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APOL1-Associated Collapsing Focal Segmental Glomerulosclerosis in a Patient With Stimulator of Interferon Genes (STING)-Associated Vasculopathy With Onset in Infancy (SAVI)

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Apolipoprotein L1 (APOL1) risk variants G1 and G2 are known to result in risk for kidney disease in patients of African ancestry. APOL1-associated nephropathy typically occurs in association with certain environmental factors or systemic diseases. As such, there has been increasing evidence of the role of interferon (IFN) pathways in the pathogenesis of APOL1-associated collapsing glomerulopathy in patients with human immunodeficiency virus (HIV) infection and systemic lupus erythematosus, 2 conditions that are associated with high IFN levels. Collapsing glomerulopathy has also been described in patients receiving exogenous IFN therapy administered for various medical conditions. We describe a patient with a genetic condition that results in an increased IFN state, stimulator of IFN genes (STING)-associated vasculopathy with onset in infancy (SAVI), who developed collapsing glomerulopathy during a flare of his disease. The patient was found to have *APOL1* G1 and G2 risk variants. This case supports the role of IFN in inducing APOL1-associated collapsing glomerulopathy.

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Introduction

Apolipoprotein L1 (APOL1), also known as the trypanolytic factor of human serum, confers protection against African trypanosomiasis.[1] Two commonly occurring risk variants in the *APOL1* gene (G1 and G2) result in significant increase in the risk for kidney disease among patients of recent African ancestry.[1,2] The renal histopathologic spectrum associated with APOL1-associated disease is heterogeneous and includes various patterns of disease, including focal segmental glomerulosclerosis; collapsing glomerulopathy, a histologic variant of focal segmental glomerulosclerosis; and nondiabetic kidney failure.[3-5]

APOL1 risk variants have incomplete penetrance, such that most patients carrying a high-risk genotype never develop meaningful kidney disease.[5,6] This observation, along with the frequent identification of environmental factors and systemic diseases in patients with APOL1-associated disease, has suggested the possibility of a "2-hit" scenario.[7] Commonly associated factors include human immunodeficiency virus (HIV) infection,[5] systemic lupus erythematosus,[4,8] and membranous glomerulopathy.[9] Additionally, APOL1-associated nephropathy has been described in patients undergoing interferon (IFN) treatment, and IFN-induced increase in podocyte expression of APOL1 has been shown in vitro.[10,11]

Stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) is a type I interferonopathy syndrome first described in 2014.[12] STING is a critical protein in type 1 IFN response to viral double-stranded DNA. In SAVI, gain-of-function mutations in *TMEM173*, the gene encoding STING, cause its activation, boosting synthesis of type 1 IFN.[12] Type I IFN then triggers a positive feedback loop leading to activation of Janus kinase 1 (JAK1) and signal transducers and activators of transcription 1 (STAT 1) and 2 (STAT 2), and transcription of proinflammatory IFN-stimulated genes.[12] Clinically, SAVI is characterized by neonatal-onset systemic inflammation, severe cutaneous vasculopathy, and interstitial lung disease.[12-14] Kidney involvement associated with SAVI has not been previously described.

We present a case of collapsing glomerulopathy in a patient with 2 *APOL1* risk alleles and endogenous overproduction of type 1 IFN secondary to SAVI in the absence of other systemic diseases or environmental factors.

Case Report

An African American boy, one of fraternal twins, presented at 4 weeks of age with swelling of a digit from his left hand. He subsequently developed multiple recurrent skin lesions, characterized by blisters that progressed to ulcers. Skin biopsy was performed, showing dermal perivascular and interstitial inflammation with vasculopathy. He also developed recurrent ischemic changes of his digits and toes. Initial laboratory evaluation showed persistently elevated levels of inflammatory markers and unexplained anemia (hemoglobin, 6.8-10.4 g/dL). He subsequently developed thrombocytopenia (platelet count, 36-130 $\times$ $10^3/\mu L$), elevated ferritin level (630-21,804 ng/mL), prolonged prothrombin time and partial thromboplastin time, and low fibrinogen level (1.06-1.80 g/L) that was concerning for macrophage activation syndrome.

