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Transplant Glomerulopathy: Pathogenesis, Morphology, and Prognosis

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Abstract

Transplant glomerulopathy (TG) has emerged as an important leading cause to late renal allograft loss. It is easily distinguished from other causes of renal allograft nephropathies, by the presence of thickened glomerular capillary loops and double contouring, in the presence of graft dysfunction and proteinuria clinically.

The association between TG with anti-HLA antibodies, C4d, and prior antibody mediated rejection episodes supported the contribution of antibody mediated process in the pathogenesis. It is now a recognized entity of chronic antibody mediated rejection, despite the growing evidence of the contribution of other factors.

TG has a poor outcome with graft loss soon after the establishment of the diagnosis. Several histological and clinical factors influenced graft survival, such as TG grade, C4d, and eGFR. So far, there is no approved and effective therapeutic modality for TG, but change in immunosuppressive therapy might stabilize the graft function and reduce proteinuria.

Keywords: Transplant glomerulopathy; Antibody mediated rejection; Pathogenesis; Prognosis

Introduction

Transplant glomerulopathy (TG) is a unique pathologic condition limited to renal allografts, contributing to late kidney allograft loss. It is characterized by duplication of the basement membranes in the absence of immune complex mediated glomerulonephritis and thrombotic microangiopathy [1]. Early changes are identified by ultrastructural examination with endothelial cell injury leading to subendothelial widening, accumulation of amorphous electron lucent material, and mesangial interpositioning [2]. TG portends a poor outcome, manifesting clinically with progressive allograft dysfunction and proteinuria [3]. It was originally classified as a variant of chronic allograft nephropathy of unknown etiology, but now it is recognized with increased frequency in patients with history of antibody mediated rejection (AMR) and is associated with deposition of C4d, suggesting that TG might be associated with humoral mediated injury [4-6].

Now, TG is widely recognized as chronic antibody mediated rejection, accounting for approximately 5-15% of transplants with chronic rejection [2,3,7]. It is diagnosed with (1) glomerular and/or peritubular capillaries (PTC) basement membrane multi-layering, (2) diffuse C4d deposition in the PTC, and (3) presence of donor specific antibodies (DSA) according to the Banff 2005 classification [6].

Incidence

The overall incidence of TG increases with time, from 4% at 1 year, 14.4% at 3 years and 20.2% at 5 years post-transplantation [8-10]. TG is also documented in 5.4% of protocol biopsies in clinically stable renal allografts by 10 years post-transplantation [11]. Moreover, Gloor et al. evaluated the incidence of TG in protocol biopsies, a 2.8% incidence rate was reported at one year, increasing to 11.5% at 5 years posttransplantation [8].

Pathogenesis

The definite pathogenesis of TG is unclear, but yet unique that distinguishes it from other chronic pathologic changes in allograft. There is increasing evidence supporting the association between alloantibody mediated injury and TG [12]. The contribution of humoral immunity was primarily based on the presence of circulating antidonor human leukocyte antigen (HLA) antibodies and the deposition of complement split product C4d in peritubular capillaries [12-14]. Early reports showed that TG is related to a higher degree of HLA mismatch, antidonor antibodies, and to prior rejection episodes [12,15], indicating that sustained repeated endothelial cell damage is contributing to the pathogenesis of TG [12].

In contrast, few reports showed no difference in the degree of HLA-mismatch or PRA levels between TG group and control group [2]. Moreover, approximately 40-50% of TG cases either lack C4d and/or DSA [15,16]. In addition, 50% of patients with AMR developed TG despite successful treatment of acute process [15]. These points argued against the contribution of humoral mediated tissue injury, but several theories were proposed to explain these findings in this context. First, both C4d and DSA titer can wax and wane, therefore at any given time these factors may or may not be demonstrable, even if AMR was present [15]. Second, some studies have showed that C4d might precede the development of TG [14,15]. Even some investigators suggested that C4d and/or DSA might be absent by the time of diagnosis, even if the lesion was triggered by humoral mediated injury [15]. Others thought that the negative C4d might indicate that at the time of diagnosis antibodies are not pathogenic or that the progression of capillary lesions does not involve complements activation [10].

Multiple factors exhibited a strong association with the development of TG (Table 1). The presence of HLA antibodies prior to transplantation has been found to correlate with the development of TG [4,8,12,13], particularly class II antibodies [12,17] which are found in conjugation with TG with greater frequency compared to class I antibodies [18]. The risk increases further by the presence of both anti-HLA class I and II together, and in cases with anti-HLA class II DSA

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Presence of anti-HLA antibodies/ DSA
Prior episode of acute rejection
Presence of non-HLA antibodies
Hepatitis C infection

Table 1: Risk factors leading to development of TG.

[8]. Gloor et al reported TG in 22% of cases with donor specific anti-HLA antibodies at a surveillance biopsy one year post-transplantation compared to 8% in conventional transplant [8]. A significant increase in the incidence and severity of TG was noted in patients with a positive cross match, while a trend toward increased glomerulopathy in ABO incompatible transplants were reported [4].

In addition to anti-HLA antibodies, patients with TG showed a higher rate of prior episodes of rejection [17]. Often, TG has a strong association with multiple rejection episodes, especially acute antibody-mediated rejection, thus it is now considered to represent chronic antibody-mediated rejection. Sis et al, found that 54% of patients with TG had prior episode of rejection, with 44% of the cases having T-cell mediated rejection and antibody mediated rejection documented in only 10% [12]. The significance of prior acute antibody mediated rejection episode was emphasized further, with a positive history of AMR documented in approximately 45% of patients with TG, compared to 6% of recipient without rejection [4,8].

Despite the growing evidence of antibody mediated injury in the development of TG, there is also some evidence hinting toward that not all cases of TG are antibody mediated [19]. Akalin et al showed that 60% of TG cases developed in the absence of DSA and positive C4d, raising the possibility of alternative mechanism [19], including T-cell mediated immune response [20]. The latter was suggested based on the presence of CXCR3+ I COS+ activated T cells within glomerular inflammatory infiltrates in cases with TG [20]. Furthermore, in the cohort conducted by Dinavah et al., they showed a significant association between TG and the presence of antibodies against non-HLA antigens, thus supporting the role of non-HLA antibodies in the pathogenesis of TG [21].

Recently, Baid-Agrawal et al. demonstrated a three overlapping mechanisms contributing to the development of TG, including chronic humoral rejection with positive C4d, hepatitis C infection, and thrombotic microangiopathy [22]. Few reports found that a substantial number of TG cases had an association with exposure to HCV [2,8,22], but in the study conducted by Suri et al., they found no significant difference between HCV seropositivity in TG compared to controls [2,23]. Few reports support the association between CMV infection and TG [24], with 5% of patients with TG having CMV [23].

Few investigators observed that in cases of TG without alloantibodies or C4d had arteriolar hyalinosis suggesting that endothelial damage secondary to calcinurine inhibitor toxicity (CNI) might act as a contributory factor in TG [12,19], but the theory lacks a significant proof [12].

One of the theories proposed by Joosten et al. is the presence of anti-glomerular basement membrane (GBM) antibodies causing endothelial injury and subsequent glomerular capillary loops duplication. The theory was supported by the presence of significantly higher IgG anti-GBM antibodies targeted against heparan sulphate proteoglycan agrin in patients with TG compared to control group [25].

Histological Diagnosis

TG has a distinct morphology which is characterized by thickened glomerular capillary walls and double contouring demonstrated by PAS and/or silver stain. The Banff 1997 classification used the extent of double contouring in the most severely affected glomerulus as the basis for TG grading [1]. On light examination, the earliest TG changes noticed are diffuse swelling of endothelial and mesangial cell with narrowing of capillary loops [3]. TG is commonly associated transplant arteriopathy [3], and the glomeruli might show increase in mesangial matrix, cellularity, and segmental scars [18]. Rarely, cellular crescents and intracapillary fibrin thrombi could also be present [3]. The Edmonton group was able to identify C4d, PTC basement membrane multi-layering, DSA, and glomerular capillary loops duplication in 73% of cases [12].

Electron microscopy served as a good tool to identify early TG, by detecting the separation of the endothelium from glomerular basement membrane, subendothelial widening with accumulation of flocculent material, new basement membrane formation, with or without interpositioning of cellular processes [26,27]. Despite that these changes were noticed as early as one month post-transplantation [27], there are no precise criteria for TG diagnosis based on ultrastructural examination [28].

The ultrastructural changes are not limited to glomerular capillary loops, but also affect peritubular capillaries (PTC) leading to multi-layering of basement membrane [29], which is documented in 90% of TG cases [12]. PTC multi-layering is identified in other glomerular diseases beside TG [30,31], but it tends to be mild [31]. On the other hand, the presence of moderate (five or six layers) or severe (seven or more layers) degree of PTC multi-layering can be safely used as a marker of chronic rejection [26,30]. Nevertheless, Wavamunno et al showed that even mild degree of PTC multi-layering in protocol biopsies are associated with TG [27].

C4d tends to be positive in approximately 50% of cases [16]. Few reports showed a higher incidence of C4d reaching up to 60% [13], while others reported C4d positivity as low as 25% [5]. In TG, C4d was significantly associated with the severity of PTC multi-layering [32].

In the early stages of TG the glomerular lesion tend to be focal involving few glomeruli, which progress with increasing percentage of affected capillary loops on sequential biopsies. The percentage of glomeruli involved also increased with advanced disease, from 26% in TG grade 1 to 73% in TG grade 3 [8]. Not surprisingly, that TG grade could progress with time or in re-biopsy, Gloor et al. showed that 35% of TG grade 1 progressed to grade 2 and 56% of cases progressed from TG grade 2 to 3, while in 24% failed to show TG on subsequent biopsies [8].

Inflammation within glomeruli, tubules, interstitium, and peritubular capillaries are common histologic findings accompanying TG [8,18]. Gloor et al. showed that a higher TG grade was significantly associated with higher degree of glomerulitis, but not tubulitis [8]. Few cases with TG even showed a concomitant cellular rejection, but the association was not of statistical significance in relation to the severity of the disease [8].

