Chronic transplant glomerulopathy (CTG), investigated in a large single-center study by Akalin et al. (1), is an interesting pathologic lesion that develops in the renal allograft. It is characterized by endothelial cell injury or loss, accumulation of flocculent material in a widened subendothelial space, and mesangial interposition with deposition of new matrix along glomerular capillary walls. These progressive changes produce a thickened glomerular capillary profile and the capillary wall “double contours” that are demonstrable on periodic acid-Schiff and silver staining and that define CTG (2). Analogous changes occur in later stages of thrombotic microangiopathy (TMA) in the native kidney, initiated by endothelial injury and/or dysfunction. Development of this lesion in the renal allograft has been associated with worse graft outcome.

CTG has been documented in the context of “chronic rejection” with antidonor antibody and may be strongly correlated with other features that are consistent with chronic/persistent/recurrent antibody-mediated rejection (AMR), including positive staining for C4d and multilayering of peritubular capillary basal lamina. Akalin et al. briefly reviewed this literature, including the seminal studies by Mauiyedi et al. (3) and Regele et al. (4); however, studies of CTG correlation with C4d staining and detection of donor-specific antibody (dsAb) are emerging, and clearly many cases of CTG do not have these features at the time of biopsy.

It is likely that the triad of CTG, C4d staining and presence of dsAb are present at variable time points in the course of chronic/recurrent/persistent AMR. It is known that both C4d staining and dsAb titers can wax and wane; therefore, at any given time, these factors may or may not be demonstrable, even if AMR is or has been present. Some studies (4) have shown that peritubular capillary C4d staining precedes development of CTG, although it is not found concurrent with the lesion. It is possible that C4d and dsAb may be absent by the time that the CTG lesion is discovered by biopsy of an allograft with proteinuria and/or dysfunction, even if the lesion was initially triggered by AMR. In the absence of current positive C4d staining and/or dsAb, however, it is doubtful that a therapeutic response is warranted, although close monitoring and possible intervention may be advisable if other morphologic features of active AMR (e.g., peritubular capillaritis, glomerulitis) are present.

Technical issues may have an impact on detection of C4d in biopsy tissue. Staining for C4d using polyclonal antibody on paraffin sections is somewhat less sensitive than staining with mAb on frozen sections (5), so C4d deposition may be underestimated by this technique. Conversely, glomerular capillary wall staining on paraffin sections may be more specific for complement activation in the glomerulus and may be more closely associated with CTG (6), although immune complex glomerulonephritis needs to be ruled out if staining is positive. C4d staining of the glomeruli was not evaluated in the study by Akalin et al.

Early CTG is best detected by electron microscopy (EM), detecting separation of the endothelium from glomerular capillary basement membrane before establishment of mesangial interposition and “double contours” that are detectable by light microscopy. In the study by Akalin et al. (1), EM was performed only on cases with proteinuria, so some more subtle cases of CTG may have been missed. In addition, “for cause” biopsies do not capture all cases with CTG, and this “partial sampling” could obscure relevant correlations. In a recent study reported by Gloor et al. (7), of 582 protocol and for-cause biopsies from conventional (cross-match negative ABO-compatible) allografts, CTG was found in 55 (9.5%) in biopsies at 1 yr after transplantation; 27 of these were protocol biopsies done on allografts without significant clinical findings. Peritubular capillary C4d was found in 26% of those with CTG, and 32% had glomerular capillary staining. Incidence of CTG rose to 20% at 5 years. Fifty-eight percent of biopsies with severe CTG had minimal other histologic findings. CTG was strongly associated with anti-HLA antibody, especially to class II antigens, with higher risk with dsAb. Fifty percent of patients with AMR developed CTG, despite successful treatment of the acute process.

Other associations with CTG in the study by Gloor et al. (7) included acute rejection and hepatitis C antibody positivity. Indeed, in the allograft kidney, a variety of other factors are known to be associated with endothelial injury and TMA, including hepatitis C infection, calcineurin inhibitor toxicity, sirolimus exposure, and potentially any of the factors that are known to produce hemolytic uremic syndrome/TMA in the native kidney. Glomerular infiltration by CXCR3+ I COS+ activated T cells has been documented in CTG/chronic allograft nephropathy biopsies, suggesting that an effector T cell re-

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sponse may also potentially produce this change (8). It is possible and even likely that, to the extent that glomerular capillaries are involved in these processes acutely, the chronic injury pattern that is recognized as CTG could evolve in these cases.

Few pathologic features in renal allograft biopsies are specific. Lymphocytic and/or necrotizing arteritis and moderate to severe (although not mild) lymphocytic tubulitis are specific enough to be regarded as sufficient to diagnose acute cellular rejection, but both of these features can be seen in some native kidney disease. In the allograft kidney, tubulitis may be found in drug reactions, infection, posttransplantation lymphoproliferative disorder, and potentially “acceptance” reactions. Interstitial inflammation alone is too nonspecific to be sufficient to diagnose rejection. Even neutrophil margination in peritubular capillaries is nonspecific and can be seen with ischemia. Positive immunostaining for Ig and/or complement components and dsAb must be present in addition to histologic features to make a definitive diagnosis of acute or chronic AMR by Banff criteria (9). These strict criteria for both cellular and AMR may lead to underdiagnosis of rejection, although the pathologist may indicate that findings are suspicious although not definitive and recommend close monitoring of the patient. Strict diagnostic thresholds, however, are designed to avoid overdiagnosis and the risks and costs of unnecessary treatment.

The literature regarding CTG is still emerging, and single-center studies such as the one by Akalin et al. are an important contribution to our understanding of the spectrum of associations and potential causes of this form of glomerular injury. As proposed by these authors, multicenter studies with serial protocol biopsies beginning before development of proteinuria and graft dysfunction and including EM, staining for C4d, and assay for anti-HLA antibody, especially dsAb, would be essential to define fully the pathogenesis of this lesion. Although CTG has been documented to evolve in only a minority of renal allografts (1 to 20%), understanding of causes and pathogenesis of the lesion could contribute to prevention or intervention to preserve optimal graft function and survival in a significant subset of renal allograft recipients.

Disclosures
None.

References