TRANSPLANT GLOMERULOPATHY: A BRIEF NARRATIVE REVIEW IN THE LIGHT OF INFORMED LITERATURE

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ABSTRACT
Transplant glomerulopathy is characterized by a post-transplant morphologic insult. It occurs as a consequence of chronic, periodic injury of endothelial cells triggered by chronic hepatitis C virus (HCV) infection, donor-specific antibodies (DSA), cell-mediated injury or thrombotic microangiopathy. The disease might not be overt; however, it often presents with obvious symptoms, such as proteinuria (nephrotic range), hypertension, and deteriorating glomerular filtration rate (GFR). Histopathology is the mainstay diagnostic tool for transplant glomerulopathy patients and electron microscopy serves the purpose to early diagnosis. The classic histopathological feature of the disease is glomerular basement membrane thickening with reduplication on light or electron microscopy without immune complex deposits. Conventional therapeutic regimens include intravenous immunoglobulins (IVIG), plasmapheresis and splenectomy, and lately rituximab, eculizumab and bortezomib. Transplant glomerulopathy patients usually have positive history for acute rejection, resulting mostly in antibody-mediated rejection. DSAs against class II is specifically linked with transplant glomerulopathy. Unfortunately, the prognosis of kidney allografts is dismal even under existing immunosuppressive regimens.

Key Words: Kidney transplantation, Transplant granulopathy, Early diagnosis and treatment

INTRODUCTION
Transplant glomerulopathy is characterized by a post-transplant morphologic insult, often linked with antibody-mediated allograft rejection. The classic histopathological feature of the disease is glomerular basement membrane thickening with reduplication on light or electron microscopy without immune complex deposits. Transplant glomerulopathy ensues as a consequence of chronic, periodic injury of endothelial cells triggered by chronic hepatitis C virus (HCV) infection, donor-specific antibodies (DSA), cell-mediated injury or thrombotic microangiopathy. Most prominent etiology is antibody-mediated rejection. Transplant glomerulopathy, in some cases, might not be overt, identifiable on biopsy, or present with obvious symptoms, such as proteinuria (nephrotic range), hypertension, and deteriorating glomerular filtration rate (GFR). It is one of the key causes of decreased allograft survival (1).

Transplant glomerulopathy is linked with worse kidney allograft outcomes (2-4). Several risk factors have been reported in the literature to be associated with transplant glomerulopathy which include age, DSA, HCV infection and post-transplant acute rejection beyond 3 months (5, 6). The diagnosis of transplant glomerulopathy post-transplantation is 1 and 5 years in 4% and 20% of the patients, respectively, suggested a study (5). However, few studies have also demonstrated lesser overall incidence of transplant glomerulopathy (6-9). Earlier study of 16 years of retrospective analysis reported transplant glomerulopathy in 4% of the transplanted patients (10). It is possible that the true prevalence of transplant glomerulopathy might be underestimated due to infrequent practice of performing protocol histology testing and most probably missing the subclinical transplant glomerulopathy (10). In biopsies, the average time duration from kidney transplantation to transplant glomerulopathy diagnosis is 2 to 9 years (6, 10-13). Lately, a study suggested that post-transplant proteinuria during 1 year might forecast the development of transplant glomerulopathy in 5 years in highly sensitized patients (3). Ironically, transplant glomerulopathy is one the less studied transplant
diseases that needs considerable attention and therefore the present paper presents the brief narrative review of transplant glomerulopathy based on informed literature.

**DIFFERENTIAL DIAGNOSIS:**
The causes for transplant glomerulopathy can be generally classified into immunological and non-immunological. The first category includes antibody-mediated rejection such as presence of HLA-antibodies, particularly DSA against Class II, T-cell mediated rejection and thrombotic microangiopathy. Non-immunological causes include age, hepatitis C virus positive serology, drug toxicity such as cyclosporine and previous acute rejection above 3 months of post-transplantation (14, 15).

