Published in final edited form as:

Am J Kidney Dis. 2019 January ; 73(1): 134–139. doi:10.1053/j.ajkd.2018.05.008.

Donor's *APOL1* Risk Genotype and “Second Hits” Associated with *De Novo* Collapsing Glomerulopathy in Deceased Donor Kidney Transplant Recipients

Jae-Hyung Chang, MD^{#1}, S. Ali Husain, MD^{#1}, Dominick Santoriello, MD², Michael B. Stokes, MD², Clifford D. Miles, MD³, Kirk W. Foster, MD⁴, Yifu Li, MD¹, Leigh-Anne Dale, MS¹, Russell J. Crew, MD¹, David J. Cohen, MD¹, Krzysztof Kiryluk, MD, MS¹, Ali G. Gharavi, MD¹, and Sumit Mohan, MD, MPH^{1,5}

¹Division of Nephrology, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY

²Department of Pathology and Cell Biology, Columbia University College of Physicians and Surgeons, New York, NY

³University of Nebraska Medical Center, Department of Internal Medicine, Omaha, NE

⁴University of Nebraska Medical Center, Department of Pathology and Microbiology, Omaha, NE

⁵Columbia University Renal Epidemiology (CURE) group, New York, NY.

These authors contributed equally to this work.

Abstract

The presence of two *APOL1* risk variants (G1/G1, G1/G2, or G2/G2) is an important predictor of focal segmental glomerulosclerosis (FSGS), and chronic kidney disease in individuals of African descent. While recipient *APOL1* genotype is not associated with allograft survival, kidneys from deceased African American donors with two *APOL1* risk variants demonstrate shorter graft survival. We present a series of cases of presumed *de novo* collapsing FSGS in five transplanted kidneys from three deceased donors later identified as carrying two *APOL1* risk alleles, including two recipients from the same donor whose kidneys were transplanted in two different institutions across United States. Four of these recipients had viremia in the period preceding the diagnosis of collapsing FSGS. Cytomegalovirus (CMV) and BK virus infection was present in three and one of our five cases, respectively, around the time collapsing FSGS occurred. We discuss viral infections including active CMV infection as possible “second hits” that may lead to glomerular injury and allograft failure in these recipients. Further studies to identify additional “second hits” are necessary to better understand the pathologic mechanisms of donor *APOL1*-associated kidney disease in the recipient.

Corresponding author: Jae-Hyung Chang, MD, FASN, Division of Nephrology, Department of Medicine, Columbia University Medical Center, 622 West 168th Street, PH4-124, New York, NY 10032, jhc2170@cumc.columbia.edu.

Financial Disclosure: The authors of this manuscript have no relevant financial interests to disclose.

Keywords

APOL1; BK virus; CMV; collapsing FSGS; donor genotype; kidney transplant outcome; second hit; viral infection

INTRODUCTION

The association of apolipoprotein-L1 (*APOL1*) risk variants and kidney disease in patients of African heritage represented a landmark finding in the understanding of mechanisms of racial differences in the prevalence of kidney failure.[1] In the non-transplant population, the presence of two risk variants in the *APOL1* gene that encodes the anti-trypanosomal protein (G1/G1, G1/G2, or G2/G2) confers an increased risk for kidney diseases including focal segmental glomerulosclerosis (FSGS), sickle cell nephropathy, and human immunodeficiency virus (HIV) associated nephropathy (HIVAN).[1–3] However, the mechanisms of APOL1-related renal disease remain incompletely understood, as only 13% of African Americans have two *APOL1* risk alleles while 50% of African Americans on hemodialysis (HD) have two *APOL1* risk variants.[4, 5] It appears that a second event, possibly an additional genetic factor or environmental trigger, is required for onset and/or progression of APOL1-related kidney disease.

Previous studies have demonstrated no association between recipient *APOL1* genotype and allograft survival, whereas kidneys from donors with two *APOL1* risk variants have an approximately twofold increased risk of allograft failure.[6–9] A better understanding of the mechanisms of APOL1-associated renal disease in kidney allografts including identification of potential “second hits” is needed to improve living and deceased donor kidney evaluation, organ allocation, and post-transplant care. Here, we present five cases of presumed *de novo* collapsing glomerulopathy in transplanted kidneys from donors with two *APOL1* risk alleles, including two recipients from the same donor whose kidneys were transplanted at different institutions.

