, bortezomib, rituximab with and without steroids and plasmapheresis[78] (Table 3).

Rationale of rituximab use: B cells in PGNMID hypersecrete an abnormal IgG. The latter have the ability of self-aggregation and glomerular deposition. Rituximab, a monoclonal antibody has been widely used post renal transplantation for PTLPD, resistant antibody-mediated rejection and recurrent glomerular disease and as a prophylactic therapy for chronic antibody mediated rejection through inhibiting antibody production and hampering the B-cell immunity[120-127].

The recent advents of rituximab in PGNMID therapy have been shown to improve allograft function with better outcome[67,76,128]. Merhi *et al*[75] (2017), reported a unique results with the use of rituximab in two male

patients one *de novo* (with IgG3κ restriction) and the other is recurrent (with IgG1κ restriction). They reported better allograft function with continuous stability and return to basal creatinine level that have been continued for almost two years with persistent stable clinical and pathological response (Table 3). To declare the magnitude of benefits of rituximab, a clear insight on the pathogenesis of PGNMID depending in a wide scale of prospective controlled randomized trials should be accomplished. The role of allograft protocol biopsy in PGNMID in immunosuppressed patients is to be also declared[75].

Treatment of de novo non-collapsing FSGS

The early interference in the course of *de novo* FSGS by CNI withdrawal and introduction of MMF or mTOR inhibitors (mammalian target of rapamycin) may induce stabilization or even improvement of allograft function. One major drawback should be expected, *i.e.*, the increased risk of rejection, particularly so, if there is associated proteinuria or the CrCl was below 40 mL/min[129]. Allograft loss due *de novo* FSGS, however, does not preclude the attempt of retransplantation as long as the factors incriminated in the pathogenesis of FSGS would be eliminated. It will be also worthy to modulate the therapeutic strategies to decrease the risk of recurrence, *e.g.*, by CNI minimization and/or considering antiviral prophylaxis[14,129] (Table 3).

Retransplantation: In patients with *de novo* FSGS due to either CNI- or mTOR inhibitors-induced toxicity, there is no contraindication to retransplantation, however, the dose of the drug should be modified. If there was an associated AMR, the risk of recurrence would be high. Donors organs that are likely to trigger a repeat challenge by corresponding antigens leading to a rise in DSA should be excluded before retransplantation and, if feasible, desensitization be considered (Table 4).

Treatment of de novo CG

There is no particular therapy for *de novo* CG. With the presence of evidence of viral infection, antiviral agents may be suggested. Despite the unpredicted results, an attempt to use abatacept may be tried if there is B7-1 (CD80) expression in the podocytes[130]. In view of scarce data as regard re-transplantation in patients who lost their grafts due to *de novo* CG, there is no specific recommendation. However, an attempt to do re-transplantation in such a situation should be preceded by meticulous screening of antibodies to angiotensin II Type I receptors, in addition to an intensive course of antiviral therapy[14].

Retransplantation: The risk of recurrence of FSGS is potentially high. Antiviral therapy and/or clearance of the circulating antibodies are recommended in view of the potential role of viral infection and/or AMR in the first transplant (Table 4).

Treatment of de novo C3 glomerulopathy

Impact of therapy on glomerular morphology: Eculizumab has been reported to induce partial reduction in glomerular inflammatory activity as well as decline in deposits distribution[100]. On the other hands, other reports showed that eculizumab may be associated with EDD[131]. However, Nahm *et al*[95] (2016) used pulse steroids, ATG, rituximab, PE and IVIG to treat the associated AMR, with good response as regard normalization of serum creatinine and reduction of glomerular C3 deposition, but unfortunately the EDD persist. They speculate that C3 deposits may be masked at the locations that they were hard to wash out.

Follow up: Serial biopsies show more intensified tubular basement membrane deposits as compared to glomerular deposits. So, the E/M examination can declare these deposits more precisely as compared to the IF studies as shown by Hou *et al*[132] (2014), with IF pattern changes in about 43% of cases in repeated biopsies.

Rationale of eculizumab use: Eculizumab has been used in 11 cases of C3GN, with mostly but not always favorable results[101,102,133-141]. Eculizumab is a humanized monoclonal antibodies with a potent affinity to complement 5 and prevents the generation of serum membrane attack complex (sMAC) and release of a very potent inflammatory mediator C5a, giving an effective target of therapy[142]. So, it has been suggested that eculizumab administration could be effective in C3GN therapy if given early in cases with minimal fibrosis, short disease course and in patients with increased sMAC with accepted results[138]. These benefits were confirmed by Kersnik Levart *et al*[143] (2016). They reported clinical as well as laboratory improvement, in addition to normalization of the sMAC levels. Moreover, a quite evident decline in glomerular inflammatory activity was observed in the latest biopsies in the form of absent neutrophilic infiltration and necrotic lesions as well as reduced glomerular proliferation activity. Active cellular crescents get transformed into inactive fibrous crescents.

Decision to commence eculizumab therapy should not be attempted until all other differential diagnoses have been excluded and failures of other immunosuppressive measures have been proved[144]. This will work only if properly guided by serial allograft biopsies as well as the clinical features before commencing to use such an expensive drug with a prolonged-term therapeutic approach[143]. Renal function recovery and decline of proteinuria could be expected even in a patient with crescentic GN with a rapidly progressive course[140]. Furthermore, patient already commenced dialysis can quit RRT after only five months of eculizumab therapy[141]. Six months, however, should be elapsed prior to reporting the failure of eculizumab therapy[141,144]. Long-term sequalae of this drug is uncertain, however, it has been tried successfully in paroxysmal nocturnal hemoglobinuria

without evidence of appearance of proteinuria or decline in renal function[145]. Serial long-term biopsies follow up declared also the new observation of eculizumab binding to the renal tissues, an evidence with no harmful impact, despite the fact that eculizumab deposits are similar to that of the monoclonal Ig deposits[143].

Treatment of de novo MCD

A sustained remission of the nephrotic syndrome is usually expected with intensification of steroid therapy and other immunosuppressive agents[14]. A good renal function can be maintained after remission with or without minimal proteinuria (Table 3).

Retransplantation: Prognosis is quite favorable, there is no contraindication to retransplantation (Table 4).

Treatment of de novo IgA

For mild and moderate *de novo* IgA, no specific therapy is advised. However, Shabaka *et al*[111] (2017) reported that potentiation of immunosuppressive therapy with CNI and augmentation of RAS blockade can lead to a complete remission and better renal function. On the other hand, Carneiro-Roza *et al*[146] (2006) reported a better initial response in decreasing urinary protein level with no improvement in renal function. In patients presented with crescentic IgAN and a rapidly progressive course, pulse steroid, cyclophosphamide and PE may be tried with expected poor results[14].

Retransplantation: No contraindication to retransplant (Table 4).

CONCLUSION

The management of *de novo* GN diseases poses unique set of challenges. For a transplanting team, it is paramount to be armed with as much information as possible about the original disease of the native kidney when proceeding with renal transplantation. A lacunae in information would raise the risk of graft loss due to recurrent GN disease. Moreover, awareness of the pathogenesis of these diseases, their clinical features as well as their potential prognosis would help in improving both allograft and patient survival. One of the greatest obstacles hampering the achievement of these targets is the scarce number of the reported *de novo* GN diseases after renal transplantation. A world-wide cooperation between transplantation centers through multicenter randomized controlled trials would address many questions in regards to making a clear diagnosis and defining a robust management plan.

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