The patient was initially treated with high-dose corticosteroids followed by a slow tapering dose and 0.5 mg/kg daily of sildenafil (3.7 mg per day), with partial response. He continued to develop skin lesions associated with high fevers and ischemic changes of his digits and had multiple

admissions to the hospital for suspected sepsis in an immunocompromised patient. He also had failure to thrive. At 7 months of age, he developed respiratory symptoms and was twice admitted to the hospital for pneumonia. Computed tomography of the chest showed diffuse parenchymal and interstitial abnormalities and findings suggestive of both acute and chronic inflammation.

The diagnosis of SAVI was made at the age of 8 months by targeted genetic testing of *TMEM173*, which showed a heterozygous variant predicted to lead to a valine to leucine substitution at amino acid 147 (V147L), which has been previously reported in SAVI.[1,2] Genetic testing for familial hemophagocytic lymphohistiocytosis (HLH), periodic fever syndromes, and deficiency of adenosine deaminase 2 was negative. Based on these findings, the patient was started on treatment with ruxolitinib, a JAK inhibitor, 1 mg twice daily. The development of new skin lesions became less frequent, as well as the frequency of hospitalizations. The ruxolitinib dose was increased to 2.5 mg and the patient did well for a few months before an acute episode of focal seizures. At that time, magnetic resonance imaging of the brain revealed multiple areas suggestive of gliosis in the superior vermis, occipital lobe, and right thalamus from a prior event such as ischemia. However, magnetic resonance angiography and magnetic resonance venography results were normal. An electroencephalogram was also unremarkable.

At the age of 14 months, the patient was admitted to the hospital for fevers and poor oral intake after routine immunizations (Pediarix [GlaxoSmithKline], pneumococcal, influenza, and *Haemophilus influenzae* type b). Before immunizations, his ruxolitinib treatment had been on hold for 11 days. During this hospitalization, he developed blisters and ulceration at the site of the immunizations, which later worsened and became more diffuse. He also had worsening digital ischemia leading to autoamputation. Workup for infection included blood culture; urine culture; a respiratory polymerase chain reaction panel that included influenza, parainfluenza, adenovirus, coronavirus, respiratory syncytial virus, rhinovirus, enterovirus, *Bordetella pertussis*, and *Mycoplasma pneumoniae*; and serologic testing for cytomegalovirus, Epstein-Barr virus, and parvovirus. This workup failed to show an infectious cause.

During this flare he developed generalized edema, proteinuria, and serum albumin level of 0.8 to 1.9 g/dL, consistent with nephrotic syndrome. Urinalysis showed protein (3+), and protein-creatinine ratio was 34 mg/mg. Before this hospitalization, he had had multiple urinalyses performed that had never shown proteinuria. He also developed high blood pressure, and treatment with 0.25 mg/kg daily of enalapril was started.

The patient was treated with methylprednisolone, 30 mg/kg daily, and treatment with ruxolitinib (2.5 mg twice daily) was restarted. He continued to have nephrotic-range proteinuria and a kidney biopsy was performed.

One core of renal cortex was available for light microscopy; this contained 23 glomeruli, 2 of which were globally sclerotic. Nonsclerotic glomeruli frequently showed collapse of the glomerular tuft associated with prominent epithelial cell hyperplasia and hypertrophy (Fig 1A and B). Reactive epithelial cells showed numerous cytoplasmic protein droplets. Additionally, focal glomeruli showed areas of segmental glomerulosclerosis. Otherwise, glomeruli showed no evidence of mesangial or endocapillary hypercellularity. Moderate interstitial fibrosis and tubular atrophy were present, involving 30% of the cortical surface. Mild mixed tubulointerstitial inflammation was noted predominantly within areas of scarring. Atrophic tubules showed a thyroidization pattern of atrophy, with focal microcystic tubular dilatation (Fig 1C and D). Nonatrophic tubules showed marked swelling of the tubular epithelium with large numbers of cytoplasmic protein resorption droplets. Arteries and arterioles were unremarkable.

