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On the Cover

What's the diagnosis? A 26-year-old man with lower extremity edema was referred to nephrology clinic for evaluation of 5.2 grams proteinuria. Past medical history was significant for multiple urinary tract infections as a child and hypertension diagnosed at age 19. Laboratory data were remarkable for a creatinine of 1.47 mg/dl, with an estimated GFR of 58 ml/min per 1.73 m². Urinalysis demonstrated 3+ protein and 3+ blood. Urine sediment revealed 5-10 monomorphic red blood cells per high power field without cellular casts. Serum complement levels were normal and tests for dsDNA, ANA, ANCA, HIV, HBV and HCV were negative. Native kidney biopsy showed focal segmental glomerular sclerosis and numerous interstitial foam cells on light microscopy (upper panel, Masson trichrome stain). Routine immunofluorescence microscopy demonstrated no staining for immunoglobulin or complement. Electron microscopy revealed podocyte foot process effacement and diffuse thickening and splitting of the lamina densa of the glomerular basement membrane (lower panel), indicative of Alport syndrome. Diagnosis was confirmed with immunofluorescence microscopy that showed absence of alpha-5 chains of type IV collagen. Alport syndrome is a basement membrane disorder arising from mutations in genes encoding type IV collagen and is often associated with sensorineural hearing loss and ocular abnormalities. The initial renal presentation is usually asymptomatic hematuria starting in childhood which progresses to proteinuria, HTN and CKD. Rare patients present with nephrotic syndrome. Light microscopy typically shows varying degrees of focal segmental and global glomerular sclerosis that can mimic FSGS. The presence of numerous interstitial foam cells is observed most often with Alport syndrome; however, foam cells also occur in patients with other causes for nephrotic syndrome, although much less often and less numerous. Characteristic glomerular basement membrane ultrastructural features with absence of immunostaining for collagen IV alpha 5 chains allows a definitive diagnosis. (Image and text provided by Fernanda Payan Schober, MD, University of North Carolina Chapel Hill, Nephrology and J. Charles Jennette, MD, University of North Carolina Chapel Hill, Pathology and Laboratory Medicine)