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Expanding the spectrum of APOL1 related renal disease: De novo collapsing glomerulopathy following kidney transplant

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Abstract

Santoriello and colleagues report a series of 38 cases de novo collapsing glomerulopathy which developed following kidney transplant. Associations included acute rejection, viral infection and *APOL1* high risk genotype (the latter in nine cases). Risk factors for collapsing glomerulopathy included acute rejection, acute vaso-occlusive disease, and an African American donor. The data are suggestive of, but do not directly establish, a role for interferon in these associations.

In the current issue of *Kidney International*, Santoriello and colleagues report on the clinicopathologic and genetic characteristics of de novo collapsing glomerulopathy, also known as collapsing focal segmental glomerulosclerosis (FSGS), presenting following kidney transplant [1]. With regard to collapsing glomerulopathy, the authors use the terms *risk factors* (which can be defined as factors that are associated, but do not necessarily play an etiologic role), *causes* (which can be defined as factors that play an etiologic role), and *mediators* (which provide a direct etiologic link between a cause and an outcome). As a practical matter, given the uncertainties about disease mechanisms in collapsing glomerulopathy at the present time, these three terms may not convey meaningful differences in this context.

The case series involves 38 adult kidney transplant recipients who developed collapsing glomerulopathy following transplant between 2005 and 2017. The total number of patients who underwent renal transplant in the relevant medical centers during this time is likely unknowable, as renal biopsy cases may have included referral cases. The diagnosis was made at a median of 231 days following transplant, with an interquartile range of 14 to 1000 days; 55% were diagnosed within one year of transplant. The clinical picture at the time of kidney biopsy was one of severe nephrotic syndrome, with a median serum creatinine of 5.5 mg/dL, serum albumin 3.2 g/d, and urine protein 3.5 mg/dL. Atypically for collapsing glomerulopathy, only 18% had nephrotic syndrome; plausibly, this was due to current exposure to immunosuppressive medication and early detection of glomerular disease with periodic clinic visits.

The attributed causes among the 38 cases fell into two categories. First, five subjects had concurrent viral infections, including cytomegalovirus (CMV, three subjects), Epstein-Barr virus (EBV, one subject) and parvovirus B19 (one subject). Second, 11 subjects experienced

acute vaso-occlusive disease, with biopsy showing cortical necrosis, athero-embolization or thrombotic microangiopathy. One subject had both viral infection and vaso-occlusive disease, so that 15 collapsing glomerulopathy cases were attributed to these traditional etiologies. The remaining 23 subjects lacked acquired risk factors for collapsing glomerulopathy.

Recurrent collapsing glomerulopathy occurring following transplant had certain notable features. Individuals tended to be older and more likely to be European-American compared subjects in the literature with collapsing glomerulopathy in native kidneys. Collapsing glomerulopathy occurred relatively late, with the biopsy performed a median of 231 days following transplant. Established non-genetic causes of collapsing glomerulopathy were seen in 39%, including viral infection, chiefly cytomegalovirus (CMV) (13%), and acute vaso-occlusive disease (29%). Nephrotic range proteinuria was seen in 51%. Most subjects with collapsing glomerulopathy (61%) developed allograft failure, at a median of 8 months after the index biopsy. Repeat kidney biopsies were obtained in 25 cases. Remarkably collapsing glomerulopathy had resolved in 15 cases and these individuals maintained allograft function to the end of follow-up.

Of 34 cases for which donor *APOL1* genotypes were available, 9 cases were associated with *APOL1* high risk status, including 8 of 9 African American donors and 1 of 10 Hispanic American donors. The authors considered clinical factors that might synergize with this genetic risk for collapsing glomerulopathy. Concurrent acute allograft rejection was seen in 23 subjects, or 60% of the total group. Univariate analyses identified two additional clinic-pathologic associations: acute vaso-occlusive disease and ($p<0.05$) and allografts from kidney donors with two *APOL1* risk alleles ($p<0.04$).

All nine subjects with *APOL1*-associated collapsing glomerulopathy had substantial proteinuria, with a range of protein/creatinine ratio of 2–12 g/g. Compared to collapsing glomerulopathy in native kidneys, transplant-associated collapsing glomerulopathy were older, less likely to be African-American, have lower grade proteinuria, have higher serum albumin, have less viral infection (chiefly less HIV infection), and more vascular occlusive disease. Renal pathology in transplant-associated collapsing glomerulopathy showed less global glomerulosclerosis, less interstitial fibrosis and tubular atrophy and few tubular microcysts. These pathologic findings suggest that the disease was characterized at an earlier stage, which would make sense when these patients are being followed closely in the post-transplant setting. Nevertheless, allograft failure occurred in 24 patients (64%) at a median of 8 months following kidney biopsy, underscoring that collapsing glomerulopathy in any setting typically has a poor prognosis. Surprisingly, repeat biopsies in 25 patients showed resolution of collapsing FSGS changes in 15 patients and these individuals experienced favorable outcomes. Of these remitting patients, 13 patients had had potentially reversible causes of glomerular injury, including acute vaso-occlusion, acute rejection and viral infection.

