Renal Allograft Rejection: Pieces of the Puzzle

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Despite a burgeoning literature on renal allograft pathology and rejection diagnosis, there are still many aspects that remain to be resolved. In this issue of JASN, two of these vexing issues are addressed. The first is the finding of isolated arteritis in allograft biopsies, without other diagnostic evidence of acute cell- or antibody-mediated rejection (AMR). The other is the identification of non-HLA/non-blood group endothelial cell antigens (ECAs) that may be targets of the alloimmune response and are associated with increased incidence of allograft rejection. These are relatively subtle aspects of allograft biopsy evaluation and diagnosis, reflecting the increasing sophistication of assessment and management of patients with renal allografts.

Sis et al.1 have taken on the issue of the significance the biopsy finding of isolated arteritis, in a multicenter study by a Banff working group.2 This lesion would meet Banff criteria for a mild “type 2” cell-mediated rejection, but is such a minimal finding in the absence of other significant inflammation in the graft that pathologists hesitated to make a diagnosis of acute rejection, and clinicians hesitated to treat it as such. This has been a controversial lesion, in part because molecular studies found minimal evidence of “rejection” signals on microarray in this setting. Sis et al. accumulated a substantial number of these cases, and compared those with isolated endarteritis with endarteritis accompanied by significant tubulointerstitial inflammation, and with negative controls (no rejection). In the isolated endarteritis group, the fall in creatinine after rejection treatment and the reduction in allograft survival were similar to the positive control group.

Perhaps this endarteritis is a very early cell-mediated rejection process. Why is there graft dysfunction and reduced survival with such a “minimal” localized lesion? It is possible that the arteritis, although seemingly an isolated finding, is really only the “tip of the iceberg,” with more florid inflammation in the organ that has not been sampled by the biopsy.3 Sampling issues could also explain the absence of molecular correlates of cell-mediated rejection in such biopsies. Despite the exclusion of HLA-incompatible transplants in the cohort, it is also possible that this mild arteritis with no associated tubulointerstitial inflammation could represent AMR in some cases. Mild arteritis is now recognized as part of the morphologic seen in antibody-mediated injury, and biopsies with “vascular AMR” may be C4d negative.4 Indeed, there was a higher incidence of two lesions associated with donor-specific antibody (DSA), chronic transplant glomerulopathy,5 and arteriosclerosis,6 and of donor-specific antibody in this group. Although more microvascular inflammation would be expected in an active AMR, the endothelium of arteries and capillaries is subtly different, and an antibody response focused preferentially on arteries with little capillaritis is theoretically possible. Anti-HLA DSAs seem to mediate many episodes of vascular rejection, but also may represent a component of a broad-based alloimmune response. Only 38% of the cohort with isolated endarteritis were tested for the presence of concomitant circulating DSA, a confounding factor in interpreting the association between isolated endarteritis, circulating DSA, response to treatment, and kidney graft survival. Even if this is early AMR, anti-T cell therapy would potentially have efficacy by suppressing T-cell help. However, further studies will be necessary to define which treatments are most effective in this setting, associated or not with circulating DSA. At any rate, analyzing significant numbers of these cases from multiple centers enables the conclusion that this lesion is an independent risk factor for allograft loss, and should not be ignored.

Jackson et al.7 address another important issue related to rejection and clinicopathologic correlation: patients with evidence of AMR without demonstrable DSAs. Identification of DSA(s) remains a necessary feature for diagnosis of AMR,8 and DSA titers are monitored to assess response to treatment in these patients. The finding of microvascular inflammation with or without positive staining for C4d in biopsy specimens without detectable antibody is frustrating for pathologists and caregivers alike. Although previous studies provide evidence of potential non-HLA ECA targets, correlation of anti-ECA antibodies of known specificity to in vivo vascular injury is needed to “complete the loop” of evidence of pathogenicity. Antibodies to the four antigens identified by protein microarray pretransplant in a discovery cohort in this study stimulated increased adhesion molecule expression and production of inflammatory cytokines in endothelial cultures in vitro. In vivo, patients with these antibodies had more microvascular inflammation, higher incidence of positive staining for C4d and early chronic transplant glomerulopathy/vasculopathy on biopsy, and a higher incidence of donor-specific anti-HLA antibodies. These are unique clinical endothelial cell antigenic targets, although most had known association with endothelial activation and extravasation of leukocytes.

At the very least, these anti-ECA antibodies may augment alloimmune-mediated endothelial injury, documented in microarray studies,9 especially in high-risk graft recipients. The robust result in this article is that the anti-ECAs are associated with microvascular pathology and anti-HLA DSA, but an unresolved issue is whether the anti-ECAs are necessarily causing pathologic changes, or are a result of injury due to
anti-HLA antibody in those cases in which DSA is demonstrable.

As highlighted in other studies, non-HLA antibodies are frequently present in HLA sensitized patients and this association still remains a major potential confounder. Further translational research is needed to define the specific contribution of HLA and non-HLA antibodies in the setting of antibody-mediated endothelial injury. A better understanding of the intersection of HLA- and defined non-HLA-related injury and mechanisms would represent a significant step toward specific targeted therapies.

The authors have used the opportunity provided by solid organ transplantation to study in humans the interaction between circulating antibodies and the injury they induce in allografts, as revealed by the histologic assessment. The strategies described in this study, combining in vitro and in vivo studies and serologic and histopathologic evaluation are a model for further investigation in this important area. ELISA-based antibody detection could enable routine testing for non-HLA anti-ECA, optimizing management of both presensitized and nonsensitized graft recipients.

DISCLOSURES

None.

REFERENCES