CASE REPORTS

A comparison of the clinical course for the cases is presented in Table 1 and Figure 1. Detailed methods for patient identification and APOL1 sequence appear in Item S1.

Donor A

Donor A (G1/G1) was a 57-year-old African American man with hypertension who died following a stroke.

Recipient A1 (G0/G0) was a 47-year-old African American woman with ESRD attributed to diabetes mellitus and hypertension (presumed, no native kidney biopsy) whose immediate post-transplant course was complicated by delayed graft function (DGF). Post-reperfusion biopsy showed only mild focal global glomerulosclerosis (3 of 26 glomeruli, 12%) and mild arteriosclerosis. Her subsequent nadir serum creatinine (SCr) was 1.6 mg/dl. During the first year after transplant, she developed recurrent acute kidney injury (AKI) and underwent five additional allograft biopsies. Of note, seven months after transplant, she developed

cytomegalovirus (CMV) viremia (22,800 copies/ml) complicated by diarrhea and AKI (peak SCr 15.8mg/dl), at which time renal biopsy showed severe diffuse tubular injury and isometric tubular vacuolization; CMV staining was negative. Immunosuppression was reduced with subsequent resolution of CMV viremia, and a follow up biopsy for persistent proteinuria (3g/g protein/creatinine) showed borderline acute T-cell mediated rejection. She continued to have nephrotic-range proteinuria, and biopsy at 10.5 months showed diffuse tubular injury, isometric tubular vacuolization, and mild FSGS, not otherwise specified (NOS) type. Follow up biopsy at 14 months for persistently elevated creatinine and proteinuria showed collapsing FSGS, with 2/15 glomeruli showing collapse and 3/15 showing global glomerulosclerosis. CMV immunostain showed rare CMV inclusions in tubular epithelium, but not in glomeruli. Progressive renal failure eventually resulted in allograft failure 17 months after transplant.

Nine months after failure of her first transplant, Recipient A1 underwent a second deceased donor kidney transplant. The donor was a 27-year-old woman who died from pulmonary embolism (APOL1 genotype unknown). Post-reperfusion biopsy showed 34 glomeruli, none of which had global or segmental sclerosis. Post-transplant course was complicated by acute cellular rejection, Banff grade 1A, 2 weeks after transplantation, followed by acute cellular rejection, Banff grade 2A, 3 months after transplantation. She had recurrent acute cellular rejection at 9 months post-transplant (borderline changes) and 18 months (Banff grade 1B). She experienced allograft failure 50 months after transplant. She never had recurrence of CMV viremia. Of 9 total allograft biopsies ranging from post-implantation to 18 months post-transplant, none showed FSGS.

Recipient A2 (G0/G0) was a 64-year-old white woman with ESRD from autosomal dominant polycystic kidney disease. Post-reperfusion biopsy showed no sclerotic glomeruli. Nadir SCr was 1.3 mg/dl two months after transplant. One year after transplant, she developed CMV viremia (8,870 copies/mL) accompanied by diarrhea, vomiting, and severe AKI (peak SCr 17mg/dl). Mycophenolate discontinuation and ganciclovir initiation resulted in resolution of viremia and diarrhea. SCr decreased to 2.4mg/dl. Two months later, she was readmitted for Pneumocystis jiroveci pneumonia that was complicated by AKI (SCr 2.9mg/dl). A biopsy performed for new nephrotic range proteinuria (7.6g/g protein/creatinine) showed acute tubular injury and collapsing FSGS (3/12 glomeruli with global sclerosis, CMV staining not performed), eventually leading to allograft failure 14 months post-transplant.

Donor B

Donor B (G1/G1) was a 46-year-old African American woman with hypertension who died from a stroke.

