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Collapsing Focal Segmental Glomerulosclerosis: A Morphological Lesion in Search of Nosologic Identity

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ABSTRACT

Collapsing focal segmental glomerulosclerosis (cFSGS) is a distinct clinicopathological variant of focal segmental glomerulosclerosis (FSGS) characterized pathologically by the segmental and/or global collapse of the glomerular capillaries, marked hypertrophy and hyperplasia of visceral epithelial cells (VECs), and severe tubulointerstitial disease. The etiology of this lesion is still elusive, but a growing list of diseases/conditions is associated with this morphologic expression of renal parenchymal injury. The pathogenesis of cFSGS involves VEC injury leading to cell cycle dysregulation and a proliferative podocyte phenotype. Clinically, collapsing glomerulopathy is characterized by black racial predisposition, a high incidence and severity of nephrotic syndrome (NS), poor response to empirical therapy, and rapid progression to end-stage renal disease (ESRD). The lesion has also been reported in transplanted kidneys either as recurrent or de novo disease, often leading to loss of the allograft. Most of the cases have been reported from the western countries, but the lesion is being increasingly recognized in the tropics as well. The optimal treatment for cFSGS is still not known. Empirical therapies include steroids or cyclosporine in addition to aggressive blood pressure control, angiotensin converting enzyme inhibitors (ACEIs) and/or angiotensin II receptor blockers (ARBs), and lipid lowering agents. The role of other immunosuppressive agents such as mycophenolate mofetil in the treatment of cFSGS awaits further studies. Newer insights into the pathogenesis may change this ominous outlook for this therapeutically resistant form of FSGS. There is still lack of awareness among the pathologists and nephrologists in the developing countries about this lesion. There is an urgent need to educate the pathologists and nephrologists from developing countries on this topic. This review describes the historical background, epidemiology, etiology, pathogenesis, pathology, treatment, and prognosis of this disorder, with an emphasis on the pathologic features on renal biopsies to facilitate its accurate diagnosis in developing countries.

Implication for health policy/practice/research/medical education:
Collapsing focal segmental glomerulosclerosis is being increasingly recognized as a common cause of end-stage renal disease. Its incidence is also increasing in the tropics. There is a need to increase its awareness among the pathologists and nephrologists in developing countries for proper management and prognostication.

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1. Background

Collapsing focal segmental glomerulosclerosis (cFSGS), also known as collapsing glomerulopathy (CG), is currently classified as a distinct clinicopathological variant of FSGS. It is becoming an important cause of end-

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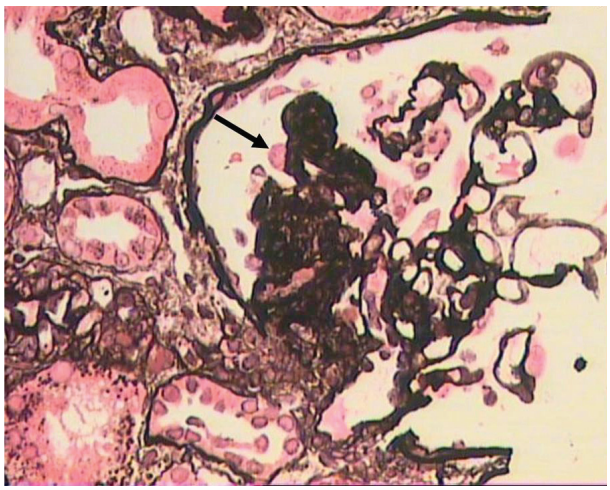
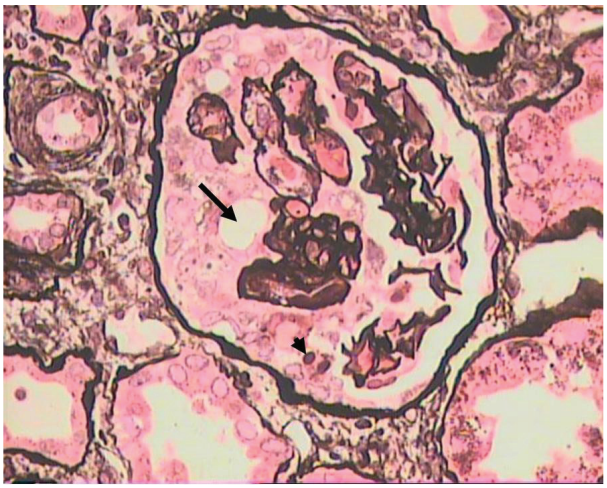
Figure 1. High-power View Showing Segmental Collapse of Capillary Tufts associated with Mild Hypertrophy of Podocytes (arrow).



