Obesity-related glomerulopathy in the presence of APOL1 risk alleles

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SUMMARY

Nephropathic apolipoprotein L1 (APOL1) risk alleles (G1/G2) have been associated with focal segmental glomerulosclerosis, HIV-associated nephropathy, Systemic lupus erythematosus (SLE)-associated collapsing glomerulopathy and other glomerulonephritides. These alleles confer protection from *Trypanosoma brucei* infections which are enriched in sub-Saharan African populations. We present a young woman with obesity, hypertension, subnephrotic range proteinuria who was found to have obesity-related glomerulopathy on kidney biopsy while harbouring two high-risk APOL1 alleles (G1/G2). Given the potential effects on lipid metabolism and their association with obesity, the presence of APOL1 risk alleles may impact cardiovascular health in addition to renal disease in these patients.

BACKGROUND

The term obesity-related glomerulopathy (ORG) was first coined in 2001 by D'Agati and colleagues when the incidence of this entity was found to have increased 10-fold from 1986 to 1990 to 1996–2000.[1] Morphologically, the renal tissue is found to have glomerulomegaly with or without focal segmental glomerulosclerosis (FSGS). Clinically, patients with ORG had a lower incidence of nephrotic range proteinuria and nephrotic syndrome, higher serum albumin, lower serum cholesterol and less oedema. We describe a case report of a young woman with obesity, hypertension (HTN) and ORG discovered on renal biopsy who was later found to harbour the apolipoprotein L1 (APOL-1) high-risk alleles (G1/G2). We discuss how these alleles may affect not only her renal outcome but also her cardiovascular health.

CASE PRESENTATION

We present a young woman in her 30s with a history of HTN for 7 years, hyperlipidaemia and obesity (body mass index (BMI) 32 kg/m^2) who was referred to the nephrology clinic for the evaluation of proteinuria and lower extremity oedema. Of note, the patient's obstetric history reveals G7P3225 with a third pregnancy that was complicated by superimposed pre-eclampsia at age 25, which led to the diagnosis of chronic HTN in the post-partum period. An evaluation for secondary causes of HTN including hyperaldosteronism, pheochromocytoma and hyperthyroidism was unrevealing. The patient also denied a history of premature birth or low birth weight for herself, although noted frequent urinary tract infections as a child but was never further evaluated. Her family history was significant for her mother who developed HTN in the mid-20s, her maternal grandmother who experienced a cerebrovascular accident at the age of 40 and her maternal grandfather who died of end-stage kidney disease (ESKD) of unknown aetiology. Her medications included atorvastatin 10 mg daily and nifedipine 60 mg daily. Physical examination revealed a blood pressure of 150/100 mm Hg, clear lungs, normal cardiac and abdominal examinations, but bilateral 2+ lower extremity pitting oedema. Infectious workups including HIV, hepatitis B and hepatitis C were non-reactive. Comprehensive autoimmune workups including Anti-nuclear antibody (ANA), C3, C4 and antibodies for ds-DNA, Smith, SCL-70, Jo 1, centromere, histone, anti–Sjögren's-syndrome-related antigen A autoantibodies(SSA), anti-Sjögren's syndrome type B (SSB), ribonucleoprotein, myeloperoxidase and proteinase-3 were negative. The remaining laboratory studies are listed in table 1. Given the subnephrotic range proteinuria with negative serological testing, a kidney biopsy was performed.

On light microscopy, 1 out of 12 glomeruli was globally sclerotic, 1 showed segmental wrinkling of basement membranes, while the remaining 10 were mildly enlarged and normocellular (figure 1A). The glomerular basement membranes appeared normal in thickness and contour. Tubular atrophy and interstitial fibrosis affected 5% of the cortex and were accompanied by patchy chronic interstitial inflammation comprised of plasma cells, lymphocytes and mononuclear leucocytes (figure 1B). Immunofluorescence staining was negative for IgG, IgM, IgA, C1, C3, kappa and lambda (figure not shown). On electron microscopy, glomerular basement membranes showed segmental thickening (figure 1C). No immune-type electron-dense deposits or endothelial cell tubuloreticular inclusions were seen. Podocytes demonstrated 5% foot process effacement. The final diagnoses were mild focal global glomerulosclerosis with glomerulomegaly with mild tubular atrophy and interstitial fibrosis. The findings of glomerulomegaly indicated glomerular hypertension/hyperfiltration, which may be related to obesity, HTN and/or reduced nephron number.

DIFFERENTIAL DIAGNOSIS

Glomerulomegaly related with either obesity, HTN and/or reduced nephron number.