Recipient B1 (G0/G0) was a 61-year-old Asian man with ESRD from biopsy-proven hypertensive nephrosclerosis and secondary FSGS (native kidney biopsy 5 years prior to transplantation showed global glomerulosclerosis attributed to hypertension, secondary FSGS/subtype NOS, severe interstitial fibrosis and tubular atrophy). Post-reperfusion biopsy showed 8/44 glomeruli with global sclerosis, 1/44 with a discrete lesion of segmental sclerosis characterized by consolidation of the glomerular tuft and adhesion to Bowman's

capsule (FSGS/subtype NOS), and moderate to severe arteriosclerosis and arteriolosclerosis. Nadir SCr was 1.4mg/dl. Fifteen months after transplant, surveillance testing showed BK viremia (14,300 copies/ml), so mycophenolate was replaced by leflunomide and levofloxacin was started. Allograft biopsy at 17 months for persistently elevated SCr (1.8mg/dl) showed BK-virus nephropathy, with positive SV40 immunostaining in the medullary tubules. He was treated with intravenous immunoglobulin (IVIg), and BK viremia improved to 49 copies/ml. At 21 months, he developed AKI (SCr 5.7mg/dl) with nephrotic range proteinuria (7.1g/g protein/creatinine). Repeat renal biopsy showed collapsing FSGS, peritubular capillaritis, and Banff grade 1A acute cellular rejection; SV40 immunostaining for BK virus was negative and out of 12 glomeruli, three were globally sclerotic, two showed segmental sclerosis, and two showed collapsing FSGS (Figure 2). Despite treatment with methylprednisolone, plasmapheresis, and IVIg, he had allograft failure 22 months after transplantation.

Recipient B2 (not genotyped) was a 47-year-old white woman with ESRD due to lupus nephritis. She had one prior failed kidney transplant (allograft failure 11 years after transplantation due to chronic rejection). A second transplantation was performed at the University of Nebraska Medical Center (UNMC) with a kidney from donor B. Twelve days after transplant, she developed acute antibody-mediated rejection (AKI, elevated anti-HLA class I donor-specific antibody (DSA), biopsy with diffusely positive C4d staining), and she was treated with plasmapheresis, IVIg, and rituximab. SCr subsequently reached post-transplant nadir of 0.9mg/dl, with disappearance of the DSA. Eleven months post-transplant, biopsy performed to evaluate AKI (SCr 2.0mg/dl) showed severe IFTA as well as FSGS: of 16 glomeruli, 7 were globally sclerotic, and 1 showed a segmental lesion of sclerosis with associated adhesion to Bowman's capsule (FSGS/subtype NOS). At 19 months, SCr rose to 2.7mg/dl with nephrotic-range proteinuria (3.4g/g protein/creatinine). Repeat renal biopsy showed collapsing FSGS and borderline acute cellular rejection. Allograft failure led to HD reinitiation at 23 months.

Donor C

Donor C (G1/G2) was a 48-year-old African American man with hypertension who died due to stroke.

Recipient C1 (G1/G2) was a 62-year-old white man with ESRD attributed to hypertension (no native kidney biopsy). Post-reperfusion biopsy showed focal glomerular fibrin thrombosis (<10% of glomeruli), and 4/36 glomeruli with global sclerosis. Nadir SCr was 1.4mg/dl. 7.5 months after transplant, he developed CMV viremia (5,570 copies/ml) with diarrhea, AKI (SCr 6.4mg/dl) and nephrotic-range proteinuria (15g/g protein/creatinine). Renal biopsy showed collapsing FSGS, with two glomeruli out of 15 showing global sclerosis and five showing collapsing FSGS. Immunostaining for SV40 and CMV was negative. He was treated with valganciclovir and IVIg, with resolution of CMV viremia, return to baseline SCr, and decrease in proteinuria to subnephrotic range. He was diagnosed with small cell lung cancer with hepatic metastases two years after transplant, with progression despite chemotherapy. Last documented SCr was 1.1mg/dl, 32 months after transplant.