Interstitial fibrosis becomes more pronounced as the glomerular changes become more severe [23], which was confirmed by Gloor et al. who showed worsening of interstitial fibrosis on follow-up biopsies, but the degree of chronic damage was not associated with increasing TG grade [8].

Clinical Characterestics

In the early stages of TG, the clinical manifestation is non-specific with progressive unexplained loss of graft function and mild

proteinuria [8,12]. TG usually manifest with proteinuria that can be of nephrotic range [10] in approximately 25% of cases [23]. A 4% of the patients with TG could develop nephrotic syndrome with >3.5g/day proteinuria, and low levels of albumin [33].

TG is rarely diagnosed clinically within the first year post-transplantation [10], but it was diagnosed at a minimum of 3.8 months after transplantation [12], and in another report at 10 weeks post-transplant [34]. Several reports diagnosed TG at 21±14-106±77 months post transplantation [8,12,19,23,32,33].

Recent studies showed that the clinical presentation lags behind the initial histologic changes of the disease [8,10], while John et al showed that a significant decline in eGFR occur approximately 1 year before renal biopsy [32]. It has been documented that neither the entity nor the duration of proteinuria could predict the severity/stage of histological lesions [23,33]. Banfi et al showed that proteinuria and graft function run an independent course in one third of patients, while the remaining had a parallel rise in proteinuria and serum creatinine as the disease progresses [23].

Outcome and Prognosis

Generally, TG exhibit a poor long-term graft survival with graft function, C4d, and the severity of GBM duplication are associated with reduced graft survival [10,17,23] (Table 2). Despite that the disease progression is variable; grafts with TG fail sooner than those without [10,23,33]. The median graft survival after diagnosis of TG was 43±7 months [17]. The overall death censored graft survival 5 years post-biopsy was 16.7% [32], while the 10 years graft survival censored by death reported by Banfi et al was 56% [23]. Others have documented a higher rate of graft loss within a shorter period of time, Maryniak et al. reported 77% graft failure within 3 years [3], and Briner et al. reported 60% graft failure within 6 months after diagnosis [35].

Several reports attempted to investigates the prognostic significance of different histological and clinical parameters in relation to TG, in an attempt to identify a subgroup of patients with a slower disease progression, forming a target group for therapy modulation.

Few Reports showed that the degree of GBM duplication has significantly influence the graft function as well as the graft survival [17]. In addition, Banfi et al. reported that a higher TG grade was associated with poor graft survival, and a graft loss incidence of 57% in TG grade 1 compared to 87.5% in TG grade 3 [23], but the difference was not statistically significant, and this finding was further supported by Gloor et al. [8]. Moreover, the combination of TG with C4d has significantly affected graft outcome [36], and C4d is considered as an independent variable related to reduce graft survival [17], while others showed that C4d had a tendency toward worse graft survival [32].

Not surprisingly, interstitial fibrosis and tubular atrophy remains a consistent predictive of graft survival in TG [32]. Other histologic parameters noted to affect graft survival are arteriolar hyalinosis, the degree of PTC multi-layering [32], and the presence of interstitial inflammation [17].

TG grade
C4d
Interstitial Fibrosis and tubular atrophy
eGFR
Degree of PTC basement membrane multi-layering
Arteriolar Hyalinosis
Proteinuria

Table 2: Prognostic factors in Transplant Glomerulopathy.

The significance of the clinical status of the patients at the time of the biopsy could not be ignored. The degree of proteinuria and eGFR has contributed to the graft survival in TG [17]. Return to dialysis was noticed to be as twice as frequent in patients with >2.5g/day of proteinuria than with lower proteinuria [23]. One report showed that DSA was also associated with poor graft outcome [37].

Differnetail Diagnosis

TG must be distinguished from ischemia, thrombotic microangiopathy, and recurrent membranoproliferative glomerulonephritis (MPGN) or other de novo immune-complex glomerulopathy. Ischemic glomeruli can be easily recognized by the presence of wrinkled capillary walls rather than double contouring, but differentiating TG from TMA purely based on histologic morphology is challenging, so clinical correlation is required for a definite diagnosis [18]. Immune complex glomerulonephritis is diagnosed based on immunofluorescence and electron microscopy

Management and Treatment

Now there is no known effective therapeutic approach for TG. Based on the experience with case series, that change in the background immunosuppression can stabilize chronic humoral rejection [38], with a rapid and sustained decrease in antibody titer when switching from cyclosporine based regimen to tacrolimus and mycophenolate mofetil [38]. Banfi et al. showed that 69% of their cohort cases had their regimen modified and 46.7% were maintained on the same regimen, and both showed stabilization and slight improvement in their graft function [23]. Rituximab was used as a trial in cases with TG, with stabilization of graft function and/or decrease in proteinuria in 50% of cases [39].

Conclusion

TG is a common entity occurring in late allografts with eventual graft loss in 40-70% of cases. It is associated with antibody mediated mechanism of tissue injury, but recently there is a growing evidence of the contribution of other factors in the pathogenesis such as non-HLA related antibodies. TG has a poor prognosis with TG grade, C4d, eGFR and proteinuria influencing the graft survival.

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