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Dual Kidney Transplant From a Donor With Alport Syndrome in a Genotypically Normal Recipient

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Alport syndrome (AS) is a genetic disorder caused by mutations in *COL4A3*, *COL4A4*, and *COL4A5* that affect the synthesis, assembly, deposition, or function of collagen IV α3α4α5 network of glomerular basement membranes (GBMs). This causes pathology from microscopic hematuria to progressive renal disease. Although early treatment with angiotensin-converting enzyme inhibitors can delay progression, patients will eventually develop end-stage renal disease (ESRD).[1] The risk and timing of ESRD are affected by sex and genotype; some AS patient subsets are at higher risk of requiring dialysis and kidney transplantation sooner.[1,2]

Several studies have shown that AS patients are great candidates for kidney transplantation, with patient and graft survival rates equal to or better than transplants secondary to other ESRD causes.[1,3] The European Renal Association-European Dialysis and Transplant Association Registry found that a group of male patients with AS had better renal graft and patient survival than matched controls (matched for age, year of transplantation, and kidney donor source).[4]

Although there have been studies showing the success of renal transplantation in patients with AS, there are scant data on renal transplantation from a donor with AS. We discuss a patient who received dual kidney transplantation from a donor with AS who regained renal function postoperatively and remains off renal replacement therapy.

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CASE DESCRIPTION

A 60-y-old woman with ESRD secondary to type 2 diabetes mellitus presented for evaluation for a kidney transplant. She had been on maintenance hemodialysis for 2.5 y on a 3 d/wk schedule. Her medical history was significant for medically managed hypertension, type 2 diabetes mellitus requiring insulin, and hyperlipidemia.

The donor was a 36-y-old female status, after an ischemic stroke resulting in brain death. The donor had a history of AS diagnosed 22 y before donation, but normal renal function at the time of death with blood urea nitrogen of 22 mg/dL and creatinine (Cr) of 0.79 mg/dL. No donor gross or microhematuria was noted before death. One wedge sample biopsy (Bx) was taken and divided into 3 parts, with one sent for light electron microscopy and the other immunofluorescence. Procurement donor kidney Bx showed 8% glomerulosclerosis in the left kidney and 22% in the right, with minimal interstitial fibrosis and arterial changes. She had associated multiple benign tumors (leiomyomas) of the esophagus, uterus, labia, and rectum and a permanent colostomy after resection of a rectal tumor. This leiomyomatosis was consistent with the diagnosis of AS.

This offer had been declined by multiple centers and was eventually accepted by our center at sequence 1335. After a multidisciplinary review, dual kidney transplant versus single was decided, given the young age of the donor, normal kidney function, and mild chronic changes in the kidney allograft Bx. The recipient was chosen because of being next in the list and with a negative crossmatch. The likelihood of some chronic kidney damage from AS and the expected better outcome with dual kidney transplant was discussed with the patient who provided informed, written consent. Cytomegalovirus status of the recipient versus donor respectively was cytomegalovirus$^{-/-}$ Epstein-Barr virus IgG$^{+/+}$ IgM$^{-/-}$, and the Kidney Donor Profile Index was 27%.

The patient underwent a deceased donor renal transplant of the left kidney allograft to the left iliac fossa and right allograft to the right fossa. Another wedge Bx was taken from both allografts on the backtable. The wedge Bx from each kidney was divided into 2, with 1 from each kidney sent for immunofluorescence and 1 for electron microscopy.

Intraoperative Bx results showed normal ultrastructural morphology with some focal interstitial fibrosis and occasional collecting tubular basement membrane thickening. Both kidneys demonstrated thin GBMs but no evidence of lamination (Figure 1). Hundred measurements over 54 different fields showed segmental thinning of the basement membrane with a minimum thickness of 132 nm. The normal basement membrane thickness in women averages between 300 and 320 nm.

The postoperative course was unremarkable. Pretransplant Cr was 5.3 mg/dL; discharge Cr was 1.3 mg/dL with excellent primary allograft function. She received thymoglobulin 4.5 mg/kg induction; maintenance with tacrolimus extended-release, mycophenolate sodium, and prednisone taper; and standard immunoprophylaxis with Bactrim, clotrimazole, and acyclovir.

She continued to have good allograft function at 2-mo follow-up, Cr 0.84. At 3 mo, a protocol allograft Bx was done. Trichrome stain revealed minimal focal interstitial fibrosis. CD3 showed a few scattered T cells with negative C4d staining. Glomeruli showed increased mesangial matrix, focal capillary basement membrane rarefication, focal visceral epithelial cell effacement, and focal mesangial electron-dense deposits. Importantly, capillary basement membranes were unremarkable besides focal rarefication. (Figure 2). A 7-mo protocol Bx showed no AS changes in the GBM, with normal thickness (Figure 3). Immunofluorescence staining for collagen IV showed a normal pattern of staining for α2 and α5 isoforms. The red staining highlights the alpha 2 chain of type IV collagen (positive internal control). The green staining is of the alpha 5 chain of type IV collagen. The image shows a normal pattern of staining with preserved linear alpha 5 staining of the GBMs (yellow star), Bowman's capsule (blue arrow), and distal tubular basement membranes (arrowhead). An ultrastructural examination of the renal allograft (Figure 4) shows, on the left, baseline Bx GBM with a minimum thickness of 132 nm (yellow arrow); right upper, Bx 3 mo posttransplant showing GBM (red arrow) measuring between 200 and 400 nm; and, right lower, Bx at 7 mo showing normal GBM thickness. Laboratory values of the patient remained stable at 15 mo from transplant with a Cr of 1.17 mg/dL. She was noted to develop 2+ proteinuria but did not develop microscopic or gross hematuria. This Cr level, although slightly elevated from baseline, remains within the normal range. Urine protein: Cr ratio was 55:86 (0.6 mg/g) at this time.

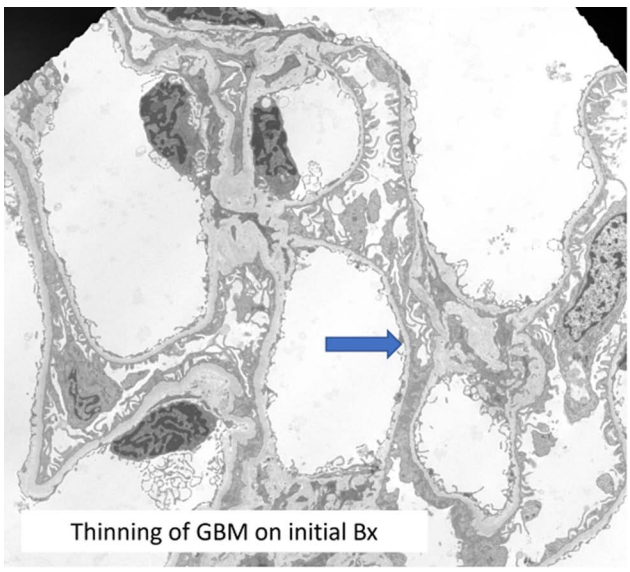

FIGURE 1. Thinning of GBM on initial Bx. Bx, biopsy; GBM, glomerular basement membrane.

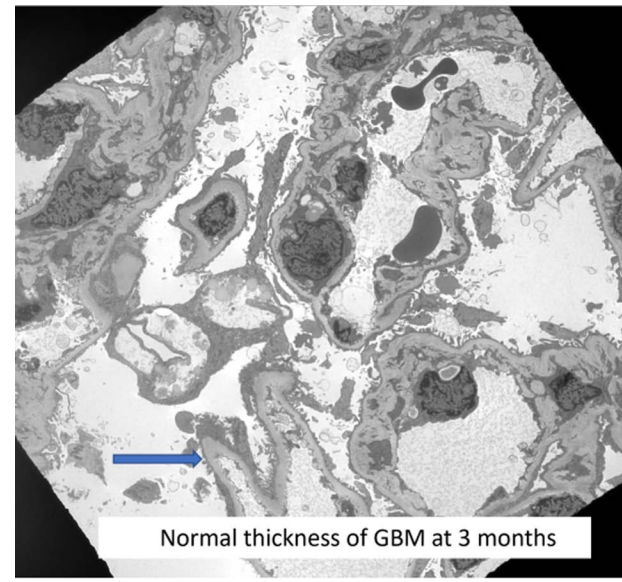

FIGURE 2. Normal thickness of GBM at 3 mo. GBM, glomerular basement membrane.

DISCUSSION

There is a paucity of data on kidney transplant outcomes from donors with AS because these donors are mostly ruled out for kidney donation. One study by Gross et al reported 6 mothers with AS with mild urinary abnormalities who donated kidneys to their affected children. All donors had microhematuria, and 1 had proteinuria preoperatively. All transplanted kidneys had good graft function at 1 and 5 y after transplant, and 1 died secondary to meningitis at 10 y, and the remaining 4 were stable.[5] Our study is the first of a kind showing good allograft function from a deceased donor Alport kidney. We also showed improvement in basement membrane morphology over time posttransplant, probably reflecting the deposition of normal collagen chains by the host fibroblasts.

AS is most commonly inherited in an X-linked pattern (85%)[6] but can be transmitted in an autosomal recessive (10%–15%) and dominant (rare) manner. X-linked AS is twice as prevalent in women but presents more severely in men. Autosomal dominant AS has slower ESRD progression with less likelihood of extrarenal manifestations.[7,8] Autosomal recessive disease presents similarly regardless of gender. Although we do not know which AS our donor had, it is likely she had X-linked AS given a concomitant history of leiomyomatosis of the gastrointestinal and genitourinary tract.[9] Having a female X-linked AS donor may have optimized outcomes given a less severe presentation of the disease. This also could have been the case in the study by Gross et al[5] as noted earlier. All donors were women; 5 of 6 mothers had X-linked disease and 1 had autosomal recessive disease.

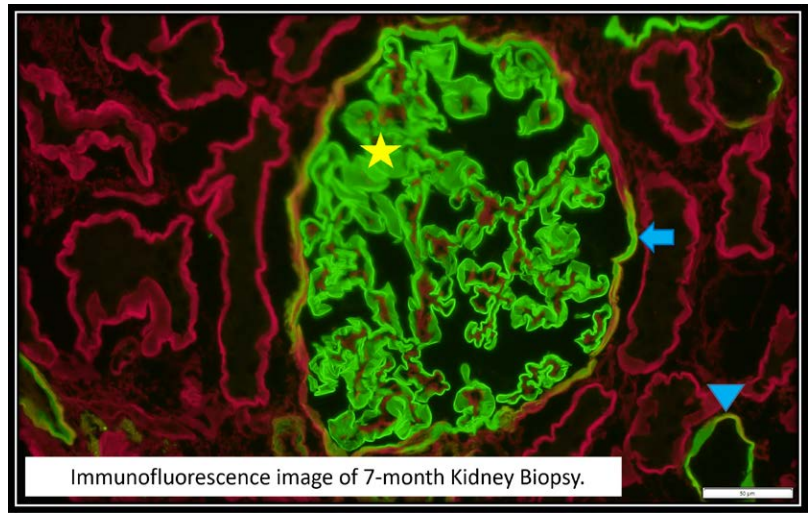

FIGURE 3. Immunofluorescence image of a 7-mo kidney biopsy.