Six glomeruli were available for immunofluorescence, none of which were globally sclerotic. All staining, including for immunoglobulin A (IgA), IgG, IgM, C3, C1q, fibrinogen, and κ and λ light chains, was negative within glomeruli (stains were obtained from Kent Laboratories, except those for fibrinogen and κ and λ light chain, which were from Agilent). For IgG and κ and λ light chain, the proximal tubule protein resorption droplets stained strongly positive.

Ultrastructural examination of a glomerulus using electron microscopy showed uniform glomerular basement membranes of normal thickness. No immune electron-dense deposits were present. Epithelial foot processes were moderately effaced, involving 30% of available capillary loops. Few endothelial tubuloreticular inclusions were noted. Tubular basement membranes were unremarkable (Fig 1E and F). Two glomeruli were examined using electron microscopy and both showed a similar degree of epithelial foot-process effacement.

DNA from the patient's peripheral blood was genotyped for *APOL1* risk alleles using TaqMan primer/probe custom design assays as previously described.[4] One of the G1 risk variants (rs73885319, encoding a serine to glycine substitution at amino acid 342) and the G2 risk variant (the insertion/deletion encoded by rs71785313) showed compound heterozygosity.

Discussion

This case of a patient heterozygous for the G1 and G2 risk alleles of *APOL1* who has a high IFN state due to his underlying condition of SAVI provides further support for IFN as an inducer of collapsing glomerulopathy in individuals with the *APOL1* high-risk genotype. IFNs are molecules secreted in response to pathogens, and their production results in an inflammatory state. As such, patients with type 1 interferonopathies who are affected by the upregulation of type I IFN signaling have persistent systemic inflammation. There is a growing body of evidence implicating IFN pathways in the pathogenesis of APOL1-associated collapsing glomerulopathy. Collapsing

