AJKD

Kidney Biopsy Teaching Case

Myoglobin Cast Nephropathy in a Kidney Transplant Patient With Normal Creatine Kinase

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Delayed graft function in kidney transplant recipients is a known complication associated with increased risk of acute rejection and reduced transplant survival after 1 year. There are multiple risk factors, including prolonged cold ischemia time, donor age, and cause of donor's death. Major causes of delayed graft function are acute kidney injury in the donor, often from prolonged terminal ischemia, reflected by acute tubular injury in the recipient. However, the differential diagnosis of delayed graft function includes acute rejection, recurrence of the primary glomerular diseases, and other less commonly encountered conditions. A transplant kidney biopsy usually is required to elucidate the correct cause and initiate the right treatment, which is crucial for transplant survival. We report a case of a transplant recipient who developed delayed graft function due to an uncommon cause. After correct diagnosis, the patient's transplant function improved.
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INDEX WORDS: Myoglobin cast nephropathy; kidney transplant; delayed graft function; creatine phosphokinase; creatine kinase; rhabdomyolysis; renal biopsy; electron-dense casts; acute tubular injury; kidney donation after cardiac death.

INTRODUCTION

Delayed graft function (DGF) is defined as failure to achieve immediate kidney transplant function after transplantation and the need for hemodialysis. Risk factors include increased donor age, donation after cardiac death, hemodynamic disturbances during the surgery, preexisting glomerular sclerosis or interstitial fibrosis of the transplant, and prolonged cold ischemia time.[1] Advanced donor age and prolonged cold ischemia time are associated with the greatest incidence of DGF. Kidney transplant recipients who experience DGF have prolonged hospital stays, greater risk for an episode of acute rejection, reduced transplant function, and reduced transplant survival after 1 year.[1,2]

There are multiple causes of DGF. Common causes include effective circulatory volume depletion secondary to hemodynamic instability, acute tubular injury/necrosis due to prolonged ischemia time, surgical complications, acute rejection, thrombotic microangiopathy, and calcineurin-inhibitor toxicity. Recurrence of the primary glomerulopathy, such as focal segmental glomerulosclerosis, also is a possible cause of DGF. Acute kidney injury (AKI) in the donor related to toxins, ischemia, or other cause also may contribute. A transplant kidney biopsy generally is required to identify the underlying pathologic findings, which are needed for correct diagnosis and treatment.

We describe a patient with an unusual pathologic diagnosis leading to further clinical investigation to identify the cause of DGF.

CASE REPORT

Clinical History and Initial Laboratory Data

A 42-year-old African American woman with chronic kidney failure secondary to hypertension underwent a 6-antigen–mismatched deceased donor kidney transplantation. Panel reactive antibody at the time of transplantation was 48%. The donor was a 26-year-old white man who died after cardiac death with a warm ischemia time of 21 minutes. Cold ischemia time was 12 hours 25 minutes. Urinalysis of the donor revealed moderate blood on dipstick with 2 red blood cells and 2 white blood cells per high-power field, without casts noted. No preimplantation or postreperfusion donor biopsy was performed. The recipient maintained hemodynamic stability throughout the perioperative period. She received induction with alemtuzumab and maintenance immunosuppression with prednisone, mycophenolate mofetil, and tacrolimus. Tacrolimus level was 2-3 ng/mL. By postoperative day 9, serum creatinine level had increased progressively to 15 mg/dL (corresponding to an estimated glomerular filtration rate [eGFR] of 3 mL/min/1.73 m^2 by the isotope-dilution mass spectrometry–traceable 4-variable MDRD [Modification of Diet in Renal Disease] Study equation), and potassium level was 4.7 mEq/L. Urinalysis revealed no casts, and urine protein-creatinine ratio was 0.45 mg/g. Transplant kidney ultrasonography revealed normal blood flow and no evidence of perinephric fluid collection or hydronephrosis. Donor-specific antibody was not detected. She required

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hemodialysis due to uremia and volume overload. A kidney transplant biopsy was performed on postoperative day 10.

Kidney Biopsy

Thirty glomeruli were present, none of which was globally sclerosed. Glomeruli were unremarkable, without proliferation, necrosis, or thrombi. Peritubular capillaries, arterioles, and large arteries were unremarkable without evidence of microvascular inflammation or endothelialitis. There was loose, early interstitial fibrosis in <5% of the specimen, with no tubular atrophy. There was no tubulitis or interstitial inflammation and no viral cytopathic changes. There was widespread diffuse acute tubular injury characterized by epithelial flattening, anisonucleosis, loss of brush border, and sloughing involving 50% to 60% of tubular profiles (Fig 1A). About 10% to 20% of tubules contained granular and globular variably reddish-pigmented casts, which stained strongly for myoglobin by immunohistochemistry (Fig 1B). In immunofluorescence and electron microscopy studies, no deposits were detected and there was no sign of C4d in the peritubular capillaries and no significant foot-process effacement. Electron microscopy showed several electron-dense casts consistent with myoglobin within tubular lumens (Fig 1C).

Diagnosis

Myoglobin cast nephropathy.

