De novo glomerulonephritis after kidney transplantation

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De novo primary idiopathic FSGS

Some patients develop primary FSGS in the transplanted kidney even though they did not have FSGS in their native kidneys. The pathogenesis of de novo primary FSGS in the transplanted kidney is likely the same as that in the native kidney . The pathogenesis of primary FSGS in the native kidney is extensively reviewed elsewhere.

Angiotensin II type 1 (AT1) receptor antibodies were found to correlate with de novo collapsing FSGS in a patient with a third kidney transplant; his original kidney disease was secondary to lupus nephritis. The collapsing FSGS resolved with plasmapheresis and angiotensin receptor blocker (ARB) therapy .

De novo primary non-idiopathic FSGS

Some patients may develop FSGS in the transplanted kidney even though they did not have FSGS in their native kidneys. In general, any of the causes of FSGS in the native kidney may also occur in the allograft; these include infections, toxins, or obesity.

Certain viruses, such as HIV, may cause FSGS in either the native kidney or the allograft. Other viruses are more likely to cause clinically significant disease in allograft recipients because of immunosuppression and have been associated with FSGS among such patients. These viruses include parvovirus B19, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and BK . Limited data suggest that the viral infection should be resolved to below the limits of detection prior to transplantation or re-transplantation.

The resolution of most viruses, except for HIV, can be determined by a negative polymerase chain reaction (PCR). Treatment of HIV results in a negative PCR, but virus is not eradicated.

Certain medications have been associated with FSGS. Of particular importance among transplant recipients, mammalian (mechanistic) target of rapamycin (mTOR) inhibitors are associated with the development of FSGS, which may improve with the discontinuation of the drug.

mTOR inhibitors are generally avoided among patients who have FSGS as the cause of end-stage renal disease (ESRD) because of the associated increased risk of proteinuria, although there are no data that suggest that mTOR inhibitors are associated with an increased risk of recurrent FSGS.

Other medications that have been associated with FSGS include pamidronate and other bisphosphonates, anabolic steroids, and interferon.

Recipients of kidneys from donors with two high-risk *APOL1* alleles may have a higher risk of developing FSGS in the allograft. In one series, 22 patients received kidneys from donors with two high-risk alleles, and eight had early allograft loss. Biopsies of the eight kidneys revealed potentially APOL1-associated FSGS in three of them, two with collapsing variants.

Secondary FSGS may result from an adaptive response to glomerular hypertrophy and hyperfiltration from scarring due to previous injury. In this context, hyperfiltration refers to an adaptive but abnormal increase in single-nephron glomerular filtration that increases the total glomerular filtration rate (GFR above the level expected from the reduced number of glomeruli.

The glomerulosclerosis in this setting may result from chronic rejection, calcineurin inhibitor nephrotoxicity, hemodynamic factors associated with the glomerular hypertrophy induced by having only one functioning kidney, or reflect age-related changes or recurrent disease other than FSGS

Patients who have recurrent primary FSGS present with proteinuria, which is frequently in the nephrotic range and is often of rapid onset. Increased protein excretion may be noted in the early posttransplant period; in children, the median time to recurrent proteinuria is approximately 10 to 14 days after transplantation. Patients usually have symptoms and signs of nephrotic syndrome, including edema, hypoalbuminemia, and hyperlipidemia.

Some patients develop anasarca (ie, generalized and massive edema), with marked peripheral edema, abdominal distension resulting from ascites, marked scrotal or vulvar edema, and severe periorbital edema resulting in swollen-shut eyelids.

Patients usually do not have gross hematuria, although microscopic hematuria may be present.

For reasons that are not well understood, patients who develop recurrent disease may be more likely to have had acute kidney injury (AKI) in the first week after transplantation and more likely to develop acute rejection . Furthermore, graft loss in these patients is most often due to acute rejection rather than progressive glomerulosclerosis.

