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The genetic fingerprint of susceptibility for transplant associated thrombotic micro-angiopathy

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Transplant-associated Thrombotic Micro-Angiopathy (TMA) occurs frequently after Hematopoietic Stem Cell Transplantation (HSCT) and can lead to significant morbidity and mortality. There are no data addressing individual susceptibility to transplant-associated TMA. We performed a hypothesis driven analysis of 17 candidate genes known to play a role in complement activation as part of a prospective study of TMA in HSCT recipients. We examined the functional significance of gene variants using gene expression profiling. Among 77 subjects undergoing genetic testing, 34 had TMA. Sixty five percent of patients with TMA had genetic variants in at least one gene, as compared to 9% of patients without TMA ($p<0.0001$). Gene variants were increased in subjects with TMA of all races, but non-Caucasians had more variants than Caucasians (2.5 (0-7) vs. 0 (0-2), $p<0.0001$). Variants in ≥3 genes were identified only in non-Caucasians with TMA and were associated with high mortality (71%). RNA seq. analysis of pre-transplant samples showed upregulation of multiple complement pathways in subjects with TMA who had gene variants, including variants predicted as possibly benign by computer algorithm, as compared to those without TMA and without gene variants. Our data reveal important differences in genetic susceptibility to HSCT-associated TMA based on recipient genotype. These data will allow prospective risk assessment and intervention to prevent TMA in highly susceptible transplant recipients. Our findings may explain, at least in part, racial disparities previously reported in transplant recipients and may guide treatment strategies to improve outcomes.

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Calcific uremic arteriolopathy

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Calcific Uremic Arteriolopathy (CUA) or Calciphylaxis is a rare and frequently fatal, necrotizing skin condition, encountered mostly in patients with ESRD on dialysis. The pathologic hallmark of calciphylaxis is medial calcification, intimal fibroplasia and luminal thrombosis of cutaneous arterioles, leading to ischemic ulceration. Clinical manifestations may include nodules or plaques that often progress to ulceration, frequently complicated by sepsis and death. The term CUA has recently been proposed over calciphylaxis to more accurately reflect the patho-physiology of the disorder, however one must realize that this entity has also been reported, albeit rarely, in non-uremic patients, including those with primary hyperparathyroidism, alcoholic liver disease, malignancy and certain connective tissue disorders. The estimated prevalence of CUA in patients with ESRD is about 4%, with an annual incidence of about 1/1000 cases. The six month mortality may reach up to 80% and a multifaceted approach to treatment is warranted, with emphasis to wound and pain management, optimization of mineral and bone parameters and possible use of sodium thiosulfate.

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