



# C4d Puzzle in ABO-incompatible kidney transplantation

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The pathological diagnosis of antibody-mediated rejection (ABMR) in allograft kidneys has posed a significant challenge for renal pathologists. According to the latest version of the Banff classification, the diagnosis of ABMR (active and chronic active) requires three categories of evidence: histologic evidence of acute tissue injury, evidence of antibody interaction with endothelial cells, and serologic evidence (presence of circulating donor-specific antibodies [DSA]) [1]. Initially, evidence of antibody interaction referred to linear C4d staining in peritubular capillaries or medullary vasa recta. Based on subsequent studies, it has been revealed that microvascular inflammation (MVI), specifically glomerulitis and peritubular capillaritis, can substitute for C4d [2,3]. This discovery has led to the emergence of C4d-negative ABMR [4].

Although ABO-incompatible (ABOi) kidney transplantation is a significant advancement against the shortage of donor kidneys, from the perspective of diagnosing ABMR, ABOi kidney transplantation presents unique challenges. In a previous study, C4d positivity in peritubular capillaries was observed in 94% (diffuse in 66%) of the protocol biopsies without connection with ABMR [5]. Therefore, C4d status cannot be used as reliable evidence of antibody-mediated

tissue injury. Moreover, the current Banff classification does not specifically address ABOi transplantation, and the molecular diagnostics suggested by the Banff meeting [6] are not yet widely available in most transplantation centers.

In this issue of *Kidney Research and Clinical Practice*, Cho et al. [7] retrospectively analyzed for-cause allograft renal biopsies. The researchers found that C4d positivity was associated with more pronounced glomerulitis, peritubular capillaritis, and MVI. Among cases with a moderate or higher degree of MVI, the group with positive DSA, and the group with negative DSA but positive C4d showed similar estimated glomerular filtration rates and graft survival. Based on these results, it can be inferred that if there is a moderate or higher degree of MVI and C4d is positive, even if DSA is negative, it is reasonable to consider it as ABMR and initiate appropriate treatment. This is the key message of this article.

Indeed, the limitations of this study are evident. Firstly, since it was based on a single center, the sample size included in the study was limited. As a result, it was not possible to draw conclusions regarding the group with only MVI in the absence of both DSA and C4d, which is a clinically significant question. It is also important to consider that the study focused solely on for-cause biopsies as the study population. This aspect should be taken into account when interpreting the results. Despite these limitations, this study has diligently performed its role in fitting a small

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puzzle piece necessary to solve the challenging question of diagnosing ABMR in ABOi kidney transplantation. There are still numerous puzzle pieces that need to be filled. For instance, how should we approach ABOi transplant patients who exhibit acute tubular injury and C4d positivity but lack MVI [8]? We still need a clear conclusion on this matter. I hope for a future where research similar to this paper is conducted more actively, providing clear evidence for diagnosing ABMR in ABOi kidney transplantation patients and enabling appropriate treatment.

### Conflicts of interest

The author is an Editorial Board member of *Kidney Research and Clinical Practice*, the official journal of the Korean Society of Nephrology, serving as an Associate Editor. There are no other conflicts of interest to be declared.

### Data sharing statement

The data presented in this study are available on request from the corresponding author.

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