TREATMENT

We encouraged healthy weight loss and a referral to a weight management clinic. The patient was maintained on losartan and atorvastatin was increased to 40 mg daily. Her blood pressure remained below 140/90 mm Hg on clinic follow-up.

Table 1 Laboratory parameters

| Laboratory variable	Laboratory value (normal range if applicable)
Blood urea nitrogen (BUN)	10 (5–26 mg/dL)
Creatinine	1.1 (0.6–1.2 mg/dL)
e*stimated glomerular filtration rate (eGFR)	65 (82–137 mL/min/1.73 m^2)
Albumin	4.4 (3.5–5.5 g/dL)
Total cholesterol	239 (120–220 mg/dL)
Low-density lipoprotein (LDL)	140 (70–160 mg/dL)
High-density lipoprotein (HDL)	68 (36–77 mg/dL)
Triglycerides	155 (35–135 mg/dL)
Urinalysis	Clear, negative glucose, >300 protein, trace leucocyte esterase, negative nitrite, pH 5.5, specific gravity 1.025, red blood cells 31, no blood, bacteria 1+, white blood cells 15 hpf
Urine microscopy	No cells or casts
Urine protein/creatinine ratio	2368 mg/g

Renal biopsy report.
*eGFR calculated by the CKD-EPI formula.[30]

OUTCOME AND FOLLOW-UP

Four months post-renal biopsy, the patient's urine protein-creatinine ratio decreased to 1618 mg/g (from 2368 mg/g before biopsy). Her Low-density lipoprotein (LDL) remained above target at 96 mg/dL. We increased losartan to 100 mg daily to minimise proteinuria and to target blood pressure to be below 130/80 mm Hg, and increased atorvastatin to 20 mg daily for a more aggressive lipid-lowering effect.

DISCUSSION

Apolipoprotein L1 (APOL1) is one of the six members of apolipoprotein L, encoded in chromosome 22.[2] APOL1 is an High-density lipoprotein (HDL)-associated protein that was described in several organs, including the pancreas, lung, liver, spleen and prostate.[3–5] In the kidneys, APOL1 is localised to podocytes and proximal tubules.[6]
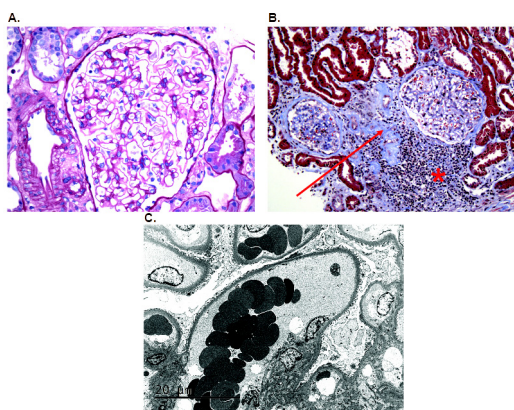
Figure 1 (A) A representative glomerulus that is enlarged and normocellular. The glomerular basement membranes appeared normal in thickness and contour (H&E, ×40). (B) The cortex demonstrated 5% tubular atrophy and interstitial fibrosis (red arrow) which was accompanied by patchy chronic interstitial inflammation comprised of plasma cells, lymphocytes and mononuclear leucocytes (red asterisk) (H&E, ×20). (C) By electron microscopy, glomerular basement membranes showed segmental thickening with 5% foot process effacement. No immune-type electron-dense deposits or endothelial cell tuboreticular inclusions were seen (electron micrograph, ×3000).

The evolution of APOL1 variants, G1 (S342G and I384M mutations) and G2 (deletion of amino acids N388 and Y389), confer protections against *Trypanosoma brucei* infections which cause sleeping sickness in sub-Saharan Africa.[7] The HDL-associated APOL1 is taken up by trypanosomes through the endocytic pathway to the lysosome, leading to pore formation, chloride influx, osmotic swelling and eventual lysis of trypanosomes.[8] Through natural selection, these alleles are commonly identified in Black Americans but rare in European Americans.[9] Approximately one-third of Black Americans possess one high-risk *APOL1* allele and 15% have two of these alleles. While the APOL1 G1 and G2 alleles protect against trypanosomiasis, they increase the risk of various kidney diseases by mechanisms that remain currently unknown.

