The Many Faces of Focal Segmental Glomerulosclerosis: A Review

*Banu SG

Abstract

Focal segmental glomerulosclerosis (FSGS), though known as a primary disorder of the glomerular podocytes, is often a morphological manifestation of many secondary events. Infections, advanced stages of hypertensive nephropathy, scarring of previously active (necrotizing, crescentic) lesions, sickle cell disease, massive obesity and renal ablation due to any cause potentially lead to FSGS. Though the name implies a focal, segmental and sclerotic lesion, the disorder may not always show these typical morphologic patterns. There are lesions where the histomorphology shows considerable deviation from the common, making us realize that FSGS is not always focal, not always segmental, and not always sclerotic. According to currently running Columbia classification, FSGS is typed into five morphological variants: (1) not otherwise specified (NOS), (2) perihilar variant, (3) tip variant, (4) cellular variant and (5) collapsing variant. Among these, the latter two show characteristic cellularity that is too different from more common variants to call these FSGS. Aetiopathogenesis, on the other hand, can be different for the same morphology, although collapsing variant usually does have some distinct causes including HIV infection. The basic ultrastructural pathology of primary FSGS, i.e. podocyte injury and effacement of foot processes with decreased number of podocytes may not be present in other forms. Thus FSGS is multifaceted and require complete clinical history, meticulous light, fluorescence and electron microscopic evaluation, and preferably genetic study to be diagnosed.

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Introduction

Focal segmental glomerulosclerosis (FSGS), though known as a primary disorder of the glomerular podocytes, is often a morphological manifestation of many secondary events.[1] Infections, advanced stages of hypertensive nephropathy, scarring of previously active (necrotizing, crescentic) lesions, sickle cell disease, massive obesity and renal ablation due to any cause potentially lead to FSGS.[2] Thus a wide variety of causes eventually develop a common histological pattern in the glomeruli, each with a different pathogenesis. As the name implies, the pattern is characterized by sclerosis of segments of some but not all glomeruli (focal = not diffuse or all, segmental = not global).[2] However, there are lesions where the histomorphology shows considerable deviation from the common, making us realize that FSGS is not always focal, not always segmental, and not always sclerotic.[3] The disease thus possesses many faces, causing difficulty in understanding the aetiopathogenesis, and hence in planning the treatment option.

The history and evolution of FSGS

Until early in the past century, focal segmental glomerulosclerosis (FSGS) was hidden under the presumption of cases of minimal change disease (MCD) with greater steroid resistance and more progression to end-stage renal disease (ESRD). In 1925, Fahr T published an image of FSGS for the first time. He described it as lipoid nephrosis with degeneration. Long after in 1957, Rich AR in a study observed the focality of the segmental sclerosing lesions in autopsy specimens of a group of children dying from nephrotic syndrome apparently caused by lipoid nephrosis.

**Dr. Sultana Gulshana Banu, Associate Professor, Department of Pathology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. sgbanu.bsmmu@gmail.com*

In 1970, FSGS emerged as a separate clinico-pathological entity different from MCD in a report of the International Study of Kidney Diseases in Children (as cited in D'Agati, 2003).[4] After extensive studies for the next several years, the entity was defined as a syndrome manifesting proteinuria, usually of nephrotic range, associated with lesions of focal and segmental glomerular sclerosis and foot process effacement.[5]

With increased performance of biopsies and improved recognition of lesions, cases of FSGS are now being diagnosed showing increasing incidence and prevalence. It is now a global burden, though with wide regional and ethnic/racial variations.[6] Sim JJ et al. (2016) showed FSGS as the most common glomerular disease in their 12 years' long population-based study in the USA. They also observed an increasing incidence rate of FSGS in their study.[7]

Classificaton of FSGS

The historical early description of FSGS depicted by Rich AR in 1957 revealed the classic segmental sclerotic lesions involving predominantly the juxtamedullary glomeruli. The nomenclature and most of the definitions so far also highlight the typical histologic picture of the lesion.[5,8-11] However, with time morphologic variants were discovered[12-17] and new aetiopathogenetic facts were unveiled.[11,16-22] Thus need for a standard classification of FSGS became compelling.

