

SIGNIFICANCE STATEMENT

Complement-activating anti-HLA donor-specific antibodies (DSAs) are associated with an increased risk of kidney allograft loss, but their specific effects on kidney allograft injury are unknown. This study uses gene expression analysis as well as histopathology and immunostaining to characterize circulating complement-activating anti-HLA DSA-mediated rejection in kidney allografts and in *in vitro* human cell cultures. The specific phenotype defined, when applied in a stratified analysis, predicted the response of antirejection treatment with eculizumab, the anti-C5 mAb; benefit was restricted to patients with pretransplant complement-activating anti-HLA DSAs. Complement-activating anti-HLA DSAs may help to define the population of kidney recipients for whom complement-targeting intervention will provide the greatest benefit.