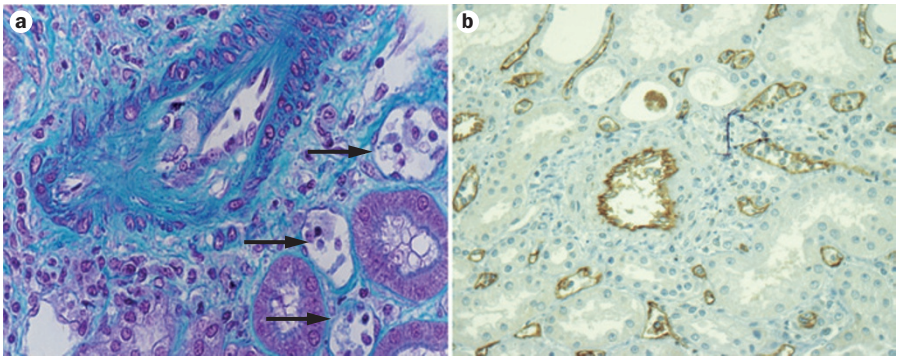
Nature Reviews Nephrology **9**, 63 (2013); published online 11 December 2012; doi:10.1038/nrneph.2012.266

TRANSPLANTATION

Antibody-mediated vascular rejection of transplanted kidneys

Humoral mechanisms are increasingly recognized as a cause of graft loss in recipients of HLA-incompatible kidney transplants; however, vascular rejection of kidney allografts has traditionally been thought of as a process mediated by T cells. A new study published in *The Lancet* now shows that vascular rejection can in fact be associated with anti-HLA antibodies. The researchers believe that recognition of this distinct phenotype could lead to the development of new treatment strategies and to the rescue of many failing kidney allografts.



Histologic and immunohistochemical pattern of lesions observed in antibody-mediated vascular rejection. **a** | Antibody-mediated vascular rejection was characterized by the coexistence of endarteritis together with glomerular and peritubular capillary inflammation (arrows). **b** | C4d staining shows diffuse intimal staining for C4d. Peritubular capillaries stain diffusely (magnification ×375). Image courtesy of G. S. Hill Department of Pathology, Georges Pompidou European Hospital, Paris, France.

Vascular allograft rejection is a severe form of acute rejection that is associated with a high risk of graft loss. It is characterized by infiltration of immune cells beneath the endothelium or by the presence of arteritis, and has previously been reported to be a T-cell-mediated disorder that does not always respond to T-cell-targeted therapies. More recent findings have, however, suggested that vascular rejection can be associated with alloantibodies. "These reports challenged the notion of a unique T-cell-mediated rejection process in vascular rejection," explains researcher Alexandre Loupy. "We therefore aimed to redefine rejection patterns by addressing their distinct clinical, histological, and immunological phenotypes and prognoses. In particular, we postulated that vascular rejection could be associated with donor-specific antibodies, which might have important clinical implications for graft survival."

The researchers retrospectively examined biospy samples from patients who had received a kidney transplant at Necker Hospital and Saint Louis Hospital, Paris, France between 1998 and 2008. Of 2,079 transplant recipients, 302 were identified as having acute biopsy-proven rejection. In addition to extensive graft phenotyping, the researchers tested all patients for donor-specific antibodies from stored sera. "A critical point was that we wanted to get rid of any preconceived conceptions of rejection diagnoses. We therefore used a mathematical assessment of rejection patterns, which included all information regarding graft lesions, C4d status in allograft biopsy samples, and donor-specific anti-HLA antibody status," says Loupy.

The researchers retrospectively identified four subtypes of acute rejection: T-cell-mediated vascular rejection (26 patients [9%]), antibody-mediated vascular rejection (64 patients [21%]), T-cell-mediated rejection without vasculitis (139 patients [46%]), and antibody-mediated rejection without vasculitis (73 patients [24%]). Antibody-mediated vascular rejection had the worst prognosis of the four subtypes. Compared to patients with T-cell-mediated rejection without vasculitis, patients with antibody-mediated vascular rejection had a 9.07-fold increased risk of graft loss. By contrast, the risk of graft loss in patients with antibody-mediated rejection without vasculitis was increased 2.93-fold and there was no increase in the risk of graft loss in patients with T-cell-mediated vascular rejection. "We demonstrated that 71% of cases of vascular rejection, which were mostly graded as v1 and v2 arteritis by the Banff schema, were associated with donor-specific antibodies," explains Loupy. "More importantly, we showed that 45% of vascular rejections with donor-specific antibodies were misclassified by the conventional assessment as being T-cell-mediated rejection." These results were validated in an independent cohort of kidney allograft recipients from Foch Hospital, Suresnes, France.

Secondary analyses showed that antibody-directed strategies were associated with improved outcome in patients with antibody-mediated vascular rejection. Of note, 42 patients with antibody-mediated vascular rejection who had been treated with a T-cell-targeted strategy had a higher risk of graft loss than those who had received an antibody-targeted strategy.In an accompanying commentary, Brian Nankivell recommends that a diagnosis of acute vascular rejection should now prompt testing for donor-specific antibodies and careful histological examination for markers of antibody deposition.

The researchers plan to continue their work to improve understanding of the deleterious effect of anti-HLA antibodies on the vasculature. They also hope to extend their findings to the study of other transplanted organs, such as the heart, pancreas and lungs, in which the deleterious effects of antibody-mediated rejection are increasingly acknowledged.

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Original article Lefaucheur, C. *et al*. Antibody-mediated vascular rejection of kidney allografts: a population-based study. *Lancet* doi:10.1016/S0140-6736(12)61265-3

Further reading Nankivell, B. J. Antibody-mediated vascular rejection: relation to causation. *Lancet* doi:10.1016/S0140-6736(12)61577-3