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Editorials

Original Articles

Acute Kidney Injury

Chronic Kidney Disease

Epidemiology and Outcomes

Original Articles (Continued)

ESRD and Chronic Dialysis

Geriatric Nephrology

Health Services Research

Nephrolithiasis

Renal Transplantation

Renal Physiology

Role of the Medical Director

Commentary

Public Policy Series

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On the Cover

What's the diagnosis? A 29-year-old man with ESRD underwent a deceased donor kidney transplant, which was complicated by delayed graft function. Despite excellent urine output, serum creatinine remained elevated and hemodialysis was initiated. Kidney biopsy was obtained on day 5 to assess the cause of delayed graft function. The glomeruli showed multiple intracapillary fibrin thrombi, mesangiolysis and numerous red blood cell fragments within the injured subendothelal and mesangial areas of the glomerular tuft. Fibrin stain on IF was strongly positive and electronmicroscopy studies showed intracapillary fibrin tactoids. The biopsy diagnosis was thrombotic microangiopathy (TMA). Thrombotic microangiopathy developing following kidney transplantation can be classified as either recurrent or de novo. Recurrent TMA is more common in adults than children following kidney transplantation. Recurrence is more likely to develop when the original cause was complement-associated atypical hemolytic uremic syndrome (HUS) as compared with infection-related TMA. In general risk of recurrent TMA depends on the mutation—more common with mutations in circulating factors such as complement factors I or H. Other factors associated with increased risk for recurrence in the allograft include older age, living related donor kidneys, calcineurin inhibitors, and short duration between disease onset and ESRD or transplantation. De novo TMA among kidney transplant recipients may be due to any of the causes that occur in the general population. However, immunosuppressive medications (calcineurin inhibitors, mTOR inhibitors), anti-platelet agents (ticlopidine, clopidogrel) and valacyclovir are notable causes in this group. Antibody-mediated rejection, which was thought to be the cause in the patient presented, is another etiology of TMA. Finally, infection with HIV, parvovirus B19, and cytomegalovirus have also been associated with TMA following kidney transplantation. Many but not all patients present with microangiopathic hemolytic anemia, thrombocytopenia, and schistocytes on peripheral smear. Urine studies reveal hematuria and low-grade proteinuria. Some may have TMA limited to the allograft without systemic abnormalities. Treatment is directed at the cause. Recurrent TMA from mutation in one the complement factors may benefit from eculizumab. Patients with de novo disease from either calcineurin or mTOR inhibitors should have the drug withdrawn and undergo plasmapheresis. Intravenous immunoglobulin and rituximab have also been utilized. Prognosis is better for de novo as compared with recurrent TMA; however, both suffer from allograft loss. (*Images and text provided by Mark A. Perazella, MD, and Gilbert Moeckel, MD, Yale University School of Medicine, New Haven, Connecticut*)