No significant proliferation of podocytes is seen in this case. (Jones' methenamine silver, ×400).

Figure 2. High-power View Showing Nearly Global Collapse of Capillary Tufts Associated with Marked Hypertrophy and Hyperplasia of Podocytes, Forming Pseudo-crescent.



Marked cytoplasmic vacuolization (arrow) and protein resorption droplets (arrow head) are seen in podocytes. (Jones' methenamine silver, ×400)

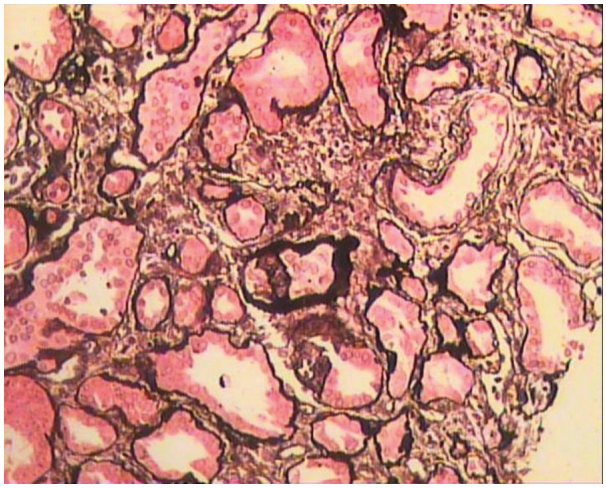
stage renal disease (ESRD) throughout the world (1, 2). cFSGS is an interesting renal parenchymal lesion which has attracted marked attention in recent years because of its increasing incidence, increasing association with diseases other than human immunodeficiency virus (HIV)-1 infection or intravenous drug abuse, propensity to occur in the blacks, rapid progression to ESRD, and its uniformly poor response to empirical therapy (3-6). The lesion has been reported mostly from United States (7-10) and Europe (11, 12), but is being increasingly reported from the tropical countries as well (13-16).

The nosologic identity of this distinctive renal parenchymal lesion has remained elusive for many years. It was first segregated from other glomerular proteinuric conditions in 1986, when Weis *et al.* described six cases of this entity in young black patients (17). However, cases with similar morphology and clinical presentation were described in the literature as "malignant FSGS" as earlier as 1970s, and attest to the fact that this lesion existed well before its formal recognition as a distinct entity (2). Its nosologic relationship with other renal glomerular diseases especially focal segmental glomerulosclerosis (FSGS) is interesting and controversial (2). The authors of the first report of this entity thought of this lesion as a unique and novel clinicopathological entity, although with a question mark (17). However, during 1990s reports appeared in literature linking this lesion to the growing spectrum of FSGS and Detwiler *et al.* (18) were the first to consider this lesion as a distinct variant of FSGS, followed by Valeri *et al.* (3). Columbia classification of FSGS officially declared this lesion as a subtype of FSGS (4, 5). However, more recently, some authors have suggested that this nosologic relationship with FSGS may not last longer, and sooner or later, it may be classified as a separate entity (2, 6, 7). A recently proposed taxonomy for the podocytopathies classifies CG apart from FSGS and recognizes three major categories: idiopathic, genetic, and secondary or reactive (6).

2. Epidemiology

Although, initially reported from USA, the disease has a worldwide prevalence (2, 3, 17, 18). Majority of cases have been reported from USA, with few reports from Europe, and other western countries (2, 7, 11, 12). Only occasional cases have been reported from the tropics (13-16). This appears to be mostly due to detection bias rather than true difference in the prevalence of the disorder, as recently, rates of its diagnosis in both native and allograft biopsies approaching the western studies have been reported (13). The growing reports of cFSGS in the literature reflects both a true increase in the incidence of this lesion and the diagnostic bias. This has been demonstrated in the studies from USA and Europe. This lesion comprised 11% of all primary FSGS at Columbia Presbyterian Medical Center from 1979 to 1985, 20% from 1986 to 1989, and 24% from 1990 to 1993 (3). Their first case with the pathologic features of cFSGS was identified in 1979 by retrospective review of renal biopsies and represents the first documented case of idiopathic cFSGS in the literature. The reason for the increase in frequency of cFSGS cases is not clear, and may be due to a possible change in exposure to certain infections, chemical agents, or other environmental factors. Haas *et al.* (9) reviewed their cases of FSGS from 1974 to 1993. Their first case of cFSGS was identified after 1980, and during the time period of 1980 to 1993 cFSGS represented 5.3% of cases of idiopathic FSGS. A second study by the same authors from 1995 to 1997 identified cFSGS in 9% of patients with idiopathic FSGS (8). A similar trend of rise of cFSGS has not been formally reported from tropical regions as yet.