**Based on Clinical Presentation:**
Based on common clinical presentations of elevated creatinine levels, proteinuria and hypertension in patients with transplant glomerulopathy, following differential diagnosis are possible:

- IgA Nephropathy
- Focal Segmental Glomerulosclerosis
- Membranous Nephropathy
- Membranoproliferative Glomerulonephritis
- Anti-Neutrophil Cytoplasmic Antibody-associated Glomerulonephritis
- Systemic Lupus Erythematosis (SLE)

**Based on Histopathology:**
Based on only morphology with glomerular basement membrane duplication, differential diagnoses will include

- Membranoproliferative Glomerulonephritis
- HCV Infection-related Glomerulonephritis
- Lupus Nephritis
- Cryoglobulinemia
- Thrombotic Microangiopathy

Usually, the diagnosis is straightforward in case if ultrastructural immunofluorescent assessment of the kidney allograft histology is performed. However, often anti-phospholipid syndrome, hemolytic-uremic syndrome or antibody-mediated chronic thrombotic microangiopathy can pose challenge in the diagnosis of transplant glomerulopathy, if there is negative C4d staining.

**Investigations:**
Histopathology is the mainstay diagnostic tool for transplant glomerulopathy patients. Transplant glomerulopathy possesses unique structural insult identified by thickness of glomerular basement membrane and duplication. In 1999, Racusen and team suggested the Banff 97 categories of kidney allograft pathology to identify the severity of double contours on grounds of transplant glomerulopathy grading (16). Other major histopathological changes include diffuse endothelial and mesangial swelling with narrow capillary loops (17), rise in cellularity, mesangial matrix and segmental scars (18), often with intracapillary thrombi of fibrin and cellular crescents (17).

Electron microscopy serves the purpose to diagnose early transplant glomerulopathy, by looking for the endothelium segregation from glomerular basement membrane, widening of subendothelium, new glomerular basement membrane development +/- cellular processes interpositioning (19, 20). However, there is no fixed criteria for diagnosis of transplant glomerulopathy through ultrastructural examination (21). The changes in ultrastructure also impact peritubular capillaries along with glomerular capillary loops culminating in multiple layering of glomerular basement membrane (22), and has been reported in 90% of transplant glomerulopathy patients (23).

Endothelial staining of C4d, which include peritubular capillaries, is crucial to assessing the kidney allograft transplant biopsies. The C4 is a part of complement system pathway and is triggered by C1q activation.
through antigen–antibody complexes or sometimes directly initiated by bacterial polysaccharides (24). Nowadays, it is a universal clinical practice to stain all the kidney allograft biopsies for C4d to investigate antibody reactivity with the help of complement fixating antibodies. This can be done through direct immunofluorescence microscopic examination on frozen tissue sample or through immunohistochemistry on fixed tissue (1).

**Treatment Options:**

Transplant glomerulopathy is a frequent reason for late kidney allograft rejection and loss, without availability of any efficacious treatment owing to long-standing and irrevocable nature of the condition (25). Conventional therapeutic regimens include intravenous immunoglobulins (IVIG), plasmapheresis and splenectomy, and lately rituximab, eculizumab and bortezomib (25, 26). In actuality, present treatment strategies are based on clinical experience, rather the randomized controlled trials or level 1 evidence (14). However, a handful of research studies have been carried out to explore new treatment regimens and their effectiveness for transplant glomerulopathy and have been summarized below.

A study by Sablik et al. (2016) treated transplant glomerulopathy patients with IVIG and pulse methylprednisolone (MPDN). The study found significant decrease in proteinuria from 0.62g/L/year to 0.11g/L/year ($P=0.003$) and concluded that IVIG and MP therapy is correlated with about 50% decline in loss of eGFR post-treatment within the first year (27). Similar research group cited decrease in progression of eGFR deterioration and improvement in proteinuria in over 60% of their transplant glomerulopathy patients administered with IVIG + MPDN (28). Abreu et al. (2017) in their retrospective analysis reported number of treatment regimens in their study for transplant glomerulopathy; Rituximab + IVIG, increase of immunosuppression, Plasmapheresis + Rituximab + IVIG, Rituximab + IVIG + Tacrolimus, Rituximab + MPDN, MPDN + increase of immunosuppression, Everolimus, Plasmapheresis + Rituximab + IVIG + Tacrolimus + increase of immunosuppression, Rituximab + IVIG + MPDN + Everolimus, Rituximab + IVIG + MPDN + increase of immunosuppression, Rituximab + IVIG + MPDN + Tacrolimus, MPDN + Tacrolimus + increase of immunosuppression, Rituximab + Tacrolimus + increase of immunosuppression, IVIG + MPDN and Rituximab. However, based on the results, neither of the treatment options improved the long-term survival of kidney allograft in transplant glomerulopathy patients (29). Another study also suggested no efficacy of IVIG + Rituximab treatment in severe cases of transplant glomerulopathy and was found to be related with high rate of adverse events (30).