D'Agati proposed an aetiological classification in 1994 that described a primary or idiopathic form and a secondary form[4]. It was later refined by D'Agati et al. (2004) to include familial/genetic, virus-associated, drug-induced, and those mediated by adaptive structural-functional responses (congenital or acquired reduction of functional renal tissue/nephron complement) in the secondary category.[6,10,11]

The histological classification of FSGS was proposed by an international working group of renal pathologists who convened at Columbia University, New York in 2000. This classification was widely known as Columbia classification. It included five histomorphological variants: (1) classic or not otherwise specified (NOS), (2) perihilar variant, (3) tip variant, (4) cellular variant and (5) collapsing variant.[10,11,23] The working group reached in a consensus about the histological criteria of each variant and the meaning of the terms used to define the lesions. The group also made recommendations on tissue processing and interpretation of immunofluorescence and electron microscopy in diagnosis of FSGS.[10]

Though typical segmental sclerosis is observed in classic, perihilar and tip variants, the cellular and collapsing variants are morphologically different and show endocapillary and extracapillary hypercellularity respectively. These two variants mimic various immune-complex mediated glomerulonephritis. Considerable morphological overlaps are also seen between the variants. Again, similar morphology is seen in primary and secondary forms and between different secondary forms.[10,11,13,23]

Beyond the usual light microscopic changes, other glomerular findings include completely normal looking glomeruli, accumulation of foam cells, glomerular hypertrophy, ischemic changes like retraction of the capillary tuft towards the vascular pole and 'atubular glomeruli' with cystic dilation of the Bowman's space. Tubular atrophy, interstitial fibrosis and inflammation, and hyperfunctioning vascular changes develop with time, especially with secondary FSGS.[4,6,11]

Aetiopathogenetic consideration

Primary FSGS is a distinct entity and a diagnosis of exclusion. The cause of underlying pathology, i.e. injury and loss of podocytes, is still unknown. However, a circulating factor, possibly a cytokine, has been suspected that makes certain individuals vulnerable. The existence and action of this factor are now evident as transplanted kidneys in FSGS patients have shown development of typical podocytopathy of FSGS that have lead to graft failure.[24,25] Primary FSGS needs exclusion of other forms that may also show podocyte injury and effacement of foot processes, e.g. adaptive, viral, genetic and medication-associated forms which are included in secondary category. It is of utmost importance because many of these secondary forms improve with treatment of the cause. Medical history, body weight, and relevant investigations including molecular study help differentiating the types. A new APOL1 (apolipoprotein L1 gene)-associated high-penetrance genetic form is considered as primary.[6,26]

Secondary FSGS mostly arises in the settings of hypertension, obesity, obstructive uropathy, sickle cell anemia, congenital oligomeganephronia, unilateral agenesis , surgical ablation and any advanced renal process with significant loss of nephrons. It is often mediated by increased glomerular capillary pressure in response to a reduced number of functioning nephrons. The vascular hilum suffers the greatest stress and undergoes scarring giving rise to perihilar sclerotic segments. Glomerular hypertrophy is also a relatively constant finding.[4,6,26] Ultrastructurally, there is mild degree of foot process fusion, affecting less than 50% of the total surface area. The findings, however, can be subjective and difficult to categorize. Again clinical information and relevant laboratory investigations are highly supportive and essential. Both primary and secondary forms of FSGS, as mentioned earlier, can display the light microscopic features of all five morphological categories.[4]

Is the lesion FSGS?

Segmental sclerosis is commonly found in lesions progressing to chronic stage. Diabetic glomerulosclerosis, membranous nephropathy, Alport's syndrome and various immune-complex mediated glomerulonephritis develop scarring with chronicity. Lesions of FSGS also gradually become global and diffuse with time.[6,11,26] Chronic glomerulonephritis is still another term that develops at the end-stage of almost all renal parenchymal disorders. It shows sclerosis in more than 50% of the biopsied glomeruli that are global or on the way to global.[2,3,4] Question can arise when examining a renal biopsy showing features of FSGS: Is the diagnosis FSGS or anything else?