Clinical Follow-up

Given the finding on the transplant biopsy, serum creatine kinase (CK) was obtained from both the donor's and recipient's serum. The recipient's CK level was 98 U/L. However, the donor CK level was 1,338 U/L, tested after the current kidney biopsy on a stored serum from the day of death and 4 days after the donor presented with multiple traumatic injuries from a motor vehicle accident. Peak CK level in the donor is unknown. The donor's terminal creatinine level was 0.73 mg/dL. Thus, clinical findings in the donor indicated the biopsy specimen was consistent with donor-origin rhabdomyolysis, causing the myoglobin cast nephropathy.

The recipient of the contralateral donor kidney also experienced slow transplant function, with creatinine level increase from 4.8 mg/dL (eGFR, 13 mL/min/1.73 m^2) at transplantation to a peak of 8.6 mg/dL (eGFR, 6 mL/min/1.73 m^2) on postoperative day 6. Urinalysis showed no casts. No dialysis or biopsy was performed, and creatinine level decreased to 1.9 mg/dL (eGFR, 35 mL/min/1.73 m^2) on postoperative day 16.

Symptomatic and supportive care included intravenous furosemide for volume management and treatment of electrolyte abnormalities. Medications that might cause rhabdomyolysis were avoided. Aggressive fluid administration was limited by volume overload. Serum electrolyte and tacrolimus levels were monitored closely. At 2 months' follow-up, creatinine level had decreased to 1.27 mg/dL (eGFR > 60 mL/min/1.73 m^2) without further hemodialysis (Fig 2).

DISCUSSION

DGF is a common complication following kidney transplantation, especially when kidneys are from an after-cardiac-death donor. Possible contributors to DGF are listed in Table 1, highlighting both donor and recipient factors. The major contributing factors to our patient's DGF included donation after cardiac death and donor-related acute tubular injury from myoglobin cast nephropathy. The recipient had a normal CK level, whereas the donor had an elevated CK level. Thus, the myoglobin cast nephropathy that occurred in the transplant was due to rhabdomyolysis that developed in the donor caused by multiple traumatic injuries, and this myoglobin cast nephropathy likely was an important contributor to the DGF. Other causes of pigmented casts in the setting of AKI include hemoglobin and bile.[3] Tacrolimus toxicity seemed less likely in our patient because levels were low,

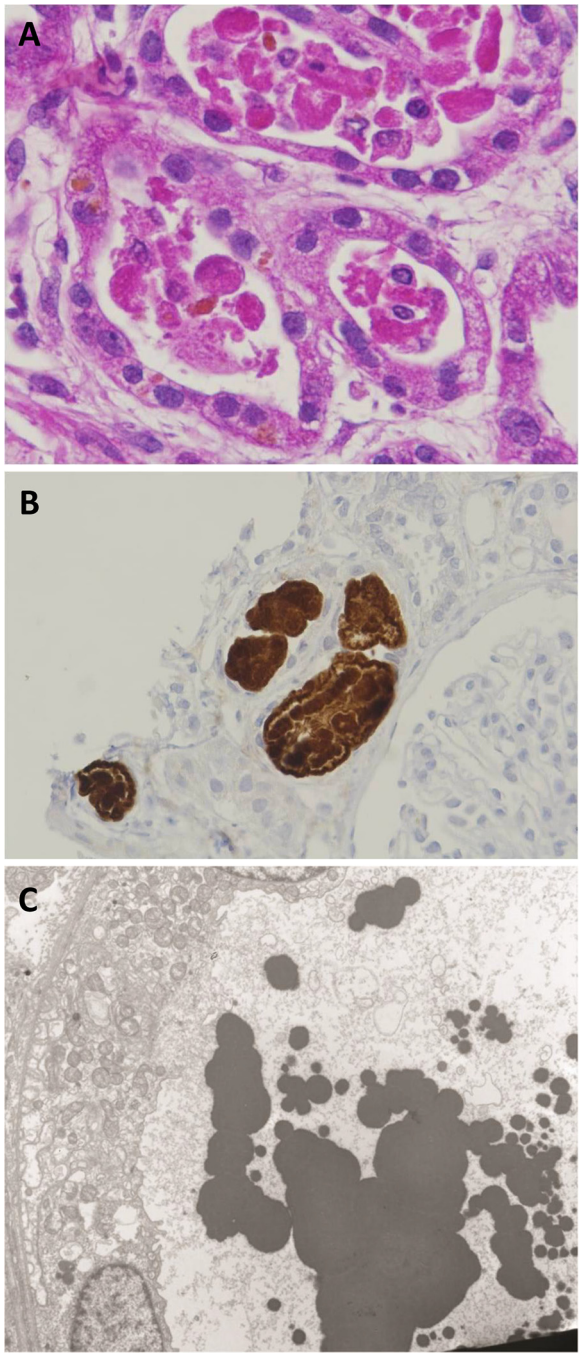

Figure 1. Transplant biopsy specimen. (A) There was widespread diffuse acute tubular injury characterized by epithelial flattening, anisonucleosis, loss of brush border, and sloughing involving about 50% to 60% of tubular profiles (hematoxylin and eosin stain; original magnification, ×100). (B) These granular and globular variably reddish-pigmented intratubular casts stained strongly for myoglobin by immunohistochemistry (original magnification, ×100). (C) Transmission electron microscopy shows several electron-dense casts, consistent with myoglobin, within tubular lumens (original magnification, ×5,000).