Focal and Segmental Glomerulosclerosis—Are We There Yet?

Focal and segmental glomerulosclerosis (FSGS) has been increasing in incidence over several decades. It is the underlying cause of nephrotic syndrome in 40% of adults and 20% of children and is the most common primary glomerular lesion resulting in end-stage kidney disease in the United States.[1] FSGS is not a single disease but a morphologic pattern of injury that develops from a wide range of etiologies. The terminology refers to the pattern of scarring in the glomerulus (glomerulosclerosis), which is focal (involving only a portion of the glomerular population) and segmental (affecting only a portion of the glomerular tuft). It should be noted that the fraction of glomeruli affected is determined on standard sectioning of a biopsy specimen and that when serial sectioning is performed to give a 3-dimensional assessment of the glomeruli, the percentage of involved glomeruli significantly increases.[2]

As FSGS reflects diverse causes of injury, the classification of FSGS has always been contentious. A morphologic classification proposed by the Columbia group subdivides the diagnosis of FSGS according to specific pathologic light microscopic findings (tip lesion, cellular, collapsing, perihilar, and not otherwise specified) and is widely used in practice.[3] In contrast, clinicians have often used a classification based more on etiology, rather than morphology. In this etiologic classification, FSGS often is considered as having primary and secondary forms.[4] Primary FSGS is considered a consequence of podocyte injury because of external circulating or other factors, often causing nephrotic syndrome. Secondary forms have many etiologies, including glomerular adaptive changes to hyperfiltration or mechanical stress, drugs, infections, genetic mutations, and metabolic disturbances, and patients tend to be non-nephrotic. The podocyte is thought to be the key participant in the development of glomerular segmental sclerosis either because of primary or secondary factors.[5] The clinical phenotype, morphologic appearance, and response to treatment are variable, depending on the underlying injury, extent of damage, and genotype of the individual.

This issue of *Advances in Chronic Kidney Disease* focuses on our current state of knowledge in FSGS, with its heterogeneous etiologies and clinical challenges. Careful morphologic studies in experimental models by Wilhelm Kriz initially highlighted the central role of podocyte injury in the development of FSGS,[6] and more recently, classical studies using targeted depletion of podocytes have confirmed that podocyte loss above a certain threshold (~20% of podocyte number) results in the development of FSGS.[7,8] Jefferson and Shankland provide an overview of these pathogenic mechanisms, reviewing the contribution of podocyte injury and depletion in the initiation and progression of FSGS and also describe the contributions from other glomerular cell types. The morphologic features and 5 pathologic variants of FSGS are reviewed by Stokes and D'Agati. Consideration of these variants provides useful prognostic information and, despite their overlapping etiologies, often proves useful in diagnosing the underlying causes of the FSGS lesion.

Several articles in this issue address specific etiologic factors in FSGS. Primary FSGS, more often associated with nephrotic syndrome and extensive podocyte foot process effacement, has long been thought to be because of circulating factors, similar to minimal change disease. This concept is supported by the rapid recurrence of FSGS after kidney transplantation (~30% of cases in adults and >50% in children) and the finding that injection of plasma or plasma fractions from patients with FSGS into rats causes proteinuria. The exact mechanisms remain to be identified. Putative factors are discussed by Reiser and Alachkar and may provide actionable treatment targets in the future. Our understanding of the role of genetics as a cause of secondary FSGS is rapidly expanding. As the intricacies of podocyte cell biology have been unraveled, the mechanisms by which genetic mutations in this specialized cell result in focal and segmental glomerular scarring are becoming clearer. Multiple rare variants have now been identified that lead to Mendelian forms of familial FSGS. This ever-growing role of podocyte genetics in familial FSGS is reviewed by Pollak. Notably, genetic mutations are a rare cause of FSGS in adults, and routine genetic screening is not recommended in this population. However, some genetic variants play important roles in the development and severity of adult FSGS. In subjects of African descent, the G1 and G2 risk alleles in the *APOL1* gene are associated with an increased frequency of kidney disease[9] and a faster rate of progression to ESKD,[10] as reviewed by Limou and others. Importantly, the authors discuss optimal approaches to analyze risk alleles to ensure generation of valid and useful data. It should be recognized that most subjects in the African American Study of Kidney Disease and Hypertension trial likely had secondary forms of FSGS rather than a permeability factor-mediated disorder.[4]

The treatment of FSGS is a work in progress; differentiating primary from secondary forms is challenging, partial or no response to therapy is common, and treatment options are not always clear. Hogan and Radhakrishnan review the current state of idiopathic FSGS treatment approaches, including treatment for those who are resistant to initial therapies. Once glomeruli have undergone segmental scarring, the goal of therapy usually is to prevent progression of injury. However, Yang and Fogo elegantly describe how mechanisms of remodeling may apply to

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human FSGS and hold out hope that patients may not only have arrest of their disease but have regression to recover functional nephrons. Unfortunately, many patients with primary FSGS are resistant to immunosuppression and progress to end-stage kidney disease. After kidney transplantation, FSGS commonly recurs (30%-50%), sometimes within the first week post-transplant, even before morphologic changes are seen on light microscopy. Leca reviews what is currently known regarding the risks, pathogenesis, clinical manifestations, and treatment of recurrent FSGS.

The lesion of FSGS remains somewhat of an enigma; although with new tools and a focus on this clinically significant form of glomerular injury, we are gaining an understanding of the pathobiologic mechanisms by which it develops. Insights into podocyte and parietal epithelial cell biology and associated genetics are providing windows into potential targeted approaches to therapy and hope that we can even reverse this progressive glomerular lesion. FSGS—we are not there yet, but we are much further down the road.

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