Renal allograft pathology with C4d immunostaining in patients with graft dysfunction

Sir,

I have read with great interest the article by Kulkarni *et al*., published in your valuable journal.[1] It is an important contribution to the growing literature on this subject in the kidney allograft biopsies, especially from the developing countries.[2] Although we have not systematically reviewed our experience with C4d immunostaining in the renal allograft biopsies, which we started doing routinely in 2004, it is our observation that C4d positivity is quite rare in our patients. In an earlier review of 1210 dysfunctional renal allograft biopsies in 575 transplant recipients, we found only three cases of C4d positive antibody-mediated rejection (ABMR).[3] We use all the three recommended modalities for the diagnosis of ABMR, i.e., the renal allograft biopsies, C4d, and donor-specific antibodies (DSA) by flow cytometric analysis, and it is extremely unlikely, that cases of ABMR are underrecognized in our laboratory. The extremely low ABMR prevalence in our transplant patients is understandable, given the live related donor program, zero to very low panel reactive antibodies (PRA), and the very low rate of second or third allografts in our set up.[3] The subject study also shares many of the features with our patients, but the rate of C4d positivity is markedly high, compared with our cohort. The studies of this sort definitely contribute new dimensions to the growing recognition of ABMR.[2,4] But a note of caution is in order. One needs to be very scrupulous, diligent, and meticulous in presenting the findings on such provocative topics. I would like to point out a few major deficiencies in the paper which need to be clarified by the authors.

1. The major point is the lack of information on the clinical significance of the 21 cases with C4d positivity; whether these represent confirmed ABMR, suspicious for ABMR, or false positive C4d results? Moreover, it is not clear how these results influenced the management of these patients. Lack of significant difference in serum creatinine in the two groups at the time of biopsy and last follow-up also casts doubt on the accuracy of these results. It is worth repeating here the criteria of ABMR on renal allograft biopsies according to the Banff 2003 classification.[2] These include morphological evidence of tissue injury, immunopathological evidence in the form of C4d positivity, and documentation of donor-specific antibody (DSA). According to this schema, for a definitive diagnosis of ABMR "Until a consistent correlation of C4d peritubular capillary staining and anti-donor antibody can be proven; however, all three criteria will be required for definitive diagnosis." Since one criterion required for definitive diagnosis of ABMR (i.e., DSA) was not done in the subject study, I wonder how the diagnosis of one case of ABMR was made?
2. The second major point is the lack of information on the immunological profile of the recipients and the donors. There are no data on HLA matching, PRA levels, pre-transplant cross match, etc. Similarly, there is also no information on the immunosuppressive regimens used in the center.

There are also many minor points in the study, such as the following:

There is no information on the results of renal panel immunoglobulins and complement, which was carried out on all biopsies according to the authors. The current

standard in C4d testing is with immunoflourescence (IF) test on fresh frozen tissue. The immunohistochemical method used by the authors is not yet sufficiently standardized and needs to be extremely carefully interpreted.[2,5,6] The number of C4d positive cases in acute rejection is given as 11 in abstract and 10 in the accompanying table. A total of 67 biopsies from 56 patients including 2 nephrectomy specimens were studied. However, the number of males and females given in study (61, 6) is 67, instead of 56, which is wrong. In Table 1, the total number of cases in the first column is 65 and not 67.

I hope the clarification of the above points will help in better understanding the increasingly recognized problem of ABMR as a significant cause of graft dysfunction throughout the world.

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