DISCUSSION

APOL1 exists both as a tissue and a secreted protein. While the circulating APOL1 protects humans against African sleeping sickness, it appears that the tissue APOL1 is the one of relevance in renal allograft survival given the absence of adverse impact of recipient *APOL1* genotype on allograft outcome.[6, 10]

It is hypothesized that some viruses that infect cells in the kidney and lower urinary tract interact with APOL1 to alter the risk for kidney disease.[11] The strongest support for this hypothesis comes from the relationship between HIV and glomerular injury.[4] While only 4% of patients with this high-risk genotype develop FSGS, among untreated HIV-infected African Americans with two *APOL1* risk alleles, 50% develop HIVAN.[4] Collapsing glomerulopathy in the setting of acute parvovirus infection has been reported in a patient with two *APOL1* risk alleles.[12] Recently, Shah and colleagues reported a white recipient with ESRD from lupus nephritis who received a kidney transplant from a deceased donor with two *APOL1* risk variants and developed collapsing glomerulopathy nine months after the transplant.[13] The patient had a significant CMV viremia, and although a CMV immunostain was negative in the allograft kidney biopsy, active CMV infection was suggested as a possible “second hit”. CMV infection was present in three of our five cases around the time collapsing FSGS occurred. BK virus, a member of the polyomavirus family, can cause tubulointerstitial nephritis in immunocompromised patients. Although Simian Virus 40 (SV40), a monkey polyomavirus that is believed to have entered the human population through contaminated vaccines has been implicated in the causation of FSGS in the non-transplant population, thus far, there is no convincing evidence that BK polyomavirus infection causes glomerular disease in kidney transplant recipients.[14, 15] The tubulointerstitium accounts for more than 90% of kidney volume, and there is some evidence that suggests that tubulointerstitial injury and inflammation may contribute to glomerular diseases.[16] It is therefore conceivable that BK virus-mediated tubular injury and inflammation may have triggered collapsing glomerular lesions in the recipient B1. Interestingly, a lower prevalence of kidney disease was observed among African Americans with two *APOL1* risk alleles with JC viruria suggesting that infection with JC virus, another member of the polyomavirus family, may protect against *APOL1*-associated nephropathy possibly by altering cell function or generating immunity against the related BK virus.[17] Viral infection induces pro-inflammatory cytokines production including interferons, and the latter appear to up-regulate APOL1 expression.[18] In a cohort of seven patients each carrying two high-risk *APOL1* alleles, therapeutic interferon (for hepatitis C, multiple sclerosis, melanoma, or interstitial pulmonary fibrosis) was associated with collapsing FSGS.[18] Hence virus-induced endogenous interferon production may have contributed to APOL1-associated collapsing glomerulopathy in our cases. Unfortunately, electron microscopy is not routinely performed on transplant kidney biopsies at our institution and therefore these results are not available for the cases presented here. Without this information, we are unable to provide a quantification of the degree of foot process effacement, or comment on the presence of tubuloreticular inclusions (which, if present, would suggest elevated interferon activity). While no contemporary viral infection could be demonstrated in the recipient B2, microvascular injury and inflammation due to acute

antibody-mediated rejection may have caused direct podocyte injury, and glomerular collapse in the allograft kidney. Chronic glomerular endothelial and podocyte injury, whether in association with severe vascular disease, chronic transplant glomerulopathy, or calcineurin inhibitor toxicity can result in glomerular hypoperfusion, ischemia, and collapsing FSGS.[19, 20] Indeed, isometric tubular vacuolization was observed in some of the biopsies. In all cases with viral infection, overall immunosuppression was reduced. While no direct causal association has been demonstrated so far between reduction in overall immunosuppression and *de novo* collapsing FSGS in transplant recipients, it is conceivable that the former will inevitably result in increased immunogenicity with chronic immunological glomerular endothelial and podocyte injury. It is, therefore, highly likely that more than one factor, or “hits” are needed to trigger *APOL1*-associated collapsing glomerulopathy.

The role of screening of either deceased or living kidney donors of recent African ancestry for *APOL1* risk variants prior to transplantation has been controversial. Currently, African American donor status is included in deceased donor graft assessment (i.e. kidney donor risk index (KDRI)), and has a hazard ratio of 1.196 indicating approximately 20% increased risk of allograft loss.[21] Recently, Julian and colleagues demonstrated that replacing donor race with *APOL1* genotype better defined the risk associated with kidneys obtained from deceased donors of recent African ancestry, and substantially improved KDRI score for 85-90% of kidneys offered.[21] These results implicate that routine screening of African American kidney donors for *APOL1* risk variants prior to transplantation may improve the allocation of better quality kidneys to patients projected to have longer post-transplant survival, and at the same time, may reduce unnecessary discard of such kidneys. If the role of these viral illnesses in triggered collapsing FSGS can be further established, recipients of kidneys from donors with two *APOL1* risk alleles may warrant tailored management. For example, regular screening for proteinuria and increased frequency of viremia screening could be considered. Further, the duration of viral prophylaxis regimens in the early post-transplant period could be extended in these patients, and more aggressive antiviral strategies could be considered at first identification of viremia.

