LETTER TO THE EDITORS

Ultrastructural changes of the glomerular basement membrane. . . unmasked by C4d staining

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Dear Editors,

We were very pleased to have read the Epub ahead of print of a Transplant International's article entitled "glomerular C4d deposits can mark structural capillary wall remodeling in thrombotic microangiopathy and transplant glomerulopathy: C4d beyond active antibody-mediated injury: a retrospective study" (Fig. 1). Until now, no studies have reported on the importance of using glomerular C4d staining in the evaluation of ultrastructural changes of the glomerular basement membrane.

Dr. Gasim and colleagues from Chapel Hill describe very nicely that the presence of pseudolinear C4d positivity along the glomerular basement membrane (GBM) can be associated with ultrastructural changes of the capillary walls. Indeed, we too use the presence of pseudolinear GBM-C4d immunohistochemical staining (IHC), in particular if seen in isolation not accompanied by C4d staining along peritubular capillaries (PTCs), as an indication for underlying structural GBM abnormalities and detailed further electron microscopic analyses: isolated GBM-C4d, an alarm signal for trouble along glomerular capillary walls! As is described in Dr. Gasim's article, in those renal biopsies in which we find pseudolinear positivity of C4d along the GBM by IHC, even if it is scant, we frequently detect in corresponding electron microscopic studies underlying alterations of the GBM (Fig. 1a and b). Since in such cases significant hematuria and proteinuria may be absent, the detection of pseudolinear GBM-C4d can be the only sign marking the necessity for further electron microscopic analyses that might be skipped otherwise. The flowchart presented in Fig. 4 of Dr. Gasim's article very nicely brings matters to the point. It highlights that pseudolinear C4d along the GBM, especially in the absence of corresponding staining along ptcs (and often seen in the absence of detectable circulating donor-specific antibodies), can be attributed to structural remodeling of glomerular capillary walls rather than active/acute antibody-mediated rejection. Thus, we fully concur with the "Chapel Hill observations": glomerular

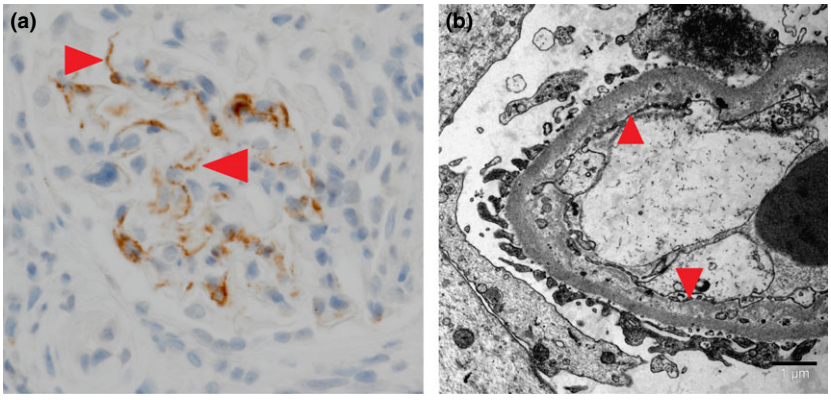

Figure 1 Immunohistochemical staining for C4d on a renal transplant biopsy with possible double contours of the glomerular basement membrane (GBM) on PAS staining shows linear, slight granular positivity along parts of the GBM, arrow heads (a, magnification 63×). Electron microscopy shows structural changes of the GBM, varying from increase of the lamina rara interna to formation of double contours of the GBM with interposition of the endothelium, arrow heads (b, magnification 11 000×). Therefore, this case has a Banff lesion score of Cg1a.

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C4d deposits can mark structural capillary wall remodeling: C4d beyond active antibody-mediated injury. We hope that these findings stimulate future detailed studies to further our understanding of C4d in glomerular remodeling in native and transplant kidneys.

REFERENCE

1. Gasim AH, Chua JS, Wolterbeek R, et al. Glomerular C4d deposits can mark structural capillary wall remodelling in thrombotic microangiopathy and transplant glomerulopathy: C4d beyond active antibody-mediated injury: a retrospective study. *Transpl Int.* 2017; **30**: 519.

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