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Prolonged Delayed Renal Graft Function Secondary to Venous Hypertension

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Abstract: The case of a 39-year-old highly sensitized woman who underwent second renal transplantation after being on warfarin because of a history of frequent thromboses of her left femoral arteriovenous graft (AVG) is reported here. The patient received a flow cytometric positive crossmatch kidney transplant from a deceased donor. Her posttransplant course was complicated by prolonged delayed graft function (DGF) lasting for 9 months. Antibody-mediated rejection occurred in the immediate postoperative period. This resolved after treatment, and resolution was confirmed by repeat biopsy. Despite this, she had persistent DGF and remained dialysis dependent. A computed tomography scan due to the development of perinephric hematoma after posttransplant biopsy demonstrated venous collateralization around the allograft. At 7 months posttransplant, a venogram during declotting of AVG revealed chronic thrombus in the inferior vena cava (IVC) above the level of native renal veins with a venous gradient of 26 mmHg. After declotting of the graft, iliac venoplasty, and subsequent IVC stent, her renal function continues to improve with a most recent creatinine of 1.4 mg/dL at 36 months posttransplant. Venous hypertension secondary to IVC thrombosis in presence of patent femoral AVG should be considered as a rare cause of prolonged DGF.

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Delayed graft function (DGF) is commonly described as a failure of the kidney allograft to function immediately in the first 7 days of transplantation with a need for dialysis.[1,2] The frequency of DGF is reported to be 1% to 7% in living-donor kidney transplantation and 20% to 60% in deceased-donor kidney transplantation.[3] Typically, DGF does not last for more than few weeks. The longest reported duration of DGF in the current literature is 5 months, in which the patient spontaneously improved after 148 days.[3]

The vascular complications after kidney transplantation are relatively uncommon but can have a significant impact on morbidity and mortality. Typically, renal vein or artery thrombosis results in acute graft loss.[4] Delayed presentation of chronic renal vein thrombosis or stenosis is possible because of alternate venous drainage. To our knowledge, only 3 case reports have been published describing collateral formation secondary to chronic renal vein thrombosis.[4-6] However, prolonged DGF due to venous hypertension and hyperdynamic flow secondary to the presence of an arteriovenous (AV) dialysis graft has not been reported before.

In this case report, we describe the first case of prolonged DGF for 9 months secondary to transplant renal vein hypertension. In this case, hyperdynamic flow because of the patent AV dialysis access graft with outflow obstruction from inferior vena cava (IVC) thrombosis contributed to allograft dysfunction.

CASE REPORT

This is a case of a 39-year-old African American woman with a history of end-stage renal disease secondary to focal segmental glomerulosclerosis. She received her first kidney transplant from a living unrelated donor in 2005, which eventually failed in 2010 because of recurrent focal segmental glomerulosclerosis, after which she went back on hemodialysis. Her transplanted kidney was removed because of ongoing chronic rejection and pain at the graft site. Her medical history was significant for a history of intradialytic hypotension requiring midodrine therapy and a right lower extremity deep vein thrombosis. She also had multiple failed hemodialysis accesses requiring multiple declotting procedures. In this

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setting, despite a negative hypercoagulable work-up, she was placed on chronic warfarin therapy. At the time of transplant, she was being dialyzed via a left femoral thigh graft because there was no possibility of a dialysis access in upper extremity because of central vein stenosis. She underwent a second deceased-donor kidney transplant in November 2013 (panel reactive antibody = 88%) with an acceptable flow cytometric crossmatch per our institutional protocol. During the perioperative period, no anticoagulation with heparin was started given her negative hypercoagulable work-up. After a brief hiatus of 5 days, her warfarin was resumed on discharge. Her transplant was performed on the right side because she had a patent left femoral AV graft (AVG) hemodialysis access. It was felt that it is imperative to salvage the graft for possible need of dialysis in postoperative period. Her surgery was uneventful with a cold ischemia time of 18 hours and 52 minutes. The allograft was from a 29-year-old standard criteria brain-dead donor with normal anatomy.