- By contrast, patients who develop de novo FSGS generally present much later; among such patients, the onset of proteinuria generally occurs three months or more after transplantation. However, rapidly progressive graft failure can occur among patients with de novo FSGS of collapsing subtype Recurrent FSGS is suspected when abnormal proteinuria is detected by routine screening or when the patient develops signs and symptoms of nephrotic syndrome and is shown to have significant proteinuria. A definitive diagnosis of FSGS in the renal allograft is made based upon renal biopsy findings in the setting of significant proteinuria (>1 gram/day). Allograft histology demonstrates characteristic features of FSGS that are identical to FSGS in the native kidney. Some have suggested that the earliest finding in recurrent FSGS is foot process effacement, observed by electron microscopy

As an example, a study of 25 patients with recurrent FSGS confirmed that the first pathological finding of recurrent FSGS is podocyte foot processes effacement by electron microscopy. Response to therapy resulted in resolution or significant decrease in podocyte effacement and prevented light microscopic changes

However, a definitive diagnosis cannot be made, unless characteristic features of FSGS are visible by light microscopy.

Patients who are diagnosed with FSGS by biopsy require evaluation for underlying causes and associated conditions since the histologic features do not reliably distinguish between idiopathic and non-idiopathic forms of FSGS or between primary and secondary FSGS, and since there is significant overlap in the clinical features.

Evaluation after diagnosis of FSGS

Once the diagnosis of FSGS is confirmed by analysis of histology obtained by allograft biopsy, viral etiologies and toxins should be excluded, if possible. Medications should be reviewed, and potentially causative medications, such as sirolimus or, among patients with collapsing FSGS, bisphosphonates, should be discontinued.

Evidence for infection should be sought, preferably via polymerase chain reaction (PCR) or direct immunostaining. We test for parvovirus B19, cytomegalovirus (CMV), Epstein-Barr virus (EBV), BK, hepatitis C virus (HCV), and, if risk factors are present, human immunodeficiency virus (HIV) by PCR. Patients who have PCR evidence of infection should be treated for the viral infection, if possible, to see if proteinuria responds. The treatment of specific viral infection among kidney transplant recipients is discussed elsewhere.

We generally evaluate all patients with recurrent FSGS for hypogammaglobulinemia, which is associated with viral infections that may cause FSGS and has been observed in recipients of solid organ transplants. Some clinicians, however, only evaluate for hypogammaglobulinemia among patients who are undergoing plasmapheresis, which is used for the treatment of primary idiopathic FSGS, in order to ascertain that patients are receiving adequate repletion of antibodies that are removed during plasmapheresis sessions.

The specific treatment of primary non-idiopathic FSGS in the allograft depends in part upon the identification of an underlying cause. Thus, viral infections, medications, and hypogammaglobulinemia should be excluded or treated prior to instituting treatment that is specifically directed at secondary FSGS. The treatment of specific viral infections among kidney transplant recipients is discussed elsewhere:

Medications should be reviewed, and all agents that are known to be associated with FSGS should be discontinued.

- Among patients who have no evidence of viral infection and who are not on a medication known to cause FSGS, primary non-idiopathic FSGS may be difficult to exclude. Our approach to treatment of such patients is determined by the timing of onset of recurrence and, in part, by the severity of proteinuria. As described above, patients who present within one year from transplantation are more likely to have primary idiopathic than primary non-idiopathic or secondary FSGS. The treatment of such patients is discussed above.

Among patients who present beyond one year from transplantation and who do not have an underlying cause (such as a viral infection) identified, the treatment depends upon the magnitude of proteinuria. We treat with immunosuppressive therapy patients who present with protein excretion >3.5 g/day. We do not treat with immunosuppressive therapy patients who present with protein excretion <3.5 g/day. Among patients who are selected for treatment, we administer cyclophosphamide 100 mg orally daily. Virtually all transplantation patients are already being treated with an antimetabolite, such as azathioprine or mycophenolate mofetil, as part of their immunosuppressive regimen. The antimetabolite must be stopped when cyclophosphamide is started.

Thus, the cyclophosphamide is a replacement for the antimetabolite. The administration of cyclophosphamide has been tried in selected cases of recurrent FSGS with variable success and in primary FSGS in the native kidney. The dose of cyclophosphamide should be adjusted for renal function.

If there is no response to this agent after 6 to 12 weeks, we attempt plasmapheresis, as described above, despite the lack of data suggesting a benefit.

The rationale for using cyclophosphamide without plasmapheresis is largely derived from studies of patients with primary idiopathic FSGS in the native kidney, for whom cyclophosphamide may be a reasonable alternative to calcineurin inhibitors. A small case series has reported the successful treatment of recurrent FSGS with cyclophosphamide 1 to 2 mg/kg per day.

Other immunosuppressive agents have been less well studied. Although cyclosporine is often beneficial for the primary disease , it does not appear to prevent recurrence in the transplant when given as part of the initial immunosuppressive regimen.Whether cyclosporine may be of some benefit in those patients who were not on a calcineurin inhibitor at the time of recurrence is not known.

By comparison, limited evidence suggests that recurrent nephrotic syndrome in children, which is most commonly due to FSGS, may be successfully treated with cyclosporine:

The mechanism by which calcineurin inhibitors decrease proteinuria may be via a direct effect on the cytoskeleton rather than an immunosuppressive effect. This is discussed elsewhere

Prolonged, daily, high-dose glucocorticoids are routinely used for the treatment of FSGS in nontransplant patients. Although there are only limited reports of this treatment modality for recurrent FSGS, there may be a role for steroids in this setting. In one report, two children developed recurrent FSGS after glucocorticoids were changed from daily to alternate day. Both patients initially responded to prolonged, daily, high-dose corticosteroids, but subsequently relapsed with lower-dose, alternate-day steroids.

Other agents, such as rituximab and galactose, have been tried with variable success. A few small studies have suggested that prophylactic rituximab may prevent recurrent disease.

Two case reports have described improved proteinuria and stabilization of eGFR with galactose.

We treat all patients who present beyond one year from transplantation with ACE inhibitors or ARBs, unless contraindications exist. Such treatment has been shown to prevent the progression of most proteinuric renal disease in the nontransplant population.

In addition, dyslipidemia should be controlled with statins.

Patients with recurrent FSGS in the setting of homozygous or compound heterozygous podocinmutations should still be offered aggressive therapy since most will respond.

De novo primary idiopathic FSGS

The treatment of patients who do not have a known cause for FSGS and are not known to have had FSGS in the native kidney is the same as that for recurrent FSGS and depends upon the timing of onset of proteinuria and the degree of proteinuria.

In an uncontrolled French study, recurrent proteinuria disappeared in 14 of 17 children after the administration of intravenous cyclosporine for a mean period of 21 days; 3 of the 14 also received plasmapheresis. At a mean follow-up of 4.1 years, 11 children remained in

remission.

In a second series, the cyclosporine dose was increased gradually in 16 patients with recurrent disease until either remission was induced or toxicity occurred; seven were also treated with plasma exchange. Remission was induced in 13 (81 percent, with four administered

plasma exchange), with doses of cyclosporine required ranging from 6 to 25 mg/kg per day.

Once remission was achieved, cyclosporine was tapered to a standard posttransplant regimen dose. At follow-up of 10 months to 12 years, 11 of 13 had a functioning allograft.

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De novo MN may occur in patients who had end-stage kidney disease due to a different primary renal disorder.

The reported incidence of de novo MN is approximately 1.5 to 2 percent. However, the incidence increases with time after transplantation and was 5.3 percent at eight years in one report.

