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The Expanding Spectrum of Antibody-Mediated Rejection: Should we Include Cases Where No Anti-HLA Donor-Specific Antibody is Detected?

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Antibody-mediated rejection (ABMR) in a renal transplant biopsy is most often diagnosed by a combination of microvascular injury (MVI), C4d deposition and presence of circulating DSA. MVI designates the leucocyte margination reaction in glomeruli (glomerulitis, Banff score g) and in peritubular capillaries (peritubular capillaritis, Banff score ptc). MVI (sum of Banff scores g+ptc) is a morphological feature rather than a diagnosis, and is not specific for ABMR. It is universally acknowledged that peritubular capillaritis can be seen in the context of T-cell mediated rejection (TCMR) and borderline for TCMR (BL). There is evidence that glomerulitis can also be noted in TCMR, although this is not formally acknowledged in the Banff Classification. Glomerular and peritubular capillary inflammation have been noted in other processes as well (Figure 1). The exact extent and degree of glomerular and peritubular capillary inflammation observed in these conditions has not yet been conclusively defined. Therefore, in individual biopsies it is difficult to determine how much of MVI represents ABMR, TCMR, or other processes. The Banff classification acknowledges this, and has introduced MVI thresholds depending on context. In the presence of concurrent features of TCMR/BL, ptc alone is insufficient to establish a diagnosis of ABMR and g must also be present; in the absence of C4d, MVI must be ≥2. There is uncertainty about what to do when MVI is present in the biopsy, but no DSA is detectable. The Banff 2017 working schema accepted C4d positivity as a surrogate for DSA in biopsies with MVI, based on a poll of 63 experts [1, 2]. In this issue, Senev et al. have tested the validity of this proposition [3]. They studied biopsies with histological features of ABMR as defined in Banff 2015/2017(ABMRh)(n = 208), subdivided into DSA+ ABMRh and DSA-ABMRh. Most of the biopsies (96.6%) had MVI, 35% had a v lesion (intimal arteritis),
53.4% had TCMR/BL. The study illustrates the numerical importance of DSA-ABMR<sub>h</sub>, which represented 123/208 (59%) of total cases of ABMR<sub>h</sub>. Compared to DSA+ ABMR<sub>h</sub>, DSA- ABMR<sub>h</sub> had more transient histology (ABMR<sub>h</sub> in next biopsy 26.6% versus 51.9%; cg in next biopsy 3.7% versus 11.4%) and less C4d staining (38.2% versus 55.3%). There was also less graft loss (15.4% versus 32.9%) irrespective of whether or not DSA- ABMR<sub>h</sub> cases were C4d-positive. Importantly, the observations essentially reflect the natural history of disease since only 6.1% of the patients received specific ABMR therapy.

These results call into question the use of C4d positivity as a proxy for circulating DSA in ABMR<sub>h</sub>. However, they differ from the multicenter DeKAF (Deterioration of Kidney Allograft Function) study, in which C4d positivity was a determinant of outcome in late graft dysfunction, even in the absence of detectable DSA [4]. This may reflect a study population of mostly sensitized patients (pre-transplant DSA+ in 69/85 DSA+ ABMR<sub>h</sub> cases), with early onset disease (median time from transplantation to index ABMR<sub>h</sub> biopsy = 78 days), with low histologic chronicity (mean interstitial fibrosis score = 0.41, 9/208 index biopsies with cg score >0). Thus, the conclusions of this study may be primarily applicable to early biopsies with ABMR<sub>h</sub> as opposed to late refractory ABMR. An important observation in this regard is that many DSA- ABMR<sub>h</sub> biopsies satisfied Banff criteria for TCMR (38%) or borderline change (18%). Although absence of TCMR was not a determinant of graft failure, other groups have highlighted the need to carefully look for changes of concomitant TCMR in biopsies that fulfil criteria for ABMR.

A notable aspect of Senev et al.’s study is that the positive predictive value of C4d staining for the presence of DSA (MFI > 500) in the context of ABMR<sub>h</sub> is only 50%. Earlier studies indicating a high specificity of C4d for DSA were conducted in non-
selected biopsies and without the use of sensitive Luminex assays and single antigen bead testing. Depending on the threshold for positivity used, 23.6-38.2% of DSA-ABMR\(_h\) biopsies were C4d positive, with no worse outcome than C4d-negative counterparts; the explanation for C4d positivity in this context remains unknown.

As with all single center investigations that include histological assessment of MVI, C4d staining and DSA testing, there are limitations to any definite conclusions that can be drawn, relating to issues of interobserver and interlaboratory variability. Of note, the C4d staining procedure was based on immunohistochemistry (not immunofluorescence) performed on frozen sections using a grading system that is not identical to the Banff schema. Variations in local transplant policies and patient characteristics also introduce potential bias. These limitations illustrate the need for multicenter studies and test standardization within the Banff community.

The work of Senev et al. would benefit from further testing for non-HLA DSA and for ABMR-related gene expression. Molecular studies have potential for clarifying the true nature of ABMR\(_h\) biopsies, but their cost, technical complexity and unknown interlaboratory reproducibility are hurdles to widespread implementation. It is also important to note that we have not yet defined the molecular signature of membranoproliferative glomerulonephritis and thrombotic microangiopathy, which enter in the differential diagnosis and have tissue injury pathways that overlap ABMR [5].

In conclusion, Senev et al. provide strong evidence that patients with DSA- ABMR\(_h\) within the 1st year post-transplant, with no specific ABMR therapy, are likely to have outcomes better than patients with DSA+ ABMR\(_h\), and similar to patients without ABMR\(_h\), including those with TCMR. From a practical perspective, biopsies with MVI
without C4d staining or DSA should be approached in a systematic manner without attempting to force them into the ABMR category (Figure 1), since the differential diagnosis of MVI is rather wide. Outcome and response to therapy in individual cases may be better predicted using probabilistic models that incorporate a combination of clinical, serological and pathologic features.

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References