Conclusion

Disorders having morphology of focal segmental glomerulosclerosis on biopsy needs exact categorization to be managed properly. Primary, a number of secondary, and many forms of nephropathies with chronicity can mask the faces of one another. The faces should be unmasked. Complete clinical history, meticulous light, fluorescence and electron microscopic evaluation, and preferably genetic study can help a correct diagnosis.

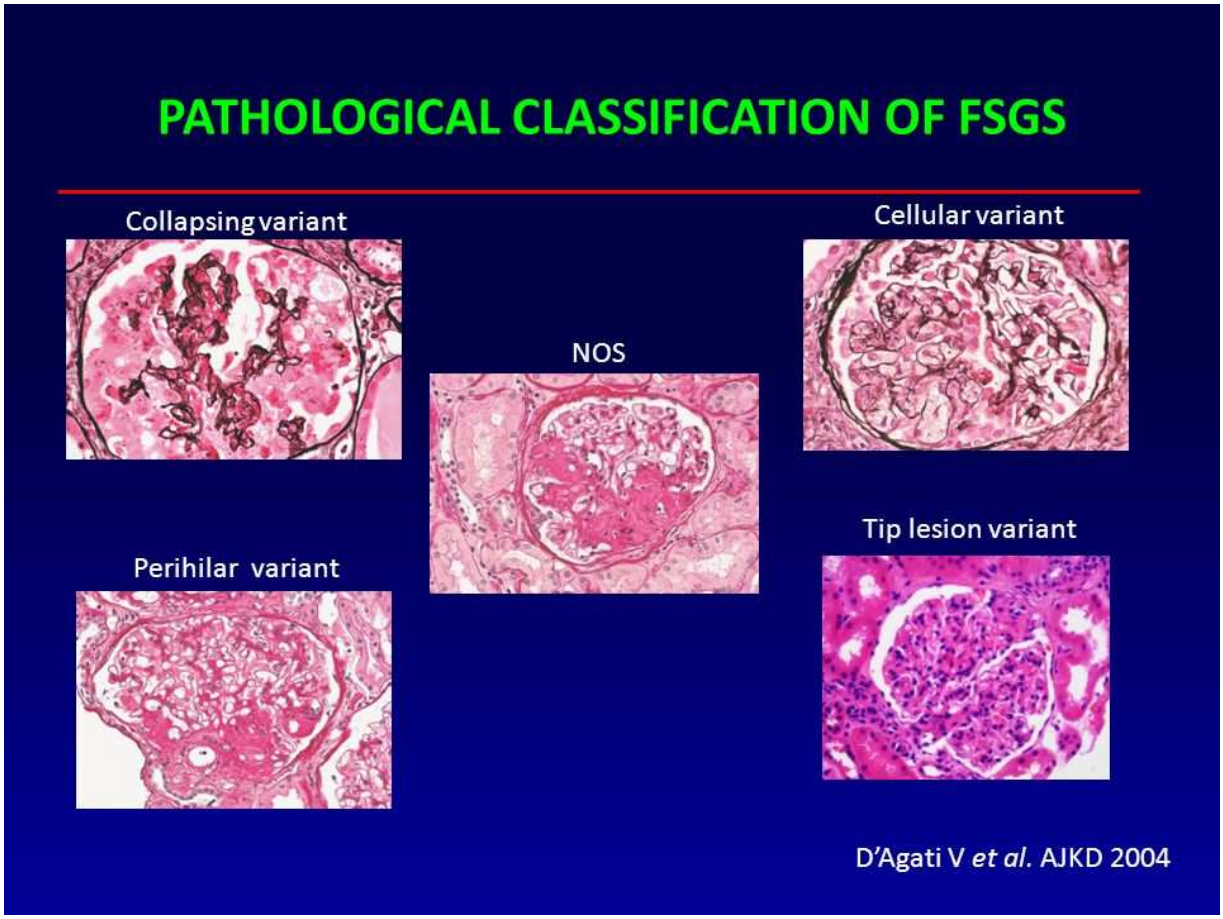

Figure 1. Variants of FSGS according to Columbia classification

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