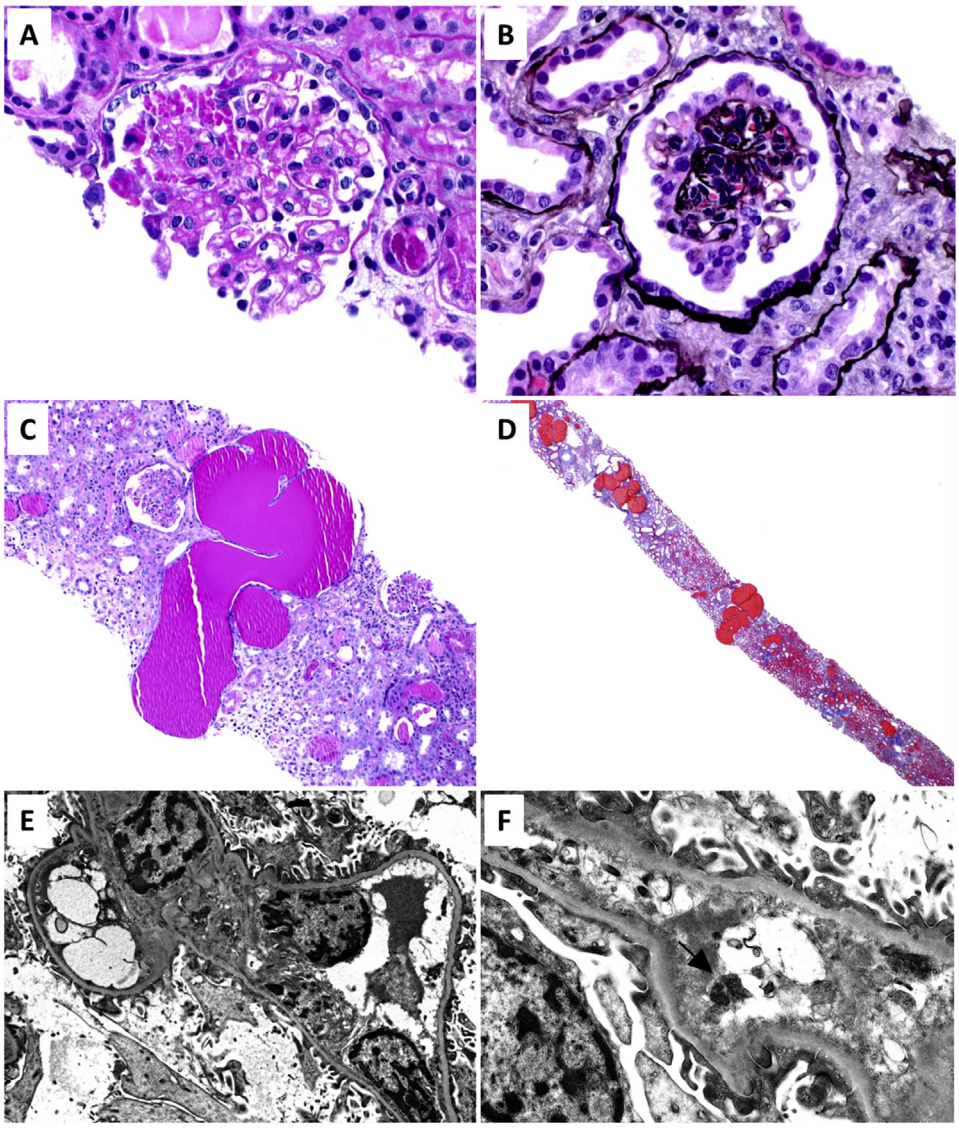

Figure 1. Collapsing glomerulopathy. (A, B) Collapse of the glomerular tuft associated with prominent epithelial cell hyperplasia and hypertrophy (A: periodic acid–Schiff; B: Jones methenamine silver; A, B: original magnification, ×400). (C, D) Tubulointerstitial changes with microcystic tubular dilatation, moderate interstitial fibrosis and tubular atrophy, and mild mixed interstitial inflammation (C: periodic acid–Schiff; original magnification, ×100; D: Masson trichrome; original magnification, ×20). (E, F) Uniform glomerular basement membranes with segmental epithelial foot-process effacement. At high magnification, endothelial tubuloreticular inclusions are seen (arrow) (E, unstained; original magnification, ×8,000; F, unstained; original magnification, ×18,000).

glomerulopathy is the most fulminant histopathologic form of APOL1-associated nephropathy. This form of glomerulopathy is well known to be associated with diseases that have increased IFN levels, such as HIV infection and systemic lupus erythematosus.[4,5,9,15]

Additionally, exogenous IFN therapy, administered for various medical conditions, has been shown to be associated with collapsing glomerulopathy in a case series of 11 patients.[10] Among these patients, all 7 tested were homozygous for *APOL1* risk variants.[11] Regardless of the associated conditions, kidney biopsies from patients with APOL1-associated nephropathy frequently show solidified and disappearing-type glomerulosclerosis, thyroidization type of tubular atrophy, and microcystic tubular dilation.[3] Some of these features are evident in the case under discussion.

In vitro, IFNs increase APOL1 expression up to 200-fold. This is pertinent because overexpression of APOL1 has been shown to be injurious to cells both in cell culture and an animal model.[11,16,17] Notably, overexpression of APOL1 risk variants is more injurious to cells than overexpression of the wild-type protein. Together, these studies demonstrate an association between increased IFN levels and APOL1-associated nephropathy.[4]

It is worth noting that although the presented case highlights the potential of IFN to cause podocyte injury, the severity of foot-process effacement in the examined

glomeruli was discrete. Studies of patients with collapsing glomerulopathy in various clinical settings have shown significant variability in the degree of foot-process effacement, with 15% to 62% of patients having absence of severe effacement by electron microscopy.[18,19]

We report a case of APOL1-associated nephropathy in the setting of the genetic disease SAVI, a type I interferonopathy syndrome, which raises the possibility of increased risk for kidney disease in African American patients with this disease. In addition, this case further establishes the pathogenic role of IFN in patients with 2 *APOL1* risk alleles. Similar to patients with exogenous IFN therapy, this patient with a condition that leads to increased endogenous IFN levels developed the most fulminant form of APOL1-associated nephropathy, collapsing glomerulopathy.

