Histologic Classification of FSGS: Does Form Delineate Function?

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In this issue of CJASN, D’Agati and colleagues assess the association of the Columbia classification system of FSGS histologic variants with clinical characteristics and outcomes in patients enrolled in the FSGS Clinical Trial (FSGS-CT) (1).

FSGS is the most common primary glomerular histology that results in ESRD (2). This is not a single disease, and it can have idiopathic, genetic, or secondary causes. FSGS patients present with diverse pathology and proceed with variable clinical courses. The Columbia classification attempts to categorize FSGS into five histologic variants (3). The collapsing variant is described as having at least one glomerulus with segmental or global glomerular capillary tuft collapse with hypertrophy and hyperplasia of overlying epithelial cells. The tip variant shows at least one glomerulus with a segmental lesion involving the outer 25% of the tuft next to the proximal tubule with adhesion of podocytes at the tubular lumen or neck, and without collapsing features. The not otherwise specified (NOS) variant is described by segmental capillary lumen obliteration by extracellular matrix, with no collapsing, tip, cellular (segmental endocapillary hypercellularity obliterating capillary lumens), or perihilar (vascular) lesions.

This study compares the presentation and outcomes in 94 NOS, 16 collapsing, and 14 tip variant patients in the FSGS-CT. Unfortunately, the perihilar (n=10) and cellular (n=4) variants had too few patients for statistical analysis. The FSGS-CT was an open-label, multi-center, randomized controlled clinical trial comparing the efficacy of 12 months of cyclosporine versus combination mycophenolate mofetil/oral pulse dexamethasone treatment in 138 biopsy-proven steroid-resistant FSGS patients (4,5). Both groups received low-dose prednisone for 6 months. Mean follow-up was 2.9±1.1 years. Patients were between 2 and 40 years of age, with estimated GFR (eGFR) values ≤40 ml/min per 1.73 m² and first morning urine protein/creatinine (Up/c) ratios >1g/g despite >4 weeks of corticosteroid treatment before enrollment. Collapsing FSGS patients were more likely to be of black race (P=0.03), and had the highest pathologic injury scores (total glomerular scarring and tubulointerstitial atrophy/fibrosis) (P=0.003) and baseline serum creatinine (P=0.003). The tip variant had the highest association with white race as well as the lowest pathologic scores and baseline creatinine. Features of the nephrotic syndrome were more pronounced in both the collapsing and tip variants compared with the NOS variant. Most importantly, 47% of collapsing patients reached ESRD at 3 years compared with 20% of NOS and 7% of tip variants. It was concluded that there was worse renal survival in the collapsing variant compared with the tip variant, despite therapy under the FSGS-CT protocol. After adjustment for baseline creatinine and Up/c, the collapsing FSGS variant was not a statistically significant predictor of ESRD.

Limitations of this study include modest sample size, short follow-up, and generalizability to adults due to the trial’s age criteria with only one-third of the cohort aged >18 years. Patients with the most aggressive FSGS may not have been eligible for the study if eGFR decreased to <40 ml/min per 1.73 m² while on corticosteroid therapy. An obvious strength is that this is a randomized controlled trial. With the poor prognosis of the collapsing variant, prior case series may be biased by undertreatment because immunosuppression may have been considered futile. In this trial, the specific variant could not influence the choice of therapy.

These findings support the association between histologic variants and clinical outcome previously reported in retrospective series. Thomas and colleagues found that the collapsing and tip variants had higher proteinuria and lower serum albumin levels than the NOS and perihilar variants in a cohort of 197 FSGS patients (6). The collapsing variant had worse renal prognosis with only 33% renal survival (not doubling serum creatinine or requiring renal replacement therapy) at 3 years compared with 76% with the tip variant and 65% in the NOS variant. Stokes and colleagues found similar results for collapsing and tip variants in a retrospective cohort of 225 FSGS patients (7). The collapsing variant had 65.3% of patients reaching ESRD compared with only 5.7% with the tip variant and 34.5% in the NOS variant. One difference between these two cohorts is that only 34% received corticosteroids in the analysis by Thomas et al. versus 72.4% in the study by Stokes et al. It is noteworthy that these two series had authors who were the pathologists that devised the original classification system. In stark contrast, Chun and colleagues examined 87 FSGS patients and found their equivalent classification of
the collapsing lesion to be steroid responsive in 64% of patients compared with 53% in the classic scar lesion and 78% in the tip lesion (8).

Practically, a classification scheme must be reproducible to be useful. Meehan and colleagues recently assessed the reproducibility of classifying 61 individual glomeruli between six renal pathologists at one center (9). Overall agreement was 75.2%, with a κ of 0.676 (1 being complete agreement and 0 being coincidental agreement) consistent with a moderate to good score. Distinguishing the cellular from the NOS variant was difficult. Stokes and colleagues similarly concluded that the cellular variant may be misclassified if there is inadequate sampling and may actually represent either tip or collapsing variants (7).

The Columbia classification, however, is not universally accepted. Haas and Yousefzadeh argued that the tip lesion can be seen in minimal change disease based on review of an autopsy series of eight patients with >400 glomeruli examined (10). The tip lesion may represent a response to heavy proteinuria and is not a disease-specific finding. The ideal histologic classification of FSGS would be mechanistic in nature and would be helpful in guiding therapy, similar to the goals of the proposed classification of membranoproliferative GN (11). Barisoni and colleagues proposed an alternative classification system for all podocyte disorders, which includes FSGS, minimal change disease, and diffuse mesangial sclerosis, placing collapsing glomerulopathy in a separate category from other forms of FSGS (12). This classification is rooted in the type of podocyte injury. Minimal change nephrophy is believed to result from podocyte injury with preserved podocyte number, whereas FSGS develops after podocyte detachment or death. In contrast, podocyte dedifferentiation and proliferation leads to collapsing glomerulopathy. Each podocytopathy may have idiopathic, genetic, and reactive forms.

With either classification system, the collapsing lesion is distinguished in most series as having a dismal prognosis. Why is there a worse prognosis with the collapsing variant? It cannot be due to the degree of proteinuria alone, because the tip variant, with a similar degree of proteinuria, has a much better prognosis. Korbet argues that the poor response to therapy in prior series may be due to more advanced renal insufficiency, widespread collapsing lesions, and irreversible damage in this variant (13). Series that have reported poor response had the majority of patients with serum creatinine >3.5 mg/dl, >50% of glomeruli with collapsing lesions, and increased >2+ tubulointerstitial fibrosis. However, the collapsing variant group in the study by D’Agati et al. (1) had an eGFR of 82 mL/min per 1.73m², with 20% interstitial fibrosis although the percentage of collapsed glomeruli is not reported. These baseline variables are worse in the collapsing variant versus other variants, but the eGFR and tubulointerstitial fibrosis would not be considered beyond the point of no return. The worse baseline may be partially but not completely responsible for poor treatment outcomes in this study. Given the association with black race, the authors postulate that there may be a relationship between APOL1 risk alleles and collapsing FSGS as there is for collapsing FSGS in HIV-associated nephropathy (14,15).

Furthermore, is the collapsing variant associated with higher levels of circulating permeability factors? Wei et al. recently investigated circulating soluble urokinase receptor (suPAR) levels in two FSGS cohorts (N=164), one of which was the FSGS-CT (n=70) (16). Elevated suPAR levels were found in 84.3% of the FSGS-CT cohort and 55.3% in the PoDoNet cohort. There was a positive association between relative reduction of suPAR after 26 weeks of treatment and reduction of proteinuria with higher levels of complete remission (P=0.04). It would be interesting to examine whether there was an association between suPAR levels and the Columbia classification histologic variants.

Lastly, collapsing FSGS is characterized by loss of podocyte maturity markers in collapsed areas and re-expression of immaturity markers (17,18). Testagrossa and colleagues retrospectively applied the Columbia classification to 131 FSGS cases and similarly found that the collapsing variant (36.6% of cases) was associated with the loss of expression of certain normal podocyte markers (P<0.05) and the gain of expression of dedifferentiation markers compared with other variants (P<0.05) (19). Perhaps novel therapies for collapsing FSGS may focus on promoting podocyte differentiation (20).

In their original article proposing the Columbia classification system, D’Agati et al. stated that “subclassifications of disease on morphological grounds are valid only if they carry meaningful clinical or pathogenetic implications” (3). It remains to be determined how the differences in morphologic subtypes of FSGS may reflect differences in etiology, pathogenesis, prognosis, or optimal therapy. It does appear that identifying the histologic form of FSGS helps delineate clinical course and prognosis. However, the clinicopathologic correlates are not quite ready for prime time. FSGS is not a single disease but a manifestion and the morphologic variants likely underpin differing mechanisms. Although our understanding of the pathogenesis of FSGS is rapidly expanding, we still lack optimal therapies to alter the clinical course.

Disclosures
M.J.C. is an unpaid co-investigator for the Sanofi study on fresolimumab versus placebo in patients with steroid-resistant primary focal segmental glomerulosclerosis. In addition, he serves on the data monitoring safety board for the GlaxoSmithKline belimumab lupus nephritis study.

References


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