In conclusion, our findings suggest that viral infections may represent potential second hits that may be associated with *APOL1*-mediated collapsing glomerular injury in recipients from donors with two *APOL1* risk alleles. To our knowledge, this is the largest case series of *de novo* collapsing FSGS in transplanted kidneys from donors with two *APOL1* risk alleles with identified second hits. Well-powered prospective genetic studies of full donor-recipient pairs are clearly needed to confirm our observations. The National Institutes of Health (NIH) has recently launched the *APOL1* Long-term Kidney Transplantation Outcomes (APOLLO) Research Network consortium that will design and conduct studies to determine the impact of *APOL1* genetic variants as susceptibility factors in US kidney transplant recipients who received kidneys from African American donors. Studies to better understand the mechanisms and predisposing factors for *APOL1*-associated kidney disease are overdue.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

Support: S.M. was supported by NIH/NIDDK R01 DK114893.

REFERENCES

1. Genovese G, Friedman DJ, Ross MD, et al., Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science*, 2010 329(5993): p. 841–5. [PubMed: 20647424]
2. Foster MC, Coresh J, Fornage M, et al., APOL1 variants associate with increased risk of CKD among African Americans. *J Am Soc Nephrol*, 2013 24(9): p. 1484–91. [PubMed: 23766536]
3. Fine DM, Wasser WG, Estrella MM, et al., APOL1 risk variants predict histopathology and progression to ESRD in HIV-related kidney disease. *J Am Soc Nephrol*, 2012 23(2): p. 343–50. [PubMed: 22135313]
4. Kopp JB, Nelson GW, Sampath K, et al., APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol*, 2011 22(11): p. 2129–37. [PubMed: 21997394]
5. Friedman DJ, Kozlitina J, Genovese G, Jog P, and Pollak MR, Population-based risk assessment of APOL1 on renal disease. *J Am Soc Nephrol*, 2011 22(11): p. 2098–105. [PubMed: 21997396]
6. Lee BT, Kumar V, Williams TA, et al., The APOL1 genotype of African American kidney transplant recipients does not impact 5-year allograft survival. *Am J Transplant*, 2012 12(7): p. 1924–8. [PubMed: 22487534]
7. Freedman BI, Julian BA, Pastan SO, et al., Apolipoprotein L1 gene variants in deceased organ donors are associated with renal allograft failure. *Am J Transplant*, 2015 15(6): p. 1615–22. [PubMed: 25809272]
8. Reeves-Daniel AM, DePalma JA, Bleyer AJ, et al., The APOL1 gene and allograft survival after kidney transplantation. *Am J Transplant*, 2011 11(5): p. 1025–30. [PubMed: 21486385]
9. Freedman BI, Pastan SO, Israni AK, et al., APOL1 Genotype and Kidney Transplantation Outcomes From Deceased African American Donors. *Transplantation*, 2016 100(1): p. 194–202. [PubMed: 26566060]
10. Perez-Morga D, Vanhollebeke B, Paturiaux-Hanocq F, et al., Apolipoprotein L-I promotes trypanosome lysis by forming pores in lysosomal membranes. *Science*, 2005 309(5733): p. 469–72. [PubMed: 16020735]
11. Palmer ND and Freedman BI, APOL1 and progression of nondiabetic nephropathy. *J Am Soc Nephrol*, 2013 24(9): p. 1344–6. [PubMed: 23813212]
12. Besse W, Mansour S, Jatwani K, Nast CC, and Brewster UC, Collapsing glomerulopathy in a young woman with APOL1 risk alleles following acute parvovirus B19 infection: a case report investigation. *BMC Nephrol*, 2016 17(1): p. 125. [PubMed: 27600725]
13. Shah PB, Cooper JE, Lucia MS, Boils C, Larsen CP, and Wiseman AC, APOL1 Polymorphisms in a Deceased Donor and Early Presentation of Collapsing Glomerulopathy and Focal Segmental Glomerulosclerosis in Two Recipients. *Am J Transplant*, 2016 16(6): p. 1923–1927. [PubMed: 26849829]
14. Chandra P and Kopp JB, Viruses and collapsing glomerulopathy: a brief critical review. *Clin Kidney J*, 2013 6(1): p. 1–5. [PubMed: 23372939]
15. Li RM, Branton MH, Tanawattanacharoen S, Falk RA, Jennette JC, and Kopp JB, Molecular identification of SV40 infection in human subjects and possible association with kidney disease. *J Am Soc Nephrol*, 2002 13(9): p. 2320–30. [PubMed: 12191976]
16. Grgic I, Campanholle G, Bijol V, et al., Targeted proximal tubule injury triggers interstitial fibrosis and glomerulosclerosis. *Kidney Int*, 2012 82(2): p. 172–83. [PubMed: 22437410]
17. Divers J, Nunez M, High KP, et al., JC polyoma virus interacts with APOL1 in African Americans with nondiabetic nephropathy. *Kidney Int*, 2013 84(6): p. 1207–13. [PubMed: 23677244]
18. Nichols B, Jog P, Lee JH, et al., Innate immunity pathways regulate the nephropathy gene Apolipoprotein L1. *Kidney Int*, 2015 87(2): p. 332–42. [PubMed: 25100047]
19. Shimizu A, Higo S, Fujita E, Mii A, and Kaneko T, Focal segmental glomerulosclerosis after renal transplantation. *Clin Transplant*, 2011 25 Suppl 23: p. 6–14. [PubMed: 21623907]