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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):841-845.
2. Tzur S, Rosset S, Shemer R, et al. Missense mutations in the APOL1 gene are highly associated with end stage kidney disease risk previously attributed to the MYH9 gene. *Hum Genet*. 2010;128(3):345-350.
3. Larsen CP, Beggs ML, Saeed M, et al. Histopathologic findings associated with APOL1 risk variants in chronic kidney disease. *Mod Pathol*. 2014;28(1):95-102.
4. Larsen CP, Beggs ML, Saeed M, Walker PD. Apolipoprotein L1 risk variants associate with systemic lupus erythematosus-associated collapsing glomerulopathy. *J Am Soc Nephrol*. 2013;24(5):722-725.
5. 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):2129-2137.
6. Dummer PD, Limou S, Rosenberg AZ, et al. APOL1 kidney disease risk variants: an evolving landscape. *Semin Nephrol*. 2015;35(3):222-236.
7. Freedman BI, Skorecki K. Gene-gene and gene-environment interactions in apolipoprotein L1 gene-associated nephropathy. *Clin J Am Soc Nephrol*. 2014;9(11):2006-2013.
8. Freedman BI, Langefeld CD, Andringa KK, et al. End-stage renal disease in African Americans with lupus nephritis associated with APOL1. *Arthritis Rheumatol*. 2014;66(2):390-396.
9. Larsen CP, Beggs ML, Walker PD, Saeed M, Ambruzs JM, Messias NC. Histopathologic effect of APOL1 risk alleles in PLA2R-associated membranous glomerulopathy. *Am J Kidney Dis*. 2014;64(1):156-163.
10. Markowitz GS, Nasr SH, Stokes MB, D'Agati VD. Treatment with IFN-α, -β, or –γ is associated with collapsing focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol*. 2010;5(4):607-615.
11. Nichols B, Jog P, Lee JH, et al. Innate immunity pathways regulate the nephropathy gene apolipoprotein L1. *Kidney Int*. 2015;87(2):332-342.
12. Lui Y, De Jesus AA, Marrero B, et al. Activated STING in a vascular and pulmonary syndrome. *N Engl J Med*. 2014;371(6):507-518.
13. Munoz J, Rodiere M, Jeremiah N, et al. Stimulator of interferon genes-associated vasculopathy with onset in infancy: a mimic of childhood granulomatosis with polyangiitis. *JAMA Dermatol*. 2015;151(8):872-877.
14. Eroglu FK, Gursel I, Gursel M, et al. STING-associated vasculopathy with onset in infancy: new clinical findings and mutation in three Turkish children. *Pediatr Rheumatol Online J*. 2015;13(suppl 1):O85.
15. Cossey LN, Larsen CP, Liapis H. Collapsing glomerulopathy: a 30-year perspective and single, large center experience. *Clin Kidney J*. 2017;10(4):443-449.
16. Olabisi OA, Zhang JY, VerPlank L, et al. APOL1 kidney disease risk variants cause cytotoxicity by depleting cellular potassium and inducing stress-activated protein kinases. *Proc Natl Acad Sci U S A*. 2015;113(4):830-837.
17. Beckerman P, Bi-Karchin J, Park AS, et al. Transgenic expression of human APOL1 risk variants in podocytes induces kidney disease in mice. *Nat Med*. 2017;23(4):429-438.
18. Salvatore SP, Barisoni LMC, Herzenberg AM, Chander PN, Nickeleit V, Seshan SV. Collapsing glomerulopathy in 19 patients with systemic lupus erythematosus or lupus-like disease. *Clin J Am Soc Nephrol*. 2012;7(6):914-925.
19. Laurinavicius A, Hurwitz S, Rennke HG. Collapsing glomerulopathy in HIV and non-HIV patients: a clinicopathological and follow-up study. *Kidney Int*. 1999;56(6):2203-2213.