

Cellular Focal Segmental Glomerulosclerosis: A Controversial Pathological Entity. Its Pathogenesis and Therapeutic Basis

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ABSTRACT

Cellular FSGS variant was described in 1980 and it was incorporated in diagnostic algorithm of Columbia Classification in 2004. This type of FSGS must show several diagnostic pathological criteria. This review highlights the key features of FSGS cellular variant in relation to histopathological changes, the differential diagnosis and discusses about pathogenesis and therapeutic advances. Although FSGS cellular variant is a recognized category in Columbia Classification it is remained as a controversial renal pathology, and it is observation open the possibility to consider other pathological diagnosis.

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Key words: FSGS; Cellular variant; Electron microscopy; Immunofluorescens

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HISTORY OF CELLULAR FSGS VARIANT

In 1925, Fahr provided the first description of focal and segmental glomerular hyalinization and capillary degeneration being considerate as degenerative changes of glomeruli in patients with lipoid nephrosis^[1]. Other authors began to report progressive renal disease in nephrotic patients coinciding with progressive glomerular sclerosis and increased interstitial scarring. In the mid-1980s other similar glomerular diseases became part of the FSGS spectrum, including collapsing, cellular, and tip lesions. The recognition in this study of the heterogeneity of clinical presentation, degree of proteinuria, and morphology has been a critical step in the history of FSGS, although it had created some controversy among pathologists. The cellular lesion was described by Schwartz and Lewis^[2] and included a group of glomerular lesions characterized by hypercellularity. After that, some authors accepted and used the term cellular lesion for all forms of severe nephritic syndrome with increased cellularity, whereas others made a distinction between those with extracapillary proliferation and collapse versus those with endocapillary proliferation; the term collapsing FSGS was used for the former, and the term cellular lesion was restricted to the latter. In 2004 an editorial on the pathologic classification of FSGS was published and standardized approach in diagnosis of the FSGS^[3].

COLUMBIA'S CLASSIFICATION OF FSGS

It comprises five histological classes of FSGS: NOS (not otherwise specified), perihilar FSGS (PHG); the tip lesion (GTL); cellular FSGS (CELL); and collapsing FSGS (COLL). The main objective for this classification is to afford uniform definitions, and to establish distinct classes of FSGS. Columbia classification has a hierarchy five classes, and the collapsing lesion is the overriding consideration when other forms of FSGS are present and therefore the cellular, tip, hilar, and NOS lesions are of descending importance in determining the diagnosis (Figure 1). Moreover the cellular and collapsing lesions are

considered separate entities and finally, the variants are not specific for primary FSGS, and the growing number of causes of secondary FSGS makes a purely morphologic classification with mutually exclusive categories less pressing: a pathogenetic classification, based on etiologic and molecular insights, is more likely to lead to therapeutic advances^[4].

Ultimately, a morphologic classification of FSGS is useful if it provides therapeutic and prognostic guidance or pathogenic insights. A critical point is the prognostic and therapeutic utility of this classification, largely because studies that have assessed the clinical relevance of the histologic variants of primary FSGS in nephrotic patients are few and conflicting^[5].

FSGS CELLULAR VARIANT

Clinical Features

Schwartz and Lewis^[2] reported that 18 of 20 patients with the called cellular lesion had protein excretion at or above 3.0 g per day compared with only 19/39 patients with FSGS without the cellular lesion, and this was reflected in a higher protein excretion. In addition, the time from onset of proteinuria to renal biopsy was significantly shorter in patients with the cellular lesion suggesting that more fulminant symptoms prompted earlier biopsy. In other studies the cellular lesion is more frequent in African Americans when nephrotic and nonnephrotic patients with FSGS are included, but in patients with nephrotic range proteinuria, the difference is no longer significant. When we consider the Columbia classification cellular variant is the least frequent, representing 3% of the case^[6]. If the criteria of the Columbia classification are applied to a pediatric population with a high prevalence of African Americans, the ratio between the different variants changes, increasing the percentage of cellular type (32%). Moreover, patients with FSGS cellular variant showed an intermediate rate of remission between COLL and GTL variant (44.5% vs 13.2% and 65.3%, respectively). CELL FSGS as well as COLL FSGS, and GTL share clinical presenting features of heavier proteinuria, more frequent nephrotic syndrome, and shorter duration of symptoms compared to FSGS NOS, suggesting that these three morphologic variants reflect acute glomerular injury, or possibly a response to heavy proteinuria.

Pathological Findings

In relation to Columbia classification of FSGS the diagnosis of cellular variant is required the presence of endocapillary hypercellularity (foam cells, endothelial cells, macrophage, neutrophils, lymphocytes) involving $\geq 25\%$ of the tuft and causing occlusion of the capillary lumen/lumina in at least 1 glomeruli. Also, there may be pyknotic or karyorrhectic debris. Furthermore, neither hyalinosis nor segmental scleroses are required features. However, endocapillary hypercellularity involving the tip domain rules out the cellular variant, as endocapillary hypercellularity may characterize lesions in tip variant. There are several problems with this definition of the cellular lesion. Cellular variant could include cases of unsampled tip or collapsing lesion, underscoring the importance of adequate sampling^[7]. Increased mesangial cellularity was seen in the cellular variant (63.6%) when compared with the glomerular tip and NOS lesions^[5]. Many cases have podocytes swollen and crowded, sometime forming pseudocrescents. Immunofluorescence (IF) only demonstrates focal and segmental deposits of IgM and C3 At ultrastructural level cellular variant shows severe and diffuse foot process effacement with segmental occlusion of capillary lumen with foam cells and hyaline. The basement glomerular membrane does not exhibit any ultrastructural change (Figure 2).

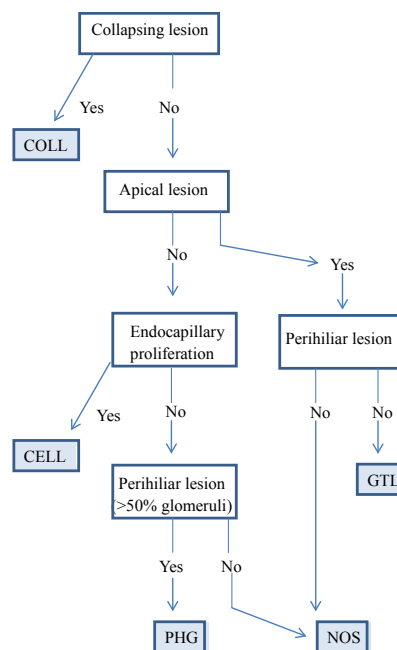


Figure 1 Kidney biopsies algorithm for the morphologic Columbia classification of FSGS in the variants COLL (collapsing); CELL (cellular); GTL (tip lesion); PHG (perihilar) and NOS (not otherwise specified).

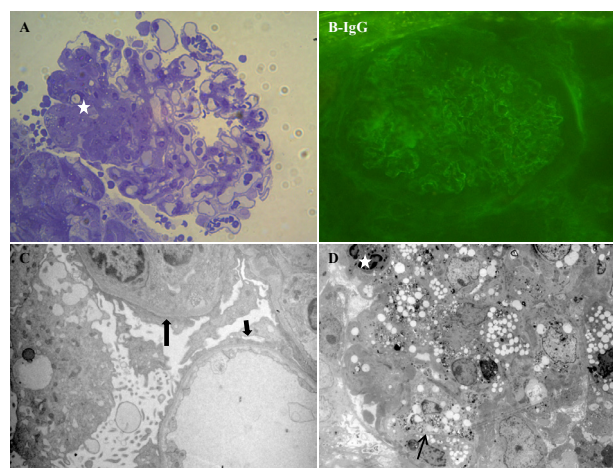


Figure 2 Cellular FSGS. A: The glomerulus shows segmental endocapillary proliferation, which includes foam cells and accompanying mild epithelial cell hypertrophy (Semi-thin sections, toluidine blue. 400X). B: Immunofluorescent staining: glomerulus show no staining for specific immunocomplex (IgG-400X). C: At electron microscopy level significant podocyte foot process effacement over the remaining glomerular capillaries and lipid and nuclear polymorph cells in a segmental sclerosing lesion (D). 7000X.

Some authors question the existence of a separate CELL variant, and claim it is merely a form of the COL variant^[8]. Others agree that both variants are very difficult to distinguish histologically, if not impossible^[9]. No clear clinical or prognostic differences between the two have been demonstrated by some authors, but common pathophysiological pathways affecting cell cycle regulatory proteins have been established^[8-9].

Laboratory findings

Majority of patients with collapsing variety (80%), NOS (82.0%) and GTL variant (77.7%) had nephrotic range proteinuria at presentation. However, the amount of proteinuria was highest in the glomerular tip variant (11.93 \pm 1.6 g), followed by the collapsing variety (9.43 \pm 1.7

g), which were statistically significant when compared with the CELL variant. A significantly higher percentage of patients with the collapsing and cellular variants of FSGS had renal failure at the time of presentation when compared with the GTL and PHG variants. However, severe degree of renal failure was seen only in the collapsing variant. The frequency of hypertension was equal in all pathological variants of FSGS^[5].

Differential Diagnosis

As we can deduce from its definition and described microscopic features, lesions may be histologically very similar to focal and segmental proliferative glomerulonephritis, such as lupus nephritis, IgA nephropathy, or pauci immune focal crescentic glomerulonephritis. It is essential in these cases a rigorous examination and analysis of IF, other histological features, clinical manifestations, and, in some cases, electron microscopy^[10].

CURRENT TREATMENT AND PROGNOSIS

Furthermore, it remains to be determined if endocapillary proliferation is associated with disease activity and progression in FSGS. In addition, in a work from Columbia University, the authors state: “cellular variant may include cases of unsampled tip or collapsing lesion”. It has been proposed that hypercellular lesions would be frequently observed in patients with severe clinical manifestations, such as observed in collapsing lesions. Implications for cellular variant diagnosis are unknown as so few patients are registered in most series reported.

Stokes *et al*^[11] have reported “intermediate rates of remission and end-stage renal disease compared to collapsing and tip lesion”, and there was not statistical differences with NOS variant. From this study it can be support the view that CELL and COLL FSGS are not equivalent and validates an approach to pathologic classification that distinguishes between COLL, CELL, and tip lesion variants of FSGS.

Predictors of end-stage renal disease (ESRD) for all FSGS patients included initial serum creatinine, % global sclerosis, % COLL lesions, chronic tubule-interstitial injury score, and lack of remission response. CELL variant showed intermediate rates of remission (44.5%) and ESRD (27.8%) compared to COLL and tip lesion^[11].

FSGS is not a disease but a lesion initially affecting the podocyte. Various factors may induce 'secondary' FSGS, including defects in molecules that contribute to the podocyte slit diaphragm permeability to albumin. They do not represent indications for immunosuppression and require symptomatic treatment only, comprising angiotensin 2 and endothelin antagonists. Primary (idiopathic) FSGS is possibly but not certainly of immunologic origin, owing to an elusive glomerular permeability factor (GPF), explaining relapse on a renal transplant and justifying an immunosuppressive treatment. The best prognostic feature of primary nephrotic FSGS is its response to corticosteroids. Alkylating agents are mostly ineffective in steroid-resistant forms. An association of corticosteroids and cyclosporine A (CsA) remains the mainstay of treatment, with a good tolerability when CsA dosage is low. A definite advantage of tacrolimus on CsA has not yet been established. Sirolimus appears ineffective and potentially harmful. Azathioprine is not indicated. A number of mostly uncontrolled trials indicate that mycophenolate mofetil might find an adjunctive place in the treatment. Plasmapheresis is of no avail outside the special case of relapse in a transplanted kidney. Immunoabsorption of the GPF has not led to practical treatment options. Anecdotal reports on rituximab

are as yet too few to determine whether this monoclonal anti-CD20 antibody will find a place in the treatment of primary FSGS^[12].

A significantly higher percentage of patients with the cellular variant were steroid non-responsive (63.63%); they had to be treated with other immunosuppressive drugs like cyclophosphamide (72.72%), cyclosporine (27.27%) and mycophenolate mofetil (9.90%)[5]. Perhaps the strongest argument for distinguishing CELL from COLL lesions is that many cases of apparent CELL proved to be undersampled GTL after examining additional (deeper) tissue sections and applying stringent criteria to define FSGS variants^[13].

PATHOGENESIS

The pathogenesis classical FSGS has not been fully elucidated; however, data from molecular studies of familial cases in the last two decades suggest that FSGS is a defect of the podocyte^[14]. Evidence from animal models and in vitro studies suggests that injury inherent within or directed to the podocyte is a central pathogenetic factor. Disruption of signaling from any of the podocyte's specialized membrane domains, including slit diaphragm, apical and basal membranes, or originating at the level of the actin cytoskeleton, may promote the characteristic response of foot process effacement. Irreversible podocyte stress leading to podocyte depletion through apoptosis or detachment is a critical mechanism in most forms of FSGS^[15].

The pathogenesis of primary CELL is unknown but a key role for podocyte injury is evidenced by the findings of diffuse foot process effacement and glomerular epithelial cell hypertrophy/hyperplasia in most cases. All forms of FSGS share podocyte damage and depletion as central mediators. In the renal allograft, recurrent FSGS often has CELL or COLL features, and this has been linked to the presence of a circulating permeability factor in some cases. However, the nature of this factor and its role in CELL in the native kidney has not been determined. The segmental lesions in CELL show variable features of endocapillary hypercellularity related to accumulation of inflammatory cells. Similar findings are seen in GTL and some case of COLL, all of which are associated with heavy proteinuria, as well as in other human and experimental diseases characterized by proteinuria, suggesting that the intracapillary hypercellularity might represent a localized inflammatory response to high transcapillary flux of a protein- and lipid-rich filtrate. Of note, the lack of correlation of CELL and GTL with serum cholesterol levels argues against hypercholesterolemia per se being a major pathogenetic factor in the morphogenesis of these lesions, although the role of other lipids is unknown.

Recent research has led to suggesting that FSGS is not a T-cell-driven autoimmune glomerulopathy. Thus, treatments considered as etiologic, including glucocorticoids and calcineurin inhibitors, are in fact endowed with a mode of action on podocytes that suggests that drugs used such as immunosuppressors also might be considered as antiproteinuric agents^[16].

Experimental toxin models have advanced our understanding of the threshold and dynamics of podocyte injury. Following initial podocyte depletion, spreading fields of podocyte injury through secondary mediators appear to be important in generating the segmental pathologic lesions. Proliferating glomerular epithelial cells are common in FSGS, although there are conflicting views about their identity. Evidence suggests potential contributions by mature parietal epithelial cells, facultative stem cells and podocyte^[17].

Glomerular IgM and C3 deposits frequently accompany idiopathic FSGS and secondary glomerulosclerosis, but it is unknown whether IgM activates complement, possibly contributing to the pathogenesis

of these diseases. We hypothesized that IgM natural antibody binds to neoepitopes exposed in the glomerulus after nonimmune insults, triggering activation of the complement system and further injury. We examined the effects of depleting B cells, using three different strategies, on adriamycin-induced glomerulosclerosis. First, we treated wild-type mice with an anti-murine CD20 antibody, which depletes B cells, before disease induction. Second, we evaluated adriamycin-induced glomerulosclerosis in Jh mice, a strain that lacks mature B cells. Third, we locally depleted peritoneal B cells via hypotonic shock before disease induction. All three strategies reduced deposition of IgM in the glomerulus after administration of adriamycin and attenuated the development of albuminuria. Furthermore, we found that glomerular IgM and C3 were detectable in a subset of patients with FSGS; C3 was present as an activation fragment and colocalized with glomerular IgM, suggesting that glomerular IgM may have bound a cognate ligand. Taken together, these results suggest that IgM activates the complement system within the glomerulus in an animal model of glomerulosclerosis. Strategies that reduce IgM natural antibody or that prevent complement activation may slow the progression of glomerulosclerosis^[18].

The pathogenesis of primary CELL is unknown but a key role for podocyte injury is evidenced by the findings of diffuse foot process effacement and glomerular epithelial cell hypertrophy/hyperplasia in most cases. In the renal allograft, recurrent FSGS often has CELL or COLL features and this has been linked to the presence of a circulating permeability factor in some cases. However, the nature of this factor and its role in CELL in the native kidney has not been determined. The segmental lesions in CELL show variable features of endocapillary hypercellularity related to accumulation of inflammatory cells (mostly foamy macrophages, with or without neutrophils and other mononuclear cells), suggesting that the intracapillary hypercellularity might represent a localized inflammatory response to high transcapillary flux of a protein- and lipid-rich filtrate. Of note, the lack of correlation of CELL and GTL with serum cholesterol levels argues against hypercholesterolemia per se being a major pathogenetic factor in the morphogenesis of these lesions, although the role of other lipids is unknown.

CONCLUSION

In concordance with Stokes *et al*^[19] I believe it is important to recognize CELL as a distinct morphologic lesion (defined by segmental expansion of the glomerular tuft with endocapillary hypercellularity, without features of COLL or GTL).

CONFLICT OF INTERESTS

The author declare no conflict of interest.

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