De novo MN may be even more prevalent in children with kidney transplants. In one report, de novo MN was present in 48 of 530 allograft biopsies in children (9 percent)

- De novo MN appears to be associated with chronic and/or antibody-mediated rejection. Support for this association is provided by the kidney biopsy, which often shows signs of both rejection and the classic findings of MN, and by the presence of donor-specific antibodies, which are characteristic of antibody-mediated rejection, in patients with de novo MN. In one study of five patients with de novo MN following transplantation, all five who were tested had donor-specific antibodies at the time of biopsy. In contrast, donor-specific antibodies were not detected in any patients without MN in this study. Capillaritis and C4d deposition in the peritubular capillaries were common in the de novo MN group, even in those cases with undetectable donor-specific antibodies. In another report, the titer of donor-specific antibodies decreased in response to immunosuppressive therapy in one patient with de novo MN.

The mechanisms underlying the association between de novo MN and rejection are unknown, although several theories have been proposed, all of which focus on the excessive formation of antigen-antibody complexes at the glomerular basement membrane. As examples:

Host factors may also be important in the susceptibility of the individual to de novo MN. One small study reported a high incidence of recurrent MN (four out of seven) in patients who had a second transplant and a history of de novo MN in the first allograft. In comparison, de novo MN was rare when the second transplant was performed in patients who did not have de novo MN in the first graft in this study.

Proteinuria due to de novo MN typically occurs many years after transplantation, which is a much later onset than that which characterizes recurrent MN. As examples, in two of the largest retrospective studies, the mean times from transplantation until biopsy diagnosis of de novo MN were 63 and 102 months compared with 13 to 15 months noted among patients with recurrent MN.

Many patients are asymptomatic, and protein excretion remains in the subnephrotic range in approximately one-third or more of cases

The diagnosis of MN is made by classic findings of the disorder on kidney biopsy. Determining whether MN in the allograft is recurrent or de novo requires an accurate diagnosis of the original cause of kidney disease, which may require reassessment of the native kidney biopsy, when available.

De novo MN is not typically associated with either circulating autoantibodies to the phospholipase A2 receptor (PLA2R) or with positive tissue staining for the PLA2R antigen within immune deposits. In one study, none of the nine subjects with de novo MN had circulating anti-PLA2R or biopsy staining

for PLA2R.

In another study, only 1 of 11 cases of de novo MN exhibited positive PLA2R staining of the allograft biopsy. In contrast to recurrent MN, in which immunoglobulin G4 (IgG4) is the dominant or codominant IgG subtype within immune deposits, IgG1 tends to predominate in de novo MN.

In addition, the kidney biopsy in de novo MN often shows signs of both the findings of MN and rejection and by the presence of donor-specific antibodies, which are characteristic of antibodymediated rejection

Donor-specific antibodies are found in 29 to 67 percent of cases of de novo MN.Evidence of transplant glomerulopathy, such as C4d staining in peritubular capillaries or duplication of glomerular basement membrane, may indicate the additional presence of chronic antibody-mediated rejection. The exact proportion of cases of de novo MN that have such Rejection leads to exposure of previously undetected glomerular antigens, leading to a humoral response.

Circulating antibodies directed against human leukocyte antigens (HLAs) or other minor histocompatibility antigens expressed in the allograft predispose the recipient to both antibodymediated rejection and de novo MN.

Infections that occur in the setting of increased immunosuppression lead to the deposition of antigens in the glomerular basement membrane, with subsequent antibody deposition.

Rejection-mediated glomerular injury alters the glomerular basement membrane, which facilitates the formation of subepithelial immune deposits.

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- The natural history of de novo MN is unclear. Although some small studies have reported a very poor outcome (50 percent graft loss), it is not known whether the loss was due to de novo MN and other concurrent factors, particularly active and/or chronic antibody-mediated rejection. As result, the optimal treatment of de novo MN in the transplanted patient is not known. In particular, it is not clear whether patients with de novo MN should be treated with additional immunosuppressive therapy such as rituximab or cytotoxic agents, since no data have conclusively shown that de novo MN causes graft loss in the absence of other factors such as rejection

Our approach, which is based upon clinical experience, is determined by the degree of proteinuria that is present and on the stability of kidney function:

Due to the strong association of de novo MN and antibody-mediated rejection, when de novo MN is identified in this context, the treatment of the rejection is paramount.