Her immunosuppression included induction with rabbit antithymocyte globulin (Thymoglobulin, Genzyme, Boston, Mass) followed by maintenance tacrolimus, mycophenolate mofetil, and prednisone. She did require hemodialysis a day after her transplant because of hyperkalemia with marginal urine output. She also had asymptomatic hypotension that required reinitiation of midodrine. Her ultrasound showed patent renal transplant vessels without any abnormality. A transplant kidney biopsy done on postoperative day 7 showed early signs of antibody-mediated rejection (AMR) with microvascular inflammation. She was also noted to have class II donor-specific antibodies with a total mean fluorescence intensity of 16 000. Thus, plasmapheresis was initiated on an alternating day regimen for a total of 6 sessions. Her warfarin was once again held during the administration of plasmapheresis and resumed thereafter. A subsequent biopsy 3 weeks posttransplant due to ongoing DGF demonstrated worsening AMR (Figure 1A). Plasmapheresis was continued in addition to administration of B-cell depletion therapy with rituximab. A repeat biopsy 1 month later demonstrated resolving AMR. After treatment, her donor-specific antibodies became undetectable. Despite this, she continued to require hemodialysis. Two months posttransplant, she required declotting of her left femoral AVG, but only her left iliac veins were visualized with venography. Two additional biopsies at 3 and 5 months posttransplant showed no signs of renal injury. A molecular profile (MMDx, Alberta, Canada) of her 5-month biopsy demonstrated moderate acute kidney injury but no evidence of any rejection or fibrosis. In this setting, she was switched from tacrolimus to belatacept based on a presumptive diagnosis of possible calcineurin inhibitor nephrotoxicity.

She developed a hematoma after her 5-month biopsy, and a computed tomography (CT) scan of the abdomen revealed extensive vascular collaterals in the subcutaneous soft tissue (Figure 2). An ultrasound also showed increasing venous collaterals around the kidney and in the pelvis. A nuclear medicine scan to evaluate renal perfusion and function showed normal perfusion with poor extraction and poor excretion with a limited response to diuretics. Therefore, at that time, it was assumed that ongoing acute tubular injury was the cause of her DGF rather than any obstructive pathology.

At 7 months posttransplant (June 2014), she had another episode of femoral AVG thrombosis for which she underwent declotting at an outside hospital. This venogram revealed a chronic IVC thrombus just above the level of the native renal veins. A repeat venogram was performed at our facility to evaluate venous pressures in the iliac vein (Figure 3). This demonstrated chronic occlusion of the suprarenal IVC with extensive venous collateral formation, with significant venous hypertension below the IVC occlusion. The venous pressure was 34 mmHg in the infrarenal IVC and 8 mmHg in the right atrium. In addition, there was reversal of flow in the right iliac venous system, with predominant outflow via body wall collaterals that extended above the occlusion. The flow became anterograde when a balloon occlusion was placed in the left femoral AVG, with infrarenal IVC pressures dropping from 34 to 27 mmHg. Therefore, it was felt that the abnormal flow pattern was a result of the IVC occlusion and increased venous return from the patent left femoral AVG. A left iliac vein balloon venoplasty was performed, and ligation of the AVG was offered to the patient to decrease venous hypertension, but the patient declined.

After venoplasty, her urine output started to improve at 9 months after transplant. Another biopsy demonstrated complete resolution of AMR with mild acute tubular injury (Figure 1B). Thus, dialysis was discontinued. Subsequently, her creatinine trended down to a baseline of 1.7 mg/dL.

Later in the course at 34 months posttransplant, she was admitted to the hospital for increasing bilateral lower extremity edema. Recanalization of the suprarenal IVC via