Several recent publications have bearing on this case series. A case of de novo collapsing glomerulopathy occurring in an African American individual following kidney transplant has been reported; the individual was not tested for *APOL1* risk allele status [2]. Kalie and

colleagues reported a case of recurrent collapsing glomerulopathy occurred, remarkably, ten years following kidney transplant; there were no history of viral infection or rejection and both donor and recipients carried two *APOL1* risk alleles [3]. Kofman et al. reported on twins, with two *APOL1* risk alleles; the recipient developed FSGS and the living donor developed proteinuria [4]. Most recently, Chang and colleagues reported 5 cases of collapsing glomerulopathy occurring in recipients of renal allografts from deceased donors with two *APOL1* risk alleles [5]. In this series, cytomegalovirus and BK virus infections occurring in the recipients were implicated in one and three cases respectively.

Collapsing glomerulopathy has been associated with many factors, including autoimmune diseases, malignancies, medications (mTOR inhibitors) and interferon or conditions that stimulate interferon production (particularly viral infections, including HIV, cytomegalovirus, and possibly parvovirus 19 and EBV). A major genetic contributor to risk for collapsing glomerulopathy is genetic variation in *APOL1*, encoding apolipoprotein L1. *APOL1* renal risk variants are exclusively seen in individuals of African descent, and particularly common among those of West African descent, as first described in association with FSGS. The two renal risk variants are termed G1 and G2, encoding, respectively, an amino acid substitution (S239G) and a six base pair deletion, leading to loss of N388 and Y389. The common variant is termed G0. *APOL1* high risk status is defined as the carriage of two renal risk alleles (G1/G1, G2/G2 or G1/G2).

The phenotypes associated with these variants has continued to expand, as summarized in Table 1. As shown, the *APOL1* risk variants are associated with higher incidence of HIV-associated nephropathy and FSGS, arterionephrosclerosis, shortened renal allograft survival, faster progression of nephropathy in type 2 diabetes mellitus, and lupus nephritis. The effect is largely recessive, although a single copy effect was seen in the risk for HIV-associated nephropathy in South Africa [6].

FSGS and especially the related condition, collapsing glomerulopathy, are the conditions most strongly associated with the *APOL1* renal risk variants. Of all the glomerular phenotypes associated with *APOL1* high risk status, the most distinctive form, with the strongest statistical association (but not necessarily the most common form) is collapsing glomerulopathy. This is the glomerular disease characteristic of HIV-associated nephropathy (HIVAN), with which *APOL1* high risk status is associated with an odds ratio of 29 in the United States and 89 in South Africa [6]. In the latter clinical setting, the relationship between HIVAN (which in its most classic form is collapsing glomerulopathy) and *APOL1* high risk genotype is so strong that a single *APOL1* risk allele confers significant risk.

APOL1 renal risk alleles are powerful drivers of glomerulosclerosis. *APOL1* protein variants, as well as the *APOL1* RNA variants which code for the protein variants, may alter podocyte biology in various ways. Data derived from glomerular RNA from FSGS patients in the NEPTUNE study [7] and replicated in transgenic mice expressing *APOL1* in podocytes [8] suggests that *APOL1* variants increase the expression of the chemokines CXCL9 and CXCL11; how this might alter the podocyte phenotype or glomerular function is not known. The transgenic mice also showed increased endoplasmic reticulum stress. Data from cultured cells suggest additional pathways of injury, including alterations in trans-

cellular ion fluxes, mitochondrial function, increased elaboration of interleukin 1 β , and activation of protein kinase R.

Collapsing glomerulopathy emerges in another and somewhat surprising setting, in association with *APOL1* risk alleles. Among a 120 African Americans with membranous nephropathy, 23 (19%) had collapsing glomerulopathy compared to 4% of those with 1 risk allele and none for those with zero risk allele [9]. In membranous nephropathy, the disease process is triggered by autoantibody deposition, directed against autoantigens associated with membranous nephropathy, most commonly phospholipase receptor 2A. It may be that the *in situ* formation of antigen-antibody complexes triggers an inflammatory process, which leads to the local release of interferon. Thus, in lupus, antigen-antibody complexes activate plasmacytoid dendritic cells to release interferon.

The strongest disease association is between *APOL1* variants and collapsing glomerulopathy, suggesting that APOL1 variant proteins alter the biology of the parietal epithelial cells, which include a subpopulation that serve as precursors of the cells in Bowman space that appear in collapsing glomerulopathy. The mechanisms by which APOL1 variant proteins might affect the behavior of these cells remain to be uncovered. Plausibly, the same pathways by which APOL1 may injure podocytes may be operative in parietal cells.

Do the new data from Santoriello et al. and the similar reports reviewed above have bearing on decisions about renal transplantation involving subjects with high-risk *APOL1* genotypes? Recipient outcomes were the focus of new study, and as there no data on the number of kidney transplants performed during the 13-year period over which renal biopsies were analyzed at the multiple institutions involved, the risk for collapsing glomerulopathy cannot be quantified. Furthermore, the benefits of receiving a kidney transplant almost certainly outweigh the relatively low risk of glomerular disease occurring in the recipient of an *APOL1* two risk allele allograft. The more pressing issue involves long-term risk of chronic kidney disease for the living kidney donor, and this topic is the subject of a multi-center, NIH-funded study.

In conclusion, the newly-identified role of APOL1 variants in collapsing glomerulopathy in kidney transplants, in association with acute rejection, acute vascular disease and acute viral infection, but also in the absence of these factors, extends the range of settings in which this characteristic histologic pattern of APOL1 nephropathy presents.

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References

1. Santoriello D, et al., Clinical, pathological and APOL1 genotypic analysis of de novo collapsing glomerulopathy in renal allografts. *Kidney Int*, 2018 in press.

2. Patel AM, Zenenberg RD, and Goldberg RJ, De novo CMV-associated collapsing focal segmental glomerulosclerosis in a kidney transplant recipient. *Transpl Infect Dis*, 2018 20(3): p. e12884. [PubMed: 29570919]
3. Kalil RS, et al., Late Reoccurrence of Collapsing FSGS After Transplantation of a Living-Related Kidney Bearing APOL1 Risk Variants Without Disease Evident in Donor Supports the Second Hit Hypothesis. *Transplant Direct*, 2017 3(8): p. e185. [PubMed: 28795137]
4. Kofman T, et al., APOL1 polymorphisms and development of CKD in an identical twin donor and recipient pair. *Am J Kidney Dis*, 2014 63(5): p. 816–9. [PubMed: 24518129]
5. Chang JH, et al., Donor's APOL1 Risk Genotype and "Second Hits" Associated With De Novo Collapsing Glomerulopathy in Deceased Donor Kidney Transplant Recipients: A Report of 5 Cases. *Am J Kidney Dis*, 2018.
6. Kasembeli AN, et al., APOL1 Risk Variants Are Strongly Associated with HIV-Associated Nephropathy in Black South Africans. *J Am Soc Nephrol*, 2015.
7. Sampson MG, et al., Integrative Genomics Identifies Novel Associations with APOL1 Risk Genotypes in Black NEPTUNE Subjects. *J Am Soc Nephrol*, 2016 27(3): p. 814–23. [PubMed: 26150607]
8. Beckerman P, et al., Transgenic expression of human APOL1 risk variants in podocytes induces kidney disease in mice. *Nat Med*, 2017.
9. Larsen CP, et al., Histopathologic effect of APOL1 risk alleles in PLA2R-associated membranous glomerulopathy. *Am J Kidney Dis*, 2014 64(1): p. 161–3. [PubMed: 24731740]

Table 1.

APOL1 risk variant associations with renal disease states.

Condition	Associations	Odds ratio or annual eGFR decline differences among <i>APOL1</i> two risk allele carriers
HIV-associated nephropathy (collapsing glomerulopathy)	Prevalence Worse prognosis	29, 89
Focal segmental glomerulosclerosis	Prevalence Worse prognosis	17
Arterionephrosclerosis	Prevalence Worse prognosis	2.6
Lupus nephritis culminating in ESKD	Worse prognosis	2.7
Diabetic nephropathy	More rapid eGFR decline	−1.32 vs −1.0 ml/min/y
Kidney transplant recipient	Shortened allograft survival	2.0, 3.8

Legend. Shown are the odds ratios for various conditions, when the subjects have 2 APOL1 risk alleles compared to 0 or 1 risk alleles. When two values are shown, this indicates results from two studies.