We generally treat all patients with de novo MN with non-immunosuppressive therapies as described above.

We treat patients with protein excretion <4 g/day and stable kidney function with an increase in the maintenance dose of one or more components of the immunosuppressive regimen, though there are no good data that support this approach.

We treat patients with protein excretion that is ≥4 g/day or deteriorating kidney function with rituximab as described above.

The standard use of calcineurin inhibitors for immunosuppression posttransplantation has not changed the incidence of de novo MN, and pulse therapy with methylprednisolone does not appear to lower protein excretion.

Among patients who do not respond to rituximab, we treat with cyclophosphamide (2 mg/kg per day) or high-dose, alternate-day glucocorticoids. Patients who are started on cyclophosphamide should discontinue any antimetabolites that they are on (such as mycophenolate or azathioprine), though other antirejection medications, including calcineurin inhibitors and glucocorticoids, may be continued.

Plasmapheresis may be considered among patients who have features of chronic rejection in addition to de novo MN.

Occasionally, patients with a different primary disease (ie, involving the native kidney) will develop de novo immune complex-mediated MPGN in the allograft. This is usually secondary to an underlying disease such as hepatitis C virus (HCV) infection. (For transplant patients who present with de novo MPGN, in addition to excluding hepatitis B and C, human immunodeficiency virus (HIV), and bacterial infection, we obtain fungal cultures, exclude parasitic infection, and obtain abdominal/pelvic computed tomography (CT) scan to exclude abscesses.

We exclude endocarditis with echocardiography and blood cultures.

As we do for patients with recurrent idiopathic MPGN, we screen for autoimmune disorders, particularly lupus, with antinuclear antibody (ANA), double-stranded DNA, and complement proteins C3 and C4. We check for monoclonal gammopathies with serum protein electrophoresis or serum free light chains and urine electrophoresis.

The treatment of de novo idiopathic MPGN is the same as for recurrent MPGN. (above.)

The treatment of secondary MPGN is a directed at the underlying cause:

— De novo HUS can affect 3 to 14 percent of kidney transplant recipients. All of the causes of HUS that are present in the general population may affect the transplant recipient. (The following causes are of particular importance to the transplant recipient:

HUS may be more likely to occur among patients on cyclosporine compared with tacrolimus, and renal transplant recipients who develop HUS while taking cyclosporine may have a high rate of graft salvage after switching to tacrolimus. In a review of 26 transplant recipients who developed thrombotic microangiopathy, 24 were on cyclosporine. Among such patients, switching the calcineurin inhibitor to tacrolimus improved graft function in 13 of 18 patients

(81 percent).

CLINICAL PRESENTATION

The clinical presentation of recurrent and de novo HUS is similar. Patients commonly present with a Medications including calcineurin inhibitors (cyclosporine and tacrolimus), mammalian (mechanistic) target of rapamycin (mTOR) inhibitors (sirolimus, everolimus), and valacyclovir.

Infections including human immunodeficiency virus (HIV), parvovirus B19, cytomegalovirus (CMV), and others.

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Antibody-mediated rejection.

microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury (AKI).

Typical laboratory abnormalities include an increased serum creatinine, evidence of hemolysis (such as increased reticulocyte percentage, reticulocytosis, schistocytes on peripheral smear, and increased serum lactate dehydrogenase [LDH]), and a low platelet count. The urinalysis typically shows hematuria and only a small amount of proteinuria.