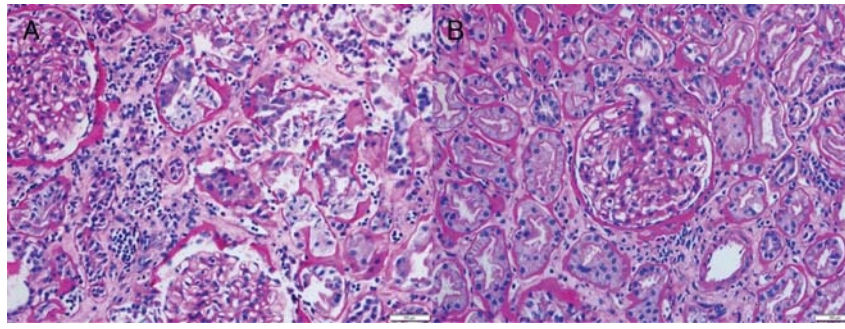

FIGURE 1. A, Acute antibody-mediated allograft rejection 3 weeks posttransplant. PAS-stained biopsies of deceased donor graft 3 weeks posttransplant demonstrating peritubular capillaritis with more than 10 leukocytes in various profiles. Mild glomerulitis with no tubulitis present. B, No evidence of rejection in allograft 9 months posttransplant. PAS-stained biopsies of deceased donor graft 9 months posttransplant demonstrating no evidence of rejection with nondistended peritubular capillaries containing only 1 to 2 leukocytes in some profiles. No glomerulitis or tubulitis is present. PAS, periodic acid–Schiff.

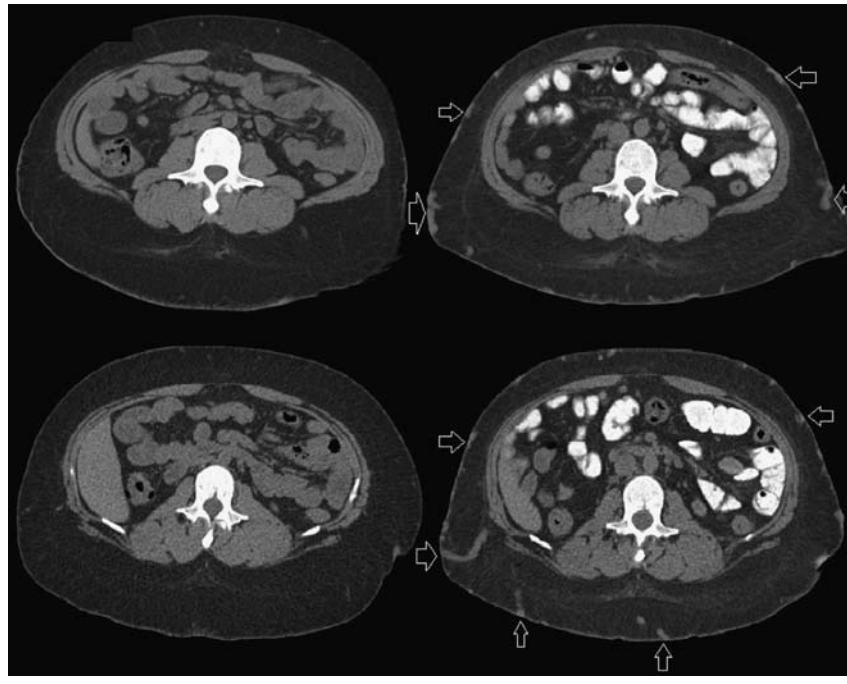

FIGURE 2. CT imaging pretransplant and posttransplant demonstrating development of extensive venous collaterals. Axial CT pretransplant (left images) demonstrating normal-appearing subcutaneous fat with absent collateral veins. Axial CT 5 months posttransplant (right images) demonstrating innumerable tortuous collateral veins in the subcutaneous fat (open white arrows delineating representative examples), formed because of the underlying inferior cava occlusion.

balloon angioplasty with overlapping self-expanding stents resulted in clinical resolution of lower extremity swelling and improvement in abdominal wall collaterals (Figure 4). Her most recent creatinine 36 months posttransplant has further improved to 1.4 mg/dL with a glomerular filtration rate of 54 mL/min per 1.73 m^2 (Figure 5).

DISCUSSION

DGF is common after kidney transplantation and can happen in up to 60% of patients.[3] DGF can be related to various donor and recipient characteristics, cold and warm ischemia time, and various perioperative factors.[2] Although vascular thrombosis can present acutely, chronic venous outflow obstruction has not been described as a cause of DGF.

In this report, we describe the first case of prolonged DGF secondary to renal venous hypertension caused by a previously unknown suprarenal IVC thrombosis with concomitant hyperdynamic flow secondary to patent left femoral AVG. Our patient had a complicated posttransplant course with early rejection. Although this likely contributed to her DGF, she continued to remain anuric despite serial normal allograft biopsies, suggesting an alternative additive etiology. Subsequent imaging procedures and venograms revealed that she had IVC thrombosis. In addition, we performed venous pressure measurements that confirmed a second cause of venous hypertension. She had a left femoral artery–to–femoral vein graft that likely contributed to retrograde flow in the right femoral vein because of the presence of suprarenal IVC thrombosis. Our theory of venous hypertension was again confirmed by the drop in the infrarenal IVC pressure from 34 to 27 mmHg with subsequent reduction in the right atrial to infrarenal IVC gradient from 26 to 19 mmHg (right atrial pressure, 8 mmHg) after the balloon occlusion of the

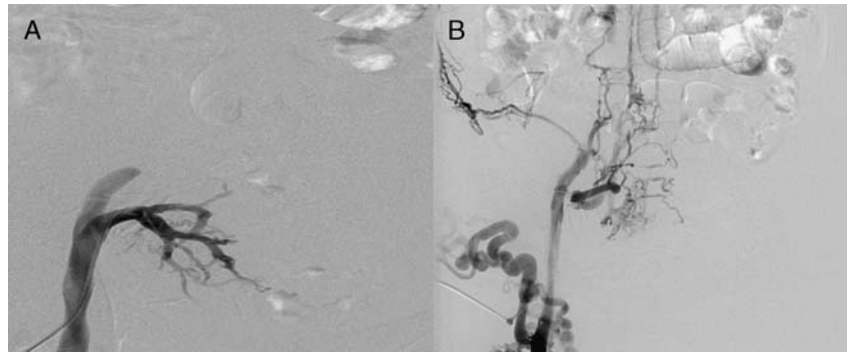

FIGURE 3. Venogram 9 months posttransplant. Digital subtraction venogram from selective catheterization of the transplant kidney vein shows a widely patent renal vein emptying into the right external iliac vein (A). Note that iodinated contrast opacifies the upstream right common femoral vein due to reversed flow in the right hemipelvis. Contrast ultimately drained through extensive subcutaneous collaterals arising from the femoral vein on later phase images (3B).

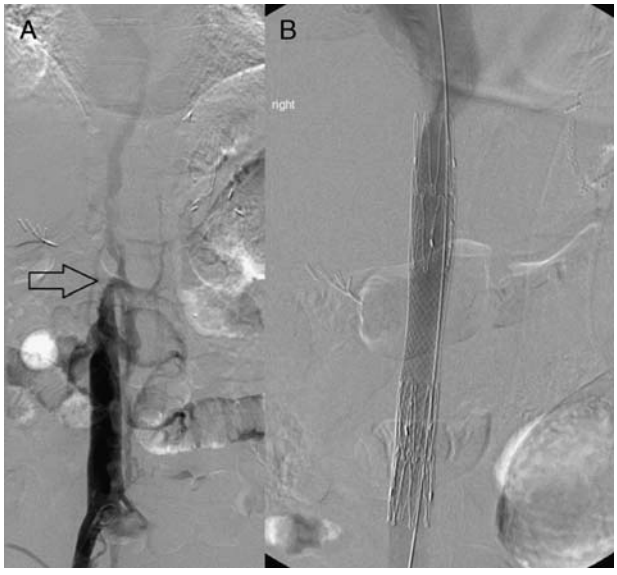

FIGURE 4. Comparison of IVC occlusion pre and postrecanalization. Digital subtraction venogram image (4A) demonstrates abrupt occlusion of the IVC (open black arrow) with no filling of the suprarenal segment. Venous drainage is back to the right atrium via azygos and hemiazygos collaterals. Digital subtraction venogram image (4B) demonstrates recanalization of the IVC with widely patent stents extending throughout the IVC with flow back to the right atrium and no filling of collaterals.

patent AVG. We hypothesize that these findings lead to the development of multiple collaterals originating from the right femoral vein. Corrective action through iliac venoplasty and development of collaterals likely resulted in improved allograft outflow and subsequent recovery of graft function.

IVC thrombosis in the absence of an identifiable hypercoagulation disorder is very rare.[7] Surveillance for IVC thrombosis is recommended in pediatric population with significant risk of anatomical problems or risk factors for thrombosis.[8] Nevertheless, no such guidelines exist for adults with end-stage kidney disease. Our patient had multiple reasons that put her at risk of the development of IVC thrombosis. She had a long-standing history of intradialytic hypotension that required the use of midodrine. Intradialytic hypotension is a known cause of vascular access thrombosis.[9] She also had multiple catheters placed that might have contributed to the development of IVC thrombosis due to chronic traumatic injury.[10] Although the acuity of IVC thrombus in our patient is difficult to determine, it is possible that her IVC thrombosis evolved during the perioperative period when she was significantly more hypotensive and off anticoagulation.

Several lessons can be learned from our experience. We chose to hold anticoagulation in the immediate perioperative setting to minimize the risk of bleeding. In the absence of a known hypercoagulable disorder this was felt to be a safe approach. Similarly, we held anticoagulation when our patient was receiving plasmapheresis. In retrospect, it is likely that her IVC thrombus could have been related to the lack of bridging with heparin during the times when she was off warfarin. Secondly, development of subcutaneous collaterals on imaging in our patient should have triggered an early investigation for venous outflow obstruction with a contrast venogram.

As per our institution protocol, the patient received a noncontrast CT of her abdomen and pelvis to assess calcifications in the iliac vasculature. A contrasted study was not performed. The possibility of venous outflow obstruction was not considered in the presence of a functioning left femoral AV access and absence of collaterals over the abdomen. In retrospect, given her history of multiple AV access thromboses, ongoing therapy with warfarin, and previous procedures with a femoral access, a pretransplant CT with intravenous contrast should have been performed to assess her vasculature. In fact, this is our current institutional protocol at the current time. With the application of this protocol, we have diagnosed 1 patient with IVC thrombosis and another patient with high-grade IVC stenosis. One patient's transplant was drained into the portal system as previously described in the literature.[11-14] The second patient underwent serial IVC venoplasties before her transplant. Both these patients have good allograft function at the time of the writing of this article.

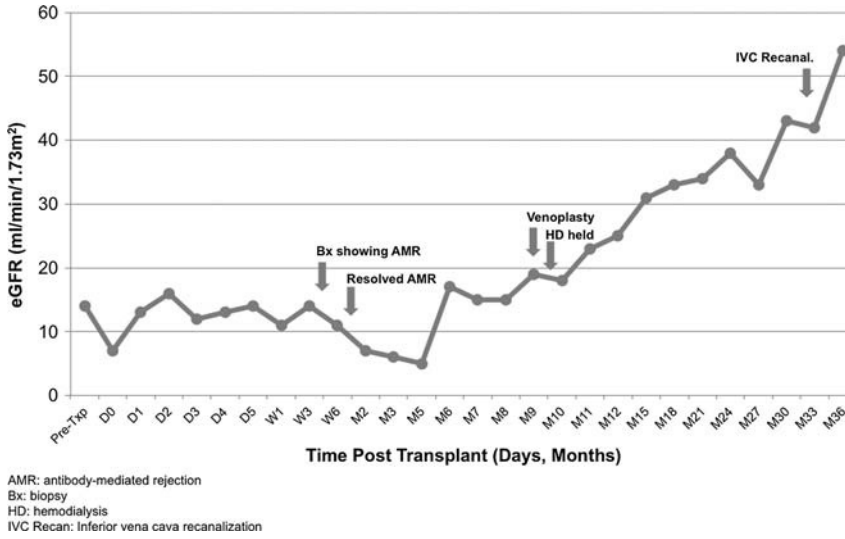

FIGURE 5. Glomerular filtration rate from transplant date to present. Patient's glomerular filtration rate (corrected for African American race) from time of transplant to 36 months posttransplant.

We conclude that renal transplant venous hypertension is a very rare but important cause of DGF. It should be considered in the differential diagnosis of DGF among patients with risk factors including intradialytic hypotension, history of multiple thromboses, and normal-appearing kidney transplant histology. We also propose that a careful assessment of vascular anatomy should be performed in patients with lower extremity dialysis grafts particularly those with a history of thrombosis. In the event of a known IVC thrombosis, alternate venous drainage should be considered prospectively to prevent DGF and chronic vascular complications.

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