C4d staining in allograft biopsies

Sir,

Thank you for the comments on our article. The authors of the letter seem to have considered our C4d positivity synonymous with ABMR. The literature on C4d is still evolving and reflects controversies in terms of technique, biopsy policies, staining pattern, and utility.[1]

1. The article contributes to expand the existing literature about C4d immunostaining with morphology of allograft biopsies in the setting of graft dysfunction.[2] As mentioned in our article, the absence of DSA was a drawback in recognizing the ABMR cases. The pattern of C4d staining in acute rejection is "focal" rather than "diffuse." The significance of such positivity has been mentioned as "controversial" in the absence of the sufficient published literature as mentioned in the discussion of our article.[2] To quote Banff 2007 publication "the prognosis of focal positive cases is intermediate between the diffuse and negative ones. Significance of these cases is not well established in the absence of consensus criteria and detection of antibody with the long-term outcome will only resolve the issue."[3,4] Banff 2003 mentions that the presence of C4d with changes of chronicity should be taken as chronic humoral rejection and helps to distinguish immune and nonimmune type of chronicity.[5] So the presence of diffuse C4d staining with features of IFTA was suggestive of a humoral component. The percentage positivity in cases of CAN is comparable to that mentioned in the literature; one of these studies is an Indian study that was the only published study from the country at the time of our publication.[6,7]
2. Ranjan *et al.* mentioned that C4d positivity has no correlation with follow up serum creatinine levels. It has been mentioned that C4d positive grafts have lower survival as compared to negative ones; however, that does not correlate with serum creatinine levels.[7] Volker *et al.* discussed the differences in management strategies between C4d positive cases with normal and increased creatinine.[8] Hence, low serum creatinine levels in our study need not be used as an indicator to suspect the accuracy of C4d results.
3. The standard immunosuppression protocol at our centre includes cyclosporine/tacrolimus with MMF and steroids. The study was retrospective and C4d results were not available at the time of treatment. The clinical details including HLA match and crossmatch were not given as it was beyond the scope of the paper. The prospective data including clinical details, treatment, and management issues will be discussed in detail in our forthcoming article.
4. Immunohistochemistry was validated by Troxell *et al.* who found it "a reliable tool to indicate the presence of C4d and the results of IF and IHC are very much comparable."[6] To quote the updates of Banff 2007 classification "the C4d scoring is based on percentage of stained tissue on IF/IHC ……." It does not mention IF alone as current standard of care testing. Hence, the argument that the technique is not standardized is not valid.[4] We also want to bring attention to a recent article published by Haas (2011) about C4d negative AMR wherein morphologically proven AHR is negative by IF also and still deserves to be treated as AHR.[9]
5. We accept the mistakes in numbers in the abstract and main text. However, it has not influenced the statistical analysis and the results.

Finally we are happy to know that the incidence of ABMR is low in the author's center. But we have about 11% cases designated as ABMR in our center (unpublished data). We have seen similar percentages from other centers in India as per the published literature.[7,10]

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