Some patients may present with only an increased serum creatinine and abnormal urinalysis due to the renal lesion associated with HUS (thrombotic microangiopathy) and without thrombocytopenia and hemolytic anemia

- Patients with recurrent HUS usually present within one year after transplantation and often within days to weeks. In one study of 16 patients with recurrent disease, eight patients presented within one month of transplantation. Patients with de novo HUS typically present within the first three months after transplantation Calcineurin and mTOR inhibitors should be stopped in all transplant recipients with de novo HUS, regardless of the underlying etiology. These medications are common causes of HUS, and withdrawal of these drugs may lead to resolution of de novo HUS. Among patients who develop de novo HUS while on cyclosporine, switching to tacrolimus is an alternative option once the acute episode of HUS resolves. For patients who have progression of disease despite withdrawal of calcineurin and mTOR inhibitors, we perform plasma exchange (1.5 volumes of fresh frozen plasma every 48 hours)

In patients with HUS that is refractory to plasma exchange, we give eculizumab at 900 mg intravenously administered weekly, followed by 1200 mg every two weeks thereafter. In addition, we perform genetic testing to screen for mutations associated with complement-mediated HUS. The optimal duration of eculizumab treatment in patients with de novo HUS is unclear, and there is no evidence from randomized controlled trials to guide this decision. Our approach, which is based upon clinical experience at our centers, is as follows:

As noted above, treatment with eculizumab is associated with life-threatening and fatal meningococcal infections.

Patients should receive vaccinations for *Neisseria* meningitis and daily antimicrobial prophylaxis against meningococcal infection, and children should receive vaccinations for *S. pneumoniae* and *H. influenza* type B (Hib) as they are at risk of developing serious infections due to these bacterial species.

Success has also been reported with intravenous immunoglobulin, rituximab, and conversion to a calcineurin inhibitorfree maintenance regimen using belatacept.

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. PGNMID is a proteinuria/hematuria syndrome with a reported incidence of only 0.17%, usually with a normal workup for paraproteinemia. 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. However, Batal et al(2014) reported that 18% of their patient with native PGNMID disease showed an evidence of low grade lymphoma. Moreover, Barbour et al (2011) and others also reported two patients with native PGNMID kidney disease with evidence of chronic lymphocytic lymphoma.

Treatment of de novo PGNMID GN :

There is no established therapy for de novo PGNMID. However, a trial of rituximab, cyclophosphamide, plasmapheresis and high dose steroids have been introduced. 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. Multiple protocols have been tried by others including: High-dose steroids, RAS blocking agents, bortezomib, rituximab with and without steroids and plasmapheresis.

- 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. The recent advents of rituximab in PGNMID therapy have been shown to improve allograft function with better outcome.

- 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. 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

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. On the other hand, in 2008, Boyer et al (2008) present two cases of de novo C3GN, however, these cases were presented as an aHUS or complement H deficiency.

- Furthermore, Nahm et al(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. They postulated an acquired complement 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. 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.

- However, C3 GN showed segmental tubular basement membrane deposits. The DDD disease may experience phenotypical transformation to C3GN in the native kidney. However, DDD usually shows more profound MP features as well as more intense complement abnormalities as compared to C3 GN. 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. 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. Of note that despite the observed decline in C3 deposition, renal function as well as histopathological changes continue to progress. 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. On the other hands, other reports showed that eculizumab may be associated with EDD. 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 (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. 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. 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. These benefits were confirmed by Kersnik Levart et al(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. 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.

- Renal function recovery and decline of proteinuria could be expected even in a patient with crescentic GN with a rapidly progressive course. Furthermore, patient already commenced dialysis can quit RRT after only five months of eculizumab therapy. Six months, however, should be elapsed prior to reporting the failure of eculizumab therapy. 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. 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 deposit

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 (1998) succeeded to report eight cases with full criteria of MCD, Truong and his associates (2002) added five more cases. Furthermore, de novo MCD have been reported in incompatible ABO transplants. With evolution of de novo MCD, a nephrotic range proteinuria developed rapidly after renal transplantation, however, some cases reported eight years after transplantation. Histopathology: LM show typically normal appearance of the glomeruli. Some cases show hypercellularity and IgM/C3 deposition.

- 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 or the soluble urokinase-plasminogen receptor, 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.

- 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. Prognosis:De novo MCD has a favorable prognosis in most cases. 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