The present treatment options are grounded on preventive recommendations, for instance, surveillance of donor specific antibodies (DSA), preventing antibody mediated allograft rejection and emphasizing medication adherence (31, 32). The use of anti-proteinuric agents (e.g., ACE and ARB) is currently ongoing (33). Desensitization protocols have also been utilized in highly sensitized transplant patients at risk for developing antibody mediated rejection (32, 33). These strategies in chronic antibody mediated rejection and/or transplant glomerulopathy patients have been used without any evidence of significant improvement (34). A study did not show significant findings with the use of rituximab in transplant glomerulopathy patients (35).

Bortezomib has been shown to be effective in cases of chronic antibody mediated rejection based on their mechanism of action of B-cells depletion in experimental studies (36-39). A randomized controlled trial is currently under process to examine whether bortezomib deters transplant glomerulopathy in patients with high levels of post-transplantation DSAs (NCT01349595 on ClinicalTrials.gov). The pathogenesis of transplant glomerulopathy also involves complement pathway; the C4d deposits in kidney biopsies of transplant glomerulopathy patients (14). Therefore, studies are determining the role of breaking this complement pathway to prevent the development of transplant glomerulopathy. Eculizumab, an anti-C5 humanized monoclonal antibody, is the new drug currently under investigation for transplant glomerulopathy. Stegall et al.
(2012) demonstrated that eculizumab reduced the antibody mediated rejection in highly sensitized patients (40).

**Prognosis:**

As mentioned earlier, transplant glomerulopathy is associated with decline in kidney allograft survival. Transplant glomerulopathy, unfortunately, has particularly poor prognosis in terms of allograft loss (41). Research literature also indicates poor prognosis linked with transplant glomerulopathy. Nair et al. (2010) reported poor allograft outcome in patients with acute transplant glomerulopathy mediated by antibody-mediated allograft rejection (42). Gloor and colleagues suggested that subclinical transplant glomerulopathy affects long term allograft kidney outcomes (5). Another study highlighted that kidney allografts after a decade of transplantation encountered 1/3rd decline in allograft survival in comparison with nearly 2/3rd in the matched control cohort (10). Other studies have also attested these findings (3, 7). One study mentioned post-diagnosis median allograft survival of 43 ± 7 months (43). The reported death censored allograft 5 years survival was 16.7% (4), whereas death censored allograft 10 years survival was 56% (44). Studies have also demonstrated high frequency of allograft loss in a very short time frame; Maryniak et al. (1985) cited 77% allograft failure within 3 years of diagnosis (17). Briner et al. (1993) documented 60% of the allograft loss within 6 months of diagnosis of transplanted glomerulopathy (45). A handful of research studies have tried to determine the prognostic value of diverse clinical and histological variables of transplanted glomerulopathy, in order to identify subpopulation with slower disease process, establishing a cohort for therapeutic adjustment. Literature communicates that severity of double contour in glomerular basement membrane substantially affects the allograft function and survival (43). Moreover, a study cited that transplant glomerulopathy severity is directly proportional to worse allograft survival (57% allograft incidence in grade I versus 87.5% in grade III (44). This result was also held by another study (46). Moreover, C4d is regarded as an independent predictor of decreased allograft survival in transplant glomerulopathy (43), and studies have shown that transplant glomerulopathy with C4d is associated with reduced allograft function (47).

**DISCUSSION:**

Transplant glomerulopathy is a pathologic diagnosis of kidney allograft that was first identified almost four decades back (48). It is mainly documented as a pathological insult of chronic kidney rejection. Transplant glomerulopathy is diagnosed in the classification of chronic allograft nephropathy (CAN) with chronic allograft kidney rejection in the Banff 97 classification, and of chronic antibody-mediated rejection in the Banff 05, 07 and 09 classifications (49).

The risk of transplant glomerulopathy is greater in patients with previous transplantation, acute rejection, presence of HLA antibodies and antibody-mediated rejection. A study by Sis et al. suggested increase incidence of antibody-mediated rejection (54%) in their biopsy-proven transplant glomerulopathy cases (50). Few other research studies communicated that about 45% of cases with antibody-mediated rejection subsequently progressed to transplant glomerulopathy in comparison with 6% of kidney recipients without rejection (51, 52). Transplant glomerulopathy manifests as progressive deterioration of kidney function, evidenced by high creatinine levels and proteinuria. In initial stages, the patients may manifest mild sub-nephrotic range proteinuria and unexplained moderate decline of kidney allograft function (1).