20. Takeda A, Morozumi K, Koyama K, et al., Severe cyclosporine arteriolopathy with focal segmental glomerulosclerosis is not a fatal finding in chronic renal allograft failure after year 5 of transplantation using cyclosporine. *Transplant Proc*, 1997 29(1–2): p. 96–9. [PubMed: 9123169]
21. Julian BA, Gaston RS, Brown WM, et al., Effect of Replacing Race With Apolipoprotein L1 Genotype in Calculation of Kidney Donor Risk Index. *Am J Transplant*, 2017 17(6): p. 1540–1548. [PubMed: 27862962]

Figure 1. Summary of clinical course by recipient.

Recipient A1 had a course complicated by multiple episodes of acute kidney injury and one episode of CMV viremia seven months after transplant. Biopsy at 14 months showed collapsing FSGS, followed by allograft failure at 17.5 months. Recipient A2 had a course complicated by CMV viremia at 12 months, followed by biopsy showing collapsing FSGS at 14 months with immediate graft failure. Recipient B1 developed persistent BK viremia at 15 months; biopsy at 21 months showed collapsing FSGS, and allograft failure occurred at 22 months. Recipient B2 had early AMR but no BK or CMV viremia. Biopsy at 19 months showed collapsing FSGS, with allograft failure at 23 months. Recipient C1 had CMV viremia at 7.5 months, with AKI due to collapsing FSGS, followed by complete renal recovery.

Figure 2. Representative glomeruli from recipients B1 and B2.

Light microscopy of representative glomeruli from recipients B1 (silver stain, 400× magnification) and B2 (PAS stain, 400× magnification) demonstrating collapsing FSGS.

Table 1.

