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Narrative Review

Advances in the Understanding of Transplant Glomerulopathy

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Transplant glomerulopathy is a sign of chronic kidney allograft damage. It has poor survival and no effective therapies. This entity develops as a maladaptive repair/remodeling response to sustained endothelial injury and is characterized by duplication/multilamination of capillary basement membranes. This review provides up-to-date information for transplant glomerulopathy, including new insights into underlying causes and mechanisms, and highlights unmet needs in diagnostics. Transplant glomerulopathy is widely accepted as the principal manifestation of chronic antibody-mediated rejection, mostly with HLA antigen class II antibodies. However, recent data suggest that at least in some patients, there also is an association with hepatitis C virus infection, autoimmunity, and late thrombotic microangiopathy. Furthermore, intragraft molecular studies reveal nonresolving inflammation after sustained endothelial injury as a key mechanism and therapeutic target. Unfortunately, current international criteria rely heavily on light microscopy and miss patients at early stages, when they likely are treatable. Therefore, better tools, such as electron microscopy or molecular probes, are needed to detect patients when kidney injury is in an early active phase. Better understanding of causes and effector mechanisms coupled with early diagnosis can lead to the development of new therapeutics for transplant glomerulopathy and improved kidney outcomes.

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Transplant glomerulopathy is a morphologic pattern of chronic kidney allograft injury that lacks detectable immune-complex deposits and is associated with poor kidney transplant outcomes.[1,2] It primarily is an endothelial pathology affecting kidney microcirculation, that is, both glomerular and peritubular capillaries. The predominant morphology is the structural remodeling of microcirculation endothelium, which is seen as a duplication (double contours) and/or multilamination of capillary basement membranes along with substantial replacement of endothelial fenestrations (pores) with a continuous endothelial lining.

Although transplant glomerulopathy has been known since the early days of kidney transplantation,[3-7] understanding of this injury pattern still is incomplete. With increased recognition of alloantibody-mediated phenotypes in kidney transplants, transplant glomerulopathy now is widely accepted as the cardinal histologic phenotype of chronic antibody-mediated rejection (ABMR).[1,2,8] However, recent retrospective observational studies raise new questions and suggest non–rejection-related diseases as possible causes in some patients. Also, state-of-the-art molecular studies conducted in patient samples have provided new insights into mechanisms of transplant glomerulopathy that open avenues for discovering drug targets to prevent the development of overt injury and thereby improve long-term kidney transplant outcomes. The aim of this article is to review our current understanding of transplant glomerulopathy, including new insights into underlying causes and mechanisms, and, in light of this advanced understanding, discuss unmet needs in diagnostics.

INCIDENCE, CLINICAL FEATURES, AND IMPACT

Transplant glomerulopathy is a time-dependent pathology of kidney allografts that usually causes clinical problems after 6 months posttransplantation.[1,9] In our series of biopsies for cause, transplant glomerulopathy was diagnosed by light microscopy at a median of 5.5 years after transplantation, with a minimum of 3.8 months.[1] Its reported prevalence based on clinical indication biopsies varies from 1.6%-7%,[1,10-14] but these numbers misleadingly underestimate its true prevalence. This is because many kidneys develop transplant glomerulopathy subclinically or insidiously, and many chronically failing kidney transplants are not biopsied by clinicians.[9] The frequency of transplant glomerulopathy is greater in crossmatch-positive presensitized kidney transplantation than in conventional (crossmatch-negative) kidney transplantation: 22% versus 4%-8%, respectively, at 1 year.[9,15] Based on data from surveillance biopsies, the incidence of transplant glomerulopathy in conventional kidney transplantation progressively increases to 20% at 5 years posttransplantation.[9]

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Clinical manifestations of transplant glomerulopathy include progressive loss of kidney allograft function, proteinuria, and hypertension.[2] Earlier stages may have mild sub–nephrotic-range proteinuria and unexplained mild deterioration in graft function. It should be noted that transplant glomerulopathy often is underdiagnosed if clinicians wait for clinical problems to perform biopsy: almost half the kidneys with histologically well-developed transplant glomerulopathy studied by Gloor et al[9] from the Mayo Clinic were subclinical and detected in protocol biopsies. This observation indicates that there is an interval between morphologic development of the disease and its inevitable clinical manifestation.

Transplant glomerulopathy is a strong predictor of poor long-term kidney transplant survival. Data from a large series of crossmatch-negative kidney recipients showed 62% graft survival for those with transplant glomerulopathy as opposed to 95% graft survival for those without at 5 years after transplantation.[2] The prognosis of kidneys with transplant glomerulopathy was even worse when associated with C4d (split product of active complement C4) positivity in peritubular capillaries.[16]

Box 1. Diagnostic Criteria for Early Transplant Glomerulopathy

Light microscopy (nondiagnostic)
- No double contours or double contours in <10% of peripheral capillary loops in the most severely affected glomerulus
- None to mild mesangial matrix expansion
- Glomerulitis and/or peritubular capillaritis usually are present

Immunofluorescence (nondiagnostic)
- Negative for significant IgA, IgG, and C1q
- Sometimes mild to moderate mesangial IgM staining and minimal mesangial or capillary loop C3 staining
- C4d ± in peritubular capillaries by immunofluorescence or immunohistochemistry
- C4d ± in glomerular capillaries by immunofluorescence or immunohistochemistry

Electron microscopy (diagnostic after correlation with the methods above)
- Few peripheral glomerular loops with duplication and/or multilayering of glomerular basement membranes present, in the absence of immune complexes, with any of the following features:
  - ◇ Widening of subendothelial space
  - ◇ Endothelial cell swelling
  - ◇ Loss of endothelial cell fenestrations
  - ◇ None to mild mesangial matrix expansion

Note: Early transplant glomerulopathy corresponds to a Banff cg score of 0.

BIOPSY DIAGNOSIS

Light Microscopy

Morphologic features of transplant glomerulopathy evolve over time. The time required to develop transplant glomerulopathy probably depends on whether the endothelial injury is sustained or episodic and whether primary endothelial injury is accompanied and escalated by persistent inflammatory stimuli.

Early transplant glomerulopathy (Box 1) starts as a focal disease and often is missed by light microscopy because it lacks overt glomerular double contours. The earliest changes are swelling of the endothelial and mesangial cells with decreased patency of the capillary loops.[11] At this early stage, glomerular basement membranes (GBMs) display rare double contours or appear relatively normal by light microscopy. In our experience, early transplant glomerulopathy in patients with donor-specific antibodies often is associated with microcirculation inflammation (aggregation and margination of leukocytes in capillary lumens), glomerulitis, and/or peritubular capillaritis. Figure 1A shows an early transplant glomerulopathy biopsy specimen with striking glomerulitis but no identifiable glomerular double contours by light microscopy. However, electron microscopy (Fig 1B) shows focal duplication of the GBM together with active features such as endothelial swelling and a microthrombus with fibrin tactoids in the lumen.

Overt or well-developed transplant glomerulopathy (Box 2) is recognized easily by prominent double contours of the GBMs (Fig 1C-F) and often accompanied by mesangial matrix expansion with no or mild mesangial hypercellularity. By light microscopy, GBM duplications are visualized best in tissue sections stained with periodic acid–Schiff and silver stain. Glomerular involvement can be focal or diffuse. Severity is scored in the most severely affected glomerulus, according to Banff criteria, as follows: glomerular double contours in <10% of capillary loops (cg0), 10%-25% (cg1), 26%-50% (cg2), and >50% (cg3).[17] Depending on the duration of the disease, other indexes of chronic kidney damage also are seen, including segmental and/or global glomerulosclerosis, interstitial fibrosis, tubular atrophy, arteriolar hyalinosis, arterial fibrous intimal thickening, and sometimes loss of peritubular capillaries.

Morphologic indicators of activity in transplant glomerulopathy are C4d staining and microcirculation inflammation (capillaritis/glomerulitis; Fig 1A and E), mostly with monocytes and natural killer (NK) cells, but also with neutrophils and T lymphocytes detected by immunohistochemistry.[18-21] We observed peritubular capillaritis and glomerulitis in 70% and 35% of transplant glomerulopathy biopsy specimens, respectively.[1] In a smaller cohort, glomerulitis and peritubular capillaritis were seen in 94% and 91% of patients with transplant glomerulopathy, respectively.[22] Another sign of active injury in transplant glomerulopathy is the presence of focal fibrin and platelet microthrombi in glomerular capillary loops,