Focal and Segmental Glomerulosclerosis (FSGS) is not a single disease entity; rather, it represents a morphologic ideogram of a spectrum of pathologic disorders involving the kidney, either as a primary process or secondary to some systemic disorders. It is one of the predominant morphologic insignia presenting with Nephrotic Syndrome (NS) in both adults and children. It accounted for 39.87% and 38.14% of nephrotic adult and pediatric patients in previously reported studies. FS GS is one of the leading causes of End-Stage Renal Disease (ESRD) in both adult and pediatric patients worldwide. The correct recognition and proper categorization of the histological spectrum of this lesion is of considerable help for better management and prediction of the outcome.

The framework for classification of FSGS is diverse, reflecting the heterogeneity of the disease. It may be classified on the basis of etiology. The other foundation, commonly employed to classify the disease, is on the basis of morphological features as detected on renal biopsies. These provide a suitable benchmark for rendering uniform and reproducible diagnostic criteria. The Columbia classification is a working proposal put forward by a collaborative panel of expert renal pathologists in 2000. This classification schema is based on an algorithmic approach towards an attempt to unify the descriptive terminologies for the histological variants of FSGS. This schema empowers renal pathologists to arrive not only at the best possible morphologic diagnosis but also guides nephrologists to consign appropriate management and speculate probable outcome of the disease.

This hierarchical classification elaborates rigorously defined diagnostic criteria for each of the five subtypes of FSGS. Furthermore, these defining hallmark features may be observed in primary as well as secondary FSGS. However, the noteworthy ultrastructural foot process effacement responsible for this podocytopathy has not been addressed. Soon after the promulgation of Columbia classification of FSGS, several retrospective as well as prospective studies from around the world elucidated the significance and clinical relevance of this dynamic classification. Despite the above mentioned shortcoming, the prognostic and therapeutic utility of this schema has been widely acknowledged.

The authors have previously reported the relative frequencies of these five variants among both adult and pediatric nephrotics at our center. There is a remarkable variation in relative frequencies of these variants as reported from various parts of the world. To illustrate the point, the prevalence of FSGS, Not Otherwise Specified (NOS) variant, varies from 42% to 77%. It is the predominant lesion among all the five variants in most of the studies from different ethnic and geographic areas. The possible reason for this may be the evolution of any of the other four variants which may ultimately result into this histological pattern. NOS variant was found in 76.6% of adult nephrotic patients. The second most common variant among our adult nephrotic population was collapsing variant, accounting for 12% of cases. This variant is markedly notorious in its clinical course and progression towards ESRD, probably due to severe tubulointerstitial damage associated with this unique glomerular lesion. This component is not a part of the defining criteria as per Columbia classification, but it reflects the morphologic signature of clinical course and progression of the disease. Indeed, at the molecular level, the collapsing variant is characterized by a lack of podocyte maturity markers, and re-expression of immaturity markers, particularly in the collapsed region. This molecular insight might help in future to develop novel therapies against these podocyte differentiation markers.

The third variant following the collapsing was tip variant, accounting for 9.8% in our series. The reported frequency of this variant also varies from 13% to 17%. The defining criteria of this variant have curious restrictions and need exclusion of other variants. Some authors even suggest that the tip lesion is simply a glomerular response to heavy proteinuria which may be observed in minimal change nephropathy, FSGS or in diabetic nephropathy. However, it has been observed that glomerular tip lesion, either defined by original definition or by Columbia classification, follows more favorable clinical course in terms of excellent response to steroid therapy.
The next variant is perihilar variant which, like the tip variant, is defined topographically and requires exclusion of all other variants. Its frequency varies from 26% to 43%. We have found a frequency of 1.1% in our series. This variant is more commonly associated with forms secondary to hyperfiltration, nephron loss or glomerular hypertension and often accompanied by glomerulonegaly. The clinical course is slowly progressive and will lead to ESRD within few years.

Last, but not the least, is the cellular variant, which is remarkable in its novel defining features. The relative frequency varies from 1% to 3% in different series. We have reported 0.5% in this study. It is not clear as to whether the low frequency of this lesion is due to real rarity of this entity or due to difficulty in categorizing this lesion accurately. There is remarkable overlap in histological features of cellular and collapsing variants, so the latter variant should be excluded carefully. Unfortunately the clinical implications of cellular variant are not very clear due to very limited number of cases in the majority of studies. However, one of the studies with largest number of cellular variants reported by Stokes et al. observed no statistically significant difference in clinical course and progression of disease with the NOS variant.

Much more important than the above glomerular changes from the prognostic point of view are the changes in the tubulointerstitial compartment. These can be both acute and chronic in nature and determine the ultimate outcome of the disease. It is important to quantify changes in this compartment in the pathology report. Vascular changes also become important, as the disease progresses, and result in additional ischemic damage to the kidney parenchyma.

In conclusion, the histological variants of FSGS are the morphologic signatures of the heterogeneous nature of the disease. An accurate identification and exact categorization of these histological variants, though difficult at times, are helpful in delineating the clinical course and prediction of progression of disease. As the understanding of the pathogenesis of disease is rapidly expanding, further detailed insight garnered through ultrastructural and novel molecular studies of these histological subtypes will help guide nephropathologists and nephrologists in tailoring optimal treatment strategies.

REFERENCES