Summary of Donor and Recipient Characteristics

	Donor A		Donor B		Donor C	
APOL1 Genotype	G1/G1		G1/G1		G1/G2	
Age (years)	57		46		48	
Gender	Male		Female		Male	
Race/Ethnicity	African American		African American		African American	
Blood Type	O		A		O	
BMI (kg/m ²)	32.1		22.4		29.5	
Hypertension	Yes		Yes		Yes	
Diabetes Mellitus	No		No		No	
EBV	Not recorded		Positive		Positive	
CMV	Not recorded		Positive		Positive	
Cause of Death	CVA/ICH		CVA/ICH		CVA/ICH	
Terminal Serum Creatinine (mg/dL)	2.2		0.9		2.3	
KDPI	Not calculated		72%		Not calculated	
	Recipient A1	Recipient A2	Recipient B1	Recipient B2	Recipient C1	Recipient C2
APOL1 Genotype	G1/G1	G0/G0	G0/G0	<i>Not performed</i>	G0/G0	<i>Recipient not identified</i>
Age at Transplant (years)	47	64	61	47	62	
Gender	Female	Female	Male	Female	Male	
Race/Ethnicity	African American	White	Asian	White	White	
Blood Type	O+	O+	A+	A+	O+	
BMI at listing (kg/m ²)	38.8	30.7	32	21	19.8	
Hypertension	Yes	Yes	Yes	Yes	Yes	
Diabetes	Yes	Yes	Yes	Yes	No	
Smoker	No	No	No	No	Former	
Hepatitis C	Negative	Negative	Negative	Negative	Negative	
HIV	Negative	Negative	Negative	Negative	Negative	
Cause of ESRD	DM, HTN	ADPKD, DM	HTN, Secondary FSGS	SLE	HTN	
CMV at time of transplant	Positive	Negative	Negative	Positive	Negative	
EBV at time of transplant	Positive	Positive	Positive	Positive	Positive	
Dialysis Type and Duration	HD, 20 months	HD, ~2 years	HD, 39 months	HD, ~12 years	HD, 35 months	
HLA Mismatch	2A 2B 1DR	2A 2B 2DR	2A 2B 1DR		2A 2B 1DR	
DSA at time of transplant	No	No	No	No	No	
Cold Ischemic Time (hours)	40	35	52	37	37	

	Donor A			Donor B		Donor C
	Thymoglobulin + Methylprednisolone	Thymoglobulin + Methylprednisolone	Thymoglobulin + Methylprednisolone	Alentuzumab + Methylprednisolone	Alentuzumab + Methylprednisolone	
Induction Immunosuppression	Tacrolimus + MPA	Tacrolimus + MPA	Tacrolimus + MPA	Tacrolimus + MPA + Prednisone	Tacrolimus + MPA	Thymoglobulin + Methylprednisolone
Initial Maintenance Immunosuppression	Yes	Yes	Yes	No	Yes	Tacrolimus + MPA
DTF	Yes	Yes	Yes	Yes	Yes	Yes
Hypertension after Transplant	Yes	Yes	Yes	Yes	Yes	Yes
Proteinuria after Transplant	Yes	Yes	Yes	Yes	Yes	Yes
Nadir Creatinine (mg/dL)	1.6	1.3	1.4	0.9	1.4	1.4
Post-transplant Complications	CMV viremia; borderline acute cellular rejection	CMV viremia and colitis; PCP pneumonia	BK viremia	Acute antibody-mediated rejection	CMV viremia	CMV viremia
Proteinuria at time of Biopsy	6.7g/g creatinine (2 months before biopsy)	7.6g/g creatinine (10 days before biopsy)	7.1g/g creatinine (day of biopsy)	3.4g/g creatinine	4+ (15g/g creatinine 2 days after biopsy)	4+ (15g/g creatinine 2 days after biopsy)
Creatinine at time of Biopsy (mg/dL)	3.7	2.9	5.7	2.7	6.4	6.4
Biopsy Timing Post-Transplant	14 months	14 months	21 months	19 months	7.5 months	7.5 months
Renal Outcome	HD initiated 17.5 months after transplant. Repeat transplant 26 months after initial transplant	HD initiated 14 months after transplant	HD initiated 22 months after transplant	HD initiated 23 months after transplant	Treated with IVIg, creatinine improved and was 1.1mg/dL 32 months after transplant	Treated with IVIg, creatinine improved and was 1.1mg/dL 32 months after transplant

BMI= body mass index; HIV= human immunodeficiency virus; CDC= Center for Disease Control; CMV= cytomegalovirus; EBV= Epstein-Barr virus, CVA= cerebrovascular accident; ICH= intracranial hemorrhage; KDPI= kidney donor profile index; ESRD= end-stage renal disease; HD= hemodialysis; DM= diabetes mellitus; HTN= hypertension; ADPKD= autosomal dominant polycystic kidney disease; PRA= panel reactive antibody; HLA= human leukocyte antigen; DSA= donor-specific antibody; MPA= mycophenolic acid; DGF= delayed graft function