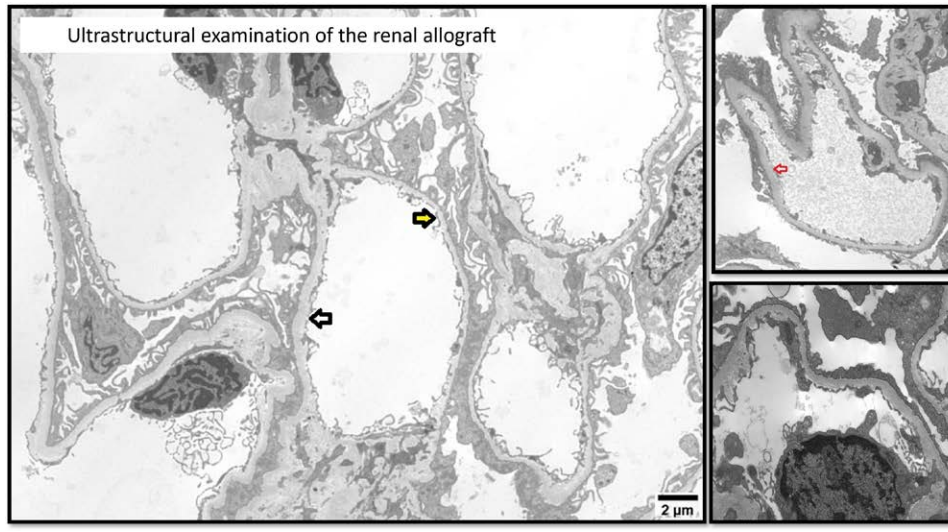

FIGURE 4. Ultrastructural examination of the renal allograft.

Women with X-linked disease have a normal X chromosome that allows tolerance of normal collagen IV α5 chain and do not develop anti-GBM disease.[10] This may also play a role in the lack of GBM disease progression after Alport kidney transplantation in a patient with normal collagen IV α5 chains.

With a shortage of organs for transplant, using organs from unconventional donors can be helpful. It is intriguing to notice the improvement in basement membrane morphology posttransplant, and it shows how the Alport kidney might have been "healed" by the recipient fibroblasts.

REFERENCES

1. Kashtan CE, Ding J, Garosi G, et al. Alport syndrome: a unified classification of genetic disorders of collagen IV α345: a position paper of the Alport syndrome classification working group. *Kidney Int*. 2018;93:1045–1051.
2. Storey H, Savige J, Sivakumar V, et al. COL4A3/COL4A4 mutations and features in individuals with autosomal recessive Alport syndrome. *J Am Soc Nephrol*. 2013;24:1945–1954.
3. Kashtan CE, McEnery PT, Tejani A, et al. Renal allograft survival according to primary diagnosis: a report of the North American Pediatric Renal transplant cooperative study. *Pediatr Nephrol*. 1995;9:679–684.
4. Temme J, Kramer A, Jager KJ, et al. Outcomes of male patients with Alport syndrome undergoing renal replacement therapy. *Clin J Am Soc Nephrol*. 2012;7:1969–1976.
5. Gross O, Weber M, Fries JW, et al. Living donor kidney transplantation from relatives with mild urinary abnormalities in Alport syndrome: long-term risk, benefit and outcome. *Nephrol Dial Transplant*. 2009;24:1626–1630.
6. Nozu K, Vorechovsky I, Kaito H, et al. X-linked Alport syndrome caused by splicing mutations in COL4A5. *Clin J Am Soc Nephrol*. 2014;9:1958–1964.
7. Fallerini C, Dosa L, Tita R, et al. Unbiased next generation sequencing analysis confirms the existence of autosomal dominant Alport syndrome in a relevant fraction of cases. *Clin Genet*. 2014;86:252–257.
8. Savige J, Colville D, Rheault M, et al. Alport syndrome in women and girls. *Clin J Am Soc Nephrol*. 2016;11:1713–1720.
9. Nozu K, Minamikawa S, Yamada S, et al. Characterization of contiguous gene deletions in COL4A6 and COL4A5 in Alport syndrome-diffuse leiomyomatosis. *J Hum Genet*. 2017;62:733–735.
10. Kashtan CE. Alport syndrome and the X chromosome: implications of a diagnosis of Alport syndrome in females. *Nephrol Dial Transplant*. 2007;22:1499–1505.