Figure 3. Medium-power View Showing Marked Tubular Atrophy Associated with Interstitial Fibrosis and Mononuclear Inflammatory Cell Infiltrate in the Interstitium. (Jones' methenamine silver, ×200)



3. Etiology

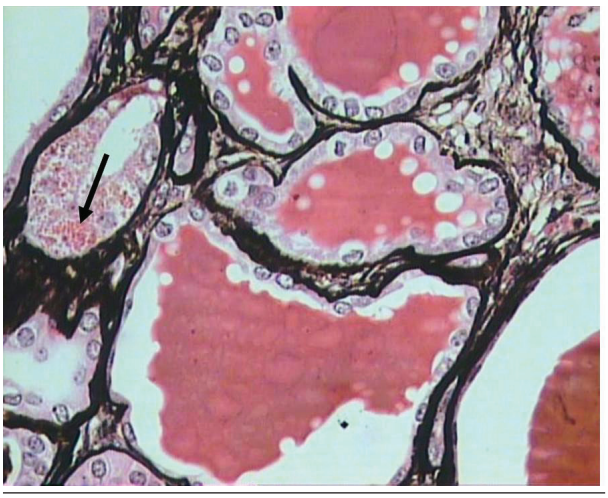
Collapsing FSGS is not a single disease entity but rather a distinctive expression of renal parenchymal injury, which may result from a multitude of causes. Most cases are idiopathic and their cause is unknown (1, 2). Among the known causes, HIV-1 infection is the most common, the lesion being called HIV associated nephropathy (HIVAN) in these patients (19, 20). Other infectious agents have also been implicated less commonly (21-23). Immunologic disorders are the next common reported associations (24-27). There are increasing reports of secondary and genetic causes of this lesion and these provide an insight into the widening etiopathogenetic pathways of the condition (1, 2). The lesion is also being increasingly recognized in renal allografts, not only from developed countries but also from developing countries (28-33). A summary of the etiologic associations/conditions is provided in *Box 1*. This wide heterogeneity of the underlying causes/associations suggests that cFSGS is not a single disease entity, but rather a unique expression of the renal parenchymal response to these various insults, unified by the morphologic appearance.

4. Pathogenesis

Although, the exact sequence of events leading to cFSGS in humans is still not completely understood, significant advancements have been made in unraveling many of the steps leading to the final common expression of the lesion. In this regard, the discovery of a number of susceptibility genes for cFSGS in humans, and the development of more than 10 independent murine models of this disease in different laboratories of the world, represent landmark achievements for studying the disease process in vivo and in different perspective (1, 2). In contrast to human disease, the triggering agents in each of the four broad categories of murine models of cFSGS are known. These are; HIV-1 gene products, immunoglobulins (Ig), oxidative stress, and podocyte paracrine/autocrine dysregulation (2). A question arises about how these seemingly different injurious agents result in the same stereotyped proliferative response in cFSGS. A "best-fit" model has been put forward to explain this phenomenon (2). The initial event consists of discrete epithelial cell injury caused by either intrinsic or extrinsic agents involving different parts of renal parenchyma, i.e., both the podocytes and the renal tubular epithelium. The surrounding neighboring cells then respond to the injury not by the normal repair or regeneration, but by dedifferentiation, proliferation and transdifferentiation of podocytes to macrophage like phenotype in the glomerular compartment. These phenotypic changes are accompanied by changes in the immunohistochemical markers, as shown in *Box 2*, and in the behavior of these cells. The immunohistochemical markers of maturity are lost, and the markers of immature phenotype, proliferation and macrophage lineage are expressed, the latter phenomenon described as transdifferentiation. The podocytes change their shape, lose primary foot processes, and detach from the GBM and proliferate to form pseudo-crescents. These changes result in profound alterations in the normal structure-function relationships of the different compartments of the nephron with consequent derangements of function. Luminal factors and the preexisting deviation in the immune system, coupled with genetic susceptibility, likely exacerbate this process (2, 34-37).

