Sequestration and Suppression of Anti-HLA Antibodies by a Failed Kidney Allograft

Vinay Nair and Peter S. Heeger

Nephrectomy of a failed kidney transplant is indicated for hematuria and local pain (usually attributed to rejection), but may be done electively to facilitate cessation of immunosuppression. Transplant nephrectomy may also limit long-term cardiovascular risk (1). Despite these potential benefits, transplant nephrectomy can be complicated by morbidities surrounding surgery, and several retrospective reports suggest that nephrectomy is associated with an increase in circulating anti-HLA antibodies (1–6). The enduring implications of the latter are significant because anti-HLA antibodies confer both an increase wait time for retransplantation and elevated risk for subsequent graft failure (7,8).

The pathogenesis of the reported increase in anti-HLA antibodies remains unclear. Tapering immunosuppression before or after nephrectomy may unleash restrained T and B cell alloreactivity directed at the remaining viable donor tissue (even after nephrectomy, residual donor ureteral tissue commonly remains), leading to new alloantibody production. Alternatively or in addition, donor-reactive memory B cells or plasma cells may be chronically producing antibodies, but while the transplanted organ is in place, these anti-HLA antibodies are absorbed by the graft. Following nephrectomy, antibody production may not change, but because removal of the graft eliminates the “anti-gen sink,” levels of circulating anti-HLA antibodies rise (9). Systematically delineating the effects of transplant nephrectomy on circulating anti-HLA antibodies and clarifying mechanisms are important because the conclusions can impact clinical decision-making. The paper by Del Bello et al. (10) in this issue of CJASN sheds new light on these issues.

In the study of Del Bello et al., the authors compared two groups of kidney transplant recipients with failed allografts: 21 patients who had their immunosuppression tapered with the graft in place and 48 who had a graft nephrectomy either for graft intolerance or as part of the center’s standard protocol. The investigators used Luminex single antigen beads, the most sensitive assay for detecting anti-HLA antibody, to quantify the kinetics, frequency, and antigen specificity of anti-HLA antibodies. They examined serum from each patient at the time of graft failure, at a time point immediately after tapering immunosuppression, and serially after nephrectomy. While the investigators detected donor specific anti-HLA antibodies (DSAs) in a low percentage of patients at the time of graft failure (12%–14%), the kinetic studies revealed the prevalence of serum DSAs increased to 35.4% after cessation of immunosuppressive therapy but prior to nephrectomy. Sixty-six percent of those who underwent nephrectomy had detectable circulating DSAs within 5 days, and this increased to 81.4% at 3 months and 84.6% at 9 months. The prevalence of serum DSAs also increased in those without nephrectomy (52.4%) but was significantly lower than those who underwent nephrectomy. There was no difference in DSAs between patients who underwent allograft nephrectomy for an indication (e.g., local pain) compared with those who had a scheduled removal of the failed graft. The predominant DSA that appeared after nephrectomy was reactive to class I HLA molecules, found in 23% in patients without nephrectomy versus 77% of patients with nephrectomy. Although the strength of the antibody as measured by mean fluorescent intensity (MFI) can only be estimated using Luminex technology, the authors did not note a significant change in the strength of the alloantibodies over the course of the study in either group. Interestingly, the emergence of anti-HLA antibodies reactive to other HLA alleles (non-DSAs) was numerically higher in patients who had a graft nephrectomy (85% versus 67%), but this did not reach statistical significance. Although no patients died, nephrectomy was associated with a 30% complication rate.

What makes this report unique is that all study subjects had their immunosuppression stopped prior to intervention, whereas other studies have either not clarified this point or stopped immunosuppression after nephrectomy (2–4). Del Bello and colleagues clearly documented an elevation in anti-HLA antibodies after stopping immunosuppression and then showed that those with a graft nephrectomy had an even further rise. Limitations of the study include the relatively small number of patients and lack of knowledge regarding the strength of the de novo DSAs. Although the authors did not report a change in MFI and included any antibody with an MFI >500, the current literature suggests that the risk of antibody-mediated rejection is directly correlated with the strength of MFI of the DSAs (11,12).

In terms of mechanisms, based on their kinetic data, the authors favor the hypothesis the transplant itself

Editorial

www.cjasn.org Vol 7 August, 2012

Copyright © 2012 by the American Society of Nephrology
is the sensitizing event, and HLA antibodies are likely present long before nephrectomy but are absorbed by the graft (9, 13). Others have indeed shown that donor-reactive anti-HLA antibodies can be eluted from nephrectomized allograft specimens (13), supporting this possibility. Because cessation of immunosuppression without nephrectomy was associated with an increase in serum DSAs in the study of Del Bello et al., it is also possible that de novo alloantibodies were induced after immunosuppression was stopped. One potential approach for further dissecting mechanisms would be to quantify donor HLA-reactive B cells (14) and plasma cells (15) in the recipient and correlate the findings with circulating antibodies. If one detected high frequencies of donor-reactive B cells/plasma cells without circulating antibodies in patients with failed transplants and this frequency did not change after nephrectomy (but circulating antibodies increased), the results would support the theory that the graft is absorbing antibodies induced by the transplant.

Regardless of specific mechanisms, the data from Del Bello et al. add to the literature by documenting that circulating anti-HLA antibody should be expected to rise after nephrectomy. How this finding should impact clinical care remains unanswerable. Retrospective analyses clouded by significant bias (1, 5, 16–18) have not yet provided clear directives regarding effects of nephrectomy (and circulating anti-HLA antibodies) on graft outcomes following retransplantation. If the patient is not a retransplant candidate and can tolerate surgery, or if a patient has a clear indication for graft removal (e.g., hematuria, graft pain, signs of chronic inflammation), the benefits of nephrectomy likely outweigh the risks. If the patient is an asymptomatic retransplant candidate, one option would be to keep the graft in place to sequester any anti-HLA antibodies, potentially avoiding the difficulties in finding a suitable donor for a sensitized individual and lowering the risk of injury to a new graft. This approach needs to be balanced against the probable cardiovascular risks and the known complications of prolonged low-dose immunosuppression. Although the study by Del Bello et al. adds evidence to a growing body of literature that graft nephrectomy leads to an elevation in circulating HLA antibody, prospective studies in which patients are randomized to nephrectomy plus retransplant or retransplant without nephrectomy, using graft survival, patient mortality, and retransplant rates as end points, are still required.

Disclosures
None.

References

Published online ahead of print. Publication date available at www.cjasn.org.

See related article, “Donor-Specific Antibodies after Ceasing Immunosuppressive Therapy, with or without an Allograft Nephrectomy,” on pages 1310–1319.