The interstitial and glomerular inflammation and thickening of the basement membrane of the peritubular capillaries are obvious in the progression of the transplant glomerulopathy, which indicates chronic and active inflammatory immune response in the glomerular basement membrane and microvasculature. This is also supported by presence of double contours and patent capillary loops with highly thickened basement membranes, endothelial and epithelial cells swelling and mild mesangial expansion. Chronic transplant glomerulopathy can have varied manifestations such as presence of focal and segmental glomerulosclerosis, glomerular basement membrane splitting, segmental sclerosis and hyalinosis, mesangial interposition and increased lucency of the lamina rara interna and infrequent interposition, with no immune complexes (53).
These manifestations have been illustrated in Figure (53). Earlier studies have confirmed the presence of glomerular, interstitial and peritubular capillary inflammation (5, 12, 54). Gloor et al. (2007) documented that transplant glomerulopathy is associated with glomerular inflammation and advances to duplication of the glomerular basement membrane. They also highlighted that progression of transplant glomerulopathy is also associated with consistent peritubular capillary inflammation (5). Sis et al. (2007) reported glomerulitis and peritubular capillary inflammation in 35% and 70% of the biopsy specimen of transplant glomerulopathy patients, respectively (50). Sun et al. (2012) found 94% glomerulitis and 90% peritubular capillary inflammation in transplant glomerulopathy patients (55). With reference to basement membrane thickening of the peritubular capillary, Aita et al. (2007) proposed that it could be a promising diagnostic biomarker of chronic allograft rejection. They suggested that peritubular capillary basement membrane thickening score calculated through light microscopy could reflect peritubular capillary basement membrane multilayering evidenced by electron microscopy (56).

Previous studies have frequently labeled transplant glomerulopathy manifestation as late, appearing after few years of kidney transplantation. In fact, it was seldom reported within one year of transplantation (57, 58). Sis et al. (2007) reported early diagnosis (3.8 months) of transplant glomerulopathy in their study (50). Studies have mentioned that the occurrence of transplant glomerulopathy is quite high, troubling 4% of the transplant patients after one year of transplantation (51, 59). Gloor et al. (2007) reported both early (4 months) and late (21 months) diagnosis of transplant glomerulopathy (51).

Peritubular capillary deposition of C4d has been observed previously in 57% of the biopsy specimens, which included 45% diffuse staining (C4d3), 11% focal staining (C4d2) (49). A handful of studies suggested that C4d deposition in the peritubular capillaries is strongly correlated with transplant glomerulopathy, and most of them possess DSAs (60, 61). Conversely, studies have also mentioned C4d-negative peritubular capillaries in transplant glomerulopathy cases with DSAs (5, 6, 50). Sis et al. (2007) reported that the occurrence of C4d deposition in transplant glomerulopathy was lesser than the presence of DSAs; C4d might be negative or varying, indicating that C4d-negative did not essentially ruled out the antibody-mediated glomerular injury (23). Diffuse C4d deposition has also been seen in the glomerular capillaries in studies (49). Gloor et al. (2007) documented that 32% of glomerular capillaries were covered with C4d in transplant glomerulopathy patients (51). Sijpkens et al. communicated that 91% of the transplant glomerulopathy biopsy specimens had segmental glomerular capillary wall staining with C4d (6).

Numerous research studies have shown that prognosis of transplant glomerulopathy is poor in the presence of DSAs, particularly against class II (62-64). Sis et al. (2007) also concluded that presence of anti-HLA, especially against class II might play a key role in advancing of transplant glomerulopathy and eventually poor outcomes (5).

CONCLUSION
In conclusion, transplant glomerulopathy is associated with glomerular and peritubular capillary basement membrane thickening along with presence of anti-HLA antibodies and often C4d deposition in the peritubular capillaries in immunostaining. Transplant glomerulopathy patients usually have positive history for acute rejection, resulting mostly in antibody-mediated rejection. DSAs against class II is specifically linked with transplant glomerulopathy. Unfortunately, the prognosis of kidney allografts is dismal even under existing immunosuppressive regimens.

Conflict of interest:
Authors declare no conflict of interest

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