In the pathogenesis of cFSGS, two major common pathways have been proposed: activation of the immune system and the dysregulation of the mitochondrial activity (2). Most of the disorders associated with cFSGS involve a deviation in immune homeostasis, suggesting some role for immune activation in the development

Figure 4. High-power View Showing Microcystic Transformation of some Tubular Segments Filled with Hyaline Proteinaceous Casts with Scalloped Margins. (Jones' methenamine silver, ×400)



One tubular cross-section also shows protein resorption droplets in the cytoplasm of tubular epithelial cells (arrow).

of cFSGS. It has been shown that many involve T helper type 1 lymphocyte responses, an immune dysregulation that already is known to aggravate and accelerate other proliferative parenchymal renal diseases, particularly crescentic glomerulonephritis (CresGN). Secondly, this lesion is known to occur in acute ischemic insult to the kidney such as thrombotic microangiopathy (TMA), cyclosporine A (CsA) toxicity and severe hyaline arteriopathy (1). Recently, three cases of cFSGS have been reported in renal allografts on renal allograft biopsies in the vicinity of areas of segmental infarction (33). We have also observed similar phenomenon in renal biopsies from patients with acute cortical necrosis (unpublished data). Thus, ischemic injury to the glomeruli does have a role in the development of cFSGS. This may be mediated by dysregulation of the mitochondrial function and/or altered autocrine/paracrine interaction of podocytes, endothelial cells, and/or parietal epithelial cells (2). The vascular and ischemic causes have been implicated for the most part in the development of cFSGS in transplanted kidneys (7).

Box 1. List of Known Conditions/Etiologic Factors Associated with Collapsing FSGS in Humans

Infections
Human immunodeficiency virus-1 infection
Parvovirus B19
Cytomegalovirus infection
Human T cell lymphotropic virus-1
Hepatitis C virus
Pulmonary tuberculosis
Leishmaniasis
Febrile illness
Autoimmune Diseases
Systemic lupus erythematosus
Adult Still's disease
Mixed connective tissue disorder
Giant cell cerebral arteritis
Malignant Tumors
Multiple myeloma
Acute monoblastic leukemia
Hemophagocytic syndrome
Genetic Disorders
Action myoclonus-renal failure syndrome
Mitochondrial cytopathy
Familial
Sickle cell anemia
Drugs/Chemothepeutic Agents
Interferon-α
Pamidronate
Posttransplantation
Recurrent
De novo
Arteriopathy
Acute vascular rejection
Thrombotic microangiopathy

5. Pathology

Collapsing FSGS is diagnosed pathologically by its characteristic histopathologic features in the glomeruli on light microscopy (LM) of the renal biopsy, the mainstay of diagnosis (1, 2). The salient morphologic features on renal biopsy examination are shown in *Box 3*. These consist of focal to diffuse, segmental to global collapse of the glomerular capillary tufts associated with hyperplasia and hypertrophy of overlying podocytes, a defining feature of this entity *(Figures 1 and 2)*. These proliferating podocytes form pseudo-crescents, which differ from the true crescents of CresGN by their visceral location, the presence of a cleft like space between the pseudo-crescents and parietal epithelium, epithelioid appearance of constituent cells, and absence of fibrin in the pseudo-crescents. The proliferating podocytes also display cytoplasmic vacuolization and prominent, hyaline, protein resorption droplets *(Figure 2)*. According to Columbia classification, a single glomerulus with collapsing lesion is sufficient for the diagnosis of cFSGS on the biopsy. There is usually also concurrent segmental and/or global glomerulosclerosis at the time of pathologic diagnosis. The tubulointerstitial disease is an important component of this condition and often appears out of proportion to the degree of glomerular sclerosis (7). In addition to the tubular atrophy, interstitial fibrosis, edema, and inflammation, there are widespread tubular degenerative and regenerative changes, including microcyst formation, as shown in *Figures 3 and 4*. Immunofluorescence microscopy (IF) shows focal segmental positivity of IgM, C3, and occasionally C1q, in

Box 2. Changes in the Immunophenotype of the Dysregulated Podocytes in cFSGS

Downregulated Markers
Maturity markers
CALLA
Glepp 1
Podocalyxin
Synaptopodin
WT-1
Cell cycle inhibitors
p27
p57
Upregulated Markers
Proliferative markers
Cyclin D1
Cyclin E
Cyclin A
Ki-67
Dedifferentiation markers
PAX2
Cytokeratin
Transdifferentiation markers
CD68
GLEPP1, glomerular epithelial protein; CALLA, common acute lymphoblastic leukemia antigen; WT1, Wilms' tumor protein

collapsed lobules of the glomeruli in some cases. The intensity of staining is typically trace to 1+ but may be up to 2+ on a scale of 0 to 3+. Staining for IgG, IgA, and C1q is negative. IF study is used primarily to exclude the secondary causes of cFSGS. On electron microscopy (EM), the collapsed tufts display wrinkling and collapse of GBM with little or no thickening of GBM. The overlying podocytes are greatly hypertrophied with diffuse foot process effacement with focal detachment. No electron dense deposits are observed. In contrast to HIVAN, no tubuloreticular inclusions are seen in idiopathic cFSGS. Once a diagnosis of cFSGS is rendered, the possibility of HIVAN must be ruled out, usually by negative HIV serologies, supported by the absence of endothelial tubuloreticular inclusions.

The differential diagnosis includes other variants of FSGS as well as other forms of glomerular disease. Among the variants of FSGS, the collapsing variant is most commonly misdiagnosed as cellular FSGS. Both the collapsing and cellular variants are characterized by marked hypertrophy and hyperplasia of VECs. The defining features that separate the two variants are the implosive wrinkling and retraction of the GBM seen in cFSGS as opposed to the expansive lesions of endocapillary hypercellularity seen in the cellular FSGS. In many cases of cFSGS, the VEC proliferation may be so exuberant as to form a pseudo-crescent. In such cases, the histologic findings may be misdiagnosed as CresGN. Appropriate integration of the clinical history and LM, IF, and EM findings will aid in this differential diagnosis.

6. Clinical Presentation

The median age of patients with idiopathic cFSGS is 30 to 40 years, however, a wide range of ages have been reported, with patients as young as 1.5 years and as old as 82 years. Only occasional reports are available in literature on cFSGS occurring exclusively in children (38). Most studies have reported a male predominance, although in one series, a female predominance was noted. cFSGS has a black racial predisposition. Since Weiss *et al.'s* original report (17), in which all six patients with cFSGS were black, a predominance of black patients in the USA has been noted. A study of eight patients in France by Bariety *et al* also noted a predominance of black patients (35). Overall, 50% of the reported patients in the literature with cFSGS belong to black race (2). The clinical features of cFSGS are generally similar to those of idiopathic non-collapsing FSGS but usually are more severe. Majority (> 80%) of patients with cFSGS present with nephrotic range proteinuria, and reports have demonstrated a significantly greater incidence of nephrotic syndrome and higher levels of proteinuria in patients with cFSGS compared with patients with non-collapsing FSGS. Other severe manifestations of the nephrotic syndrome are frequent, including

Box 3. The Characteristic Morphologic Features of cFSGS observed on Renal Biopsy Examination.

Light Microscopic Features

Glomeruli

- Collapse: segmental or global wrinkling and folding of the GBM with occlusion or sub-occlusion of the capillaries
- Pseudo-crescents: podocyte hyperplasia (proliferation)
- Hypertrophic podocytes with occasional large nuclei
- Protein reabsorption droplets and vacuoles in the cytoplasm of podocytes
- Segmental and/or global sclerosis (in advanced stages)

Tubulo-interstitial Compartment

- Microcysts: dilated, often serpentineshaped, tubules with flat epithelium containing eosinophilic proteinaceous casts with peripheral scalloping
- Acute tubular injury: flattening of the tubular epithelium, large epithelial cells, large, occasionally atypical, nuclei with prominent nucleoli
- Tubular atrophy
- Interstitial edema
- Interstitial inflammation
- Interstitial fibrosis

Vessels

- Nonspecific changes except for cases associated with thrombotic microangiopathy

Immunofluorescence

- Nonspecific segmental positivity of IgM and C3 in areas of collapse

Electron Microscopy

- Large cuboidal podocytes with pale cytoplasm
- Retraction of primary processes
- Diffuse and severe foot process effacement
- Loss of detectable actin-based cytoskeleton
- Electron dense protein reabsorption droplets in podocyte cytoplasm
- Detachment of podocytes from underlying GBM and deposition of newly formed extracellular matrix in between GBM and podocytes
- Absence of tubulo-reticular inclusions in idiopathic cFSGS

hypoalbuminaemia, hypercholesterolemia, and edema, but none of these manifestations are significantly different than in patients with non-collapsing FSGS. There is also significantly greater renal insufficiency in patients with cFSGS at presentation than patients with non-collapsing FSGS (14).

7. Treatment

There is no specific treatment for cFSGS at present (1, 2). The therapeutic approaches used currently are empirical, and based on anