INTRODUCTION

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide, contributing significantly to the socioeconomic burden of end-stage renal disease. Immune complexes formed by IgG autoantibodies against galactose-deficient IgA1 molecules deposit in the glomerular mesangium, triggering an immune reaction that causes kidney fibrosis and end-stage renal disease in 15% to 40% of patients within 30 years of diagnosis. IgAN classically presents in the second to third decades of life as macroscopic hematuria following an upper respiratory infection, or as subnephrotic range proteinuria and microscopic hematuria. Pathology of IgAN shows mesangial expansion, hypercellularity, and pathognomonic IgA immune complexes in the mesangium and along glomerular capillary walls. Standard of care treatment for IgAN is renin-angiotensin-aldosterone-system blockade to decrease proteinuria and prevent disease progression. For patients with persistent proteinuria despite renin-angiotensin-aldosterone-system inhibition, administration of steroids or other immunosuppressive agents are sometimes indicated.

The genetic factors predisposing an individual to IgAN are incompletely understood. Genome-wide association studies have identified nearly 20 loci for IgAN, but specific genes have yet to be determined. Notably, there is no known association between IgAN and high-risk apolipoprotein L1 (APOL1) genetic variants, which are strongly associated with many causes of nondiabetic chronic kidney disease, including collapsing focal segmental glomerulosclerosis (FSGS), HIV-associated nephropathy, lupus nephritis, and COVID-associated nephropathy. Here, we present a unique case of IgAN and FSGS in an individual who is homozygous for the high-risk G1/G1 APOL1 variant.

CASE PRESENTATION

A 50-year old woman of African ancestry with a 5-year history of hypertension, obesity (body mass index 41.45 kg/m²), 20-year history of psoriasis, and psoriatic arthritis, with a prior poor response to etanercept and adalimumab. The patient had been on biweekly brodalimumab for 2 years with interim complete resolution of active skin lesions, and was referred to nephrology for chronic kidney disease stage 3a (creatinine 1.44 mg/dl, estimated glomerular filtration rate 50 ml/min) with microscopic hematuria and subnephrotic range proteinuria (0.3–1.3 g/day).

At the time of nephrology evaluation, her Psoriasis Area and Severity Index was zero, with only post-inflammarry hyperpigmentation noted by her dermatologist. There was no axial spondylarthritis, but she had diffuse low-grade pain in her knees, hips, shoulders, hands and wrists, which were relieved with acetaminophen. The patient endorsed occasional frothy urine, but denied gross hematuria and periorbital or lower extremity edema. She underwent serological work-up, which was unrevealing as follows: negative phospholipase A1 antibodies, negative antineutrophil cytoplasmic antibodies, negative antiglomerular basement membrane antibodies, negative antinuclear antibodies, negative hepatitis B and C virus, and negative human immunodeficiency virus. Glycosylated hemoglobin was
5.6% and lipid panel revealed elevated total cholesterol of 219 mg/dl; and elevated low-density lipoprotein of 129 mg/dl.

With increasing proteinuria, the decision was made to perform a kidney biopsy. At the time of biopsy, she had a spot urine protein-to-creatinine ratio of 3.0 g/g, serum albumin of 3.1 g/dl, serum creatinine of 1.52 mg/dl, and blood urea nitrogen of 35 mg/dl. Urinalysis showed 4–10 red blood cells per high power field. Her erythrocyte sedimentation rate ranged 78 mm/h (reference range 0–24 mm/h) and C reactive protein level 5.4 mg/l (reference range <5.1 mg/l). Her biopsy had 17 glomeruli on light microscopic analysis, of which 7 were completely sclerosed. Two glomeruli showed segmental sclerosis and one had a fibrous crescent. Nonsclerosed glomeruli showed mild mesangial expansion and hypercellularity without evidence of endocapillary proliferation or necrosis. There was patchy interstitial fibrosis and tubular atrophy.
comprising 20% to 30% of the cortex. There was evidence of arteriosclerosis with mild and focal prominent hyalinosis. Immunofluorescence microscopy of one nonsclerosed glomerulus revealed granular mesangial staining for IgA (3+), C3 (3+), IgG (1+), fibrinogen (1+), kappa (1+), and lambda light chains (2+). Electron microscopy showed scattered immune-type electron dense deposits in mesangial and paramegansla areas, as well as patchy podocyte foot process effacement (Figure 1). The patient had a Renasight kidney gene panel by Natera and was found to be a homozygous carrier of the high risk G1 APOL1 variant (G1/G1) (1024A>G; 1152T>G; Ser342Gly; Ile384Met).

The patient was diagnosed with IgAN, Oxford criteria M1, E0, S1, T1, C1. Current management of her IgAN includes continuation of valsartan-hydrochlorothiazide, and the more recent additions of spironolactone and dapagliflozin. Her most recent serum albumin was 4.3 g/dl, and blood urea nitrogen and serum creatinine were 32 mg/dl and 1.65 mg/dl, respectively. Her most recent urine studies showed 3 to 10 red blood cells per high power field, urine protein-to-creatinine ratio of 137 mg/g and microalbumin-to-creatinine ratio of 43 mg/g, demonstrating a notable improvement in urinary protein loss (Figure 2).

**DISCUSSION**

This case presents an individual who is homozygous for the high-risk G1/G1 APOL1 variant with biopsy proven IgAN and secondary FSGS. The histopathology strongly suggests IgAN as the predominant disease, with mesangial expansion and hypercellularity as well as 3+ IgA mesangial deposits. Her clinical presentation is also typical of IgAN, with hypertension, subnephrotic proteinuria, and microscopic hematuria. The absence of a known association of IgAN with high-risk APOL1 genotypes makes this case noteworthy.

Though specific disease-causing genes are yet to be identified, IgAN is known to have a strong hereditary component. In patients with a genetic predisposition, secondary triggers, including environmental factors and comorbid conditions, are believed to play a role in the clinical manifestations of IgAN. This patient’s history of psoriasis and psoriatic arthritis are strong risk factors for the development of IgAN, although the exact pathophysiology behind this association remains unclear. One theory postulates that a defective host response to mucosal infections predisposes patients to both IgAN and psoriasis. Another suggests that overactivation of humoral and cellular immunity in patients with psoriasis triggers the clinical manifestations of an otherwise subclinical IgAN. The patient’s prior use of 2 tumor necrosis factor alpha inhibitors, adalimumab and infliximab, for treatment of psoriasis is another purported risk factor. With tumor necrosis factor alpha inhibitor use, aberrant IgA molecules cross-react with antidrug antibodies, forming complexes that deposit in the mesangium. Overall, in the context of psoriasis, the IgAN is considered a secondary disease.

This patient’s biopsy reveals histologic evidence of concurrent FSGS, which has been shown to confer worse prognosis in patients with IgAN. In one cohort study, subjects with mild IgAN (grade 1 or 2) and concurrent FSGS had significantly greater proteinuria at time of biopsy, and histology demonstrated significantly more obsolete glomeruli, tubular atrophy and interstitial fibrosis compared to control subjects with mild IgAN and no concurrent FSGS. After a 3-year follow up period, these subjects had a significantly faster decline in estimated glomerular filtration rate compared to controls. This patient is homozygous for the high-risk G1/G1 APOL1 alleles, a known risk factor for the development of FSGS. APOL1 is not completely penetrant and a secondary insult is required for development of the disease.
Interferon-γ, one of the main drivers of APOL1 associated kidney disease, is upregulated in psoriasis or psoriatic arthritis and likely served as a second hit promoting the development of APOL1 associated FSGS in this case. Elevated levels of inflammatory biomarkers (erythrocyte sedimentation rate and C reactive protein) and persistent arthritic symptoms support the likelihood of an underlying inflammatory milieu precipitating podocyte injury in the presence of high risk APOL1 variants.

In conclusion, to our knowledge this case is the first report of APOL1 associated kidney disease in a patient with concurrent secondary IgAN. The findings reinforce the need to better understand the pathogenesis of APOL1 nephropathy, an evolving clinical entity for which targeted therapeutics are being developed (Table 1).

### DISCLOSURE

KNC reports consulting fees from Travere, Goldfinch, ANI, Chinook and grants from Aurinia, outside the submitted work. All the other authors declared no competing interests.

### PATIENT CONSENT

Written consent was obtained from the patient for publication of the information about her that appears within this Case Report.

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