The *APOL1* gene follows a recessive genetic model. Therefore, possession of two high-risk alleles leads to an increased rate of Chronic kidney disease (CKD) progression and ESRD compared with zero or one copy.[10] These risk alleles are also associated with increased risks of primary FSGS,[11] HIV-associated nephropathy,[11] lupus nephritis,[12] SLE-associated collapsing glomerulopathy,[13] PLA2R-associated membranous glomerulopathy,[14] non-diabetic CKD[15] and hypertension-associated ESKD.[9]

Obesity is an independent risk factor for the development of CKD after adjusting for diabetes and HTN.[16] ORG is characterised by variable proteinuria although usually subnephrotic, with the absence of oedema and hypoalbuminemia, even in cases with massive proteinuria.[17] Pathologically, there is glomerulomegaly with or without FSGS lesions, with less extensive foot process effacement as compared with idiopathic FSGS.[1] Single-nephron hyperfiltration is observed in early stages of CKD in patients with ORG compared with obese and non-obese controls.[18] Glomerulomegaly is thought to be a compensatory response to single-nephron hyperfiltration.[18] The hyperfiltration leads to increased proximal tubular sodium reabsorption.[19] This leads to a decrease in the solute delivery to the macula densa, leading to afferent arteriolar dilation and glomerular hyperfiltration.[20] Additionally, adipose tissues have their intrinsic renin-angiotensin-aldosterone (RAAS) system, independent of the kidneys.[21] The overactivation of the RAAS system associated with obesity also increases sodium and water reabsorption at the proximal tubules, further potentiating glomerular hyperfiltration. This increases tensile stress in the glomerular capillaries, leading to expansion of the glomerular basement membrane and hypertrophy of the overlying podocytes.[22] Eventually, these stressed podocytes undergo detachment and cell death.[22] The long-term outcome of ORG is ESRD.[1 23] Patients with ORG have low glomerular density and a reduced number of functioning nephrons, which are implicated in CKD progression in this population.[18] The mainstay treatment for ORG includes weight loss and the use of renin-angiotensin blockers.[17]

Not all obese patients develop ORG, a cross-sectional study of renal biopsies of morbidly obese patients revealed that only 12% of biopsies develop this entity,[24] begging the question of which factors are contributory. With our emerging understanding of APOL1 risk alleles, obesity may serve as a 'second hit'' to develop ORG. Moreover, APOL1 risk alleles may be associated with increased cardiovascular and metabolic derangements. A higher prevalence of obesity, high LDL cholesterol, uncontrolled HTN and left ventricular hypertrophy was found in African American children with two high-risk APOL1 alleles and FSGS as compared with those with zero or one risk variant, despite treatment with antihypertensives and adjustment for indicators of socioeconomic status.[25] Both the Jackson Health Study and

Patient's perspective

I did not realize that my body weight can affect the kidneys. I will try my best to lose weight and eat a healthy diet for a better outcome.

Learning points

► Obesity may act as a 'second hit' in patients with two APOL-1 risk alleles to develop obesity-related glomerulomegaly (ORG).
► The presence of APOL-1 risk alleles is associated with metabolic and cardiovascular abnormalities.
► The treatment of ORG in the setting of two APOL-1 risk alleles may need to include aggressive lipid control in addition to weight loss and renin-angiotensin blockade.
► Understanding the mechanism of APOL-1 G1/G2 variants in cardiovascular and renal disease pathogenesis is paramount to unlocking potential treatment strategies to prevent cardiac and renal failure.

the Women's Health Initiative found that adult participants with two high-risk APOL1 alleles had an increased cardiovascular disease risk after correcting for traditional risk factors and CKD as compared with those without the high-risk alleles.[26] High-risk variants were associated with BMI and obesity in an additive manner in a genotype-phenotype association study.[27] Since APOL1 is an important component of HDL 3 particles that attenuate LDL oxidation, it may play a role in reverse cholesterol transport. APOL1 risk alleles, on the other hand, have been found to impair reverse cholesterol transport through decreased expression of cholesterol efflux transporters.[28] Thus, APOL1 risk variants might promote foam cell formation and the growth of a necrotic core with increased plaque instability. Indeed, patients with two high-risk alleles have demonstrated larger necrotic cores with greater plaque areas that are enriched for APOL1.[29] These epidemiological and histopathological studies pose an intriguing link between high-risk APOL1 alleles and metabolic/cardiovascular abnormalities which need to be further studied.

To our knowledge, this is the first case showing the association between APOL1 risk alleles and ORG. Given the substantial morbidity and mortality from the combination of cardiovascular disease and CKD, knowledge of APOL1 risk allele status may help to better stratify cardiovascular and renal risks to help guide clinical care. In particular, aggressive control of hyperlipidaemia should be emphasised in these patients, in addition to weight loss and the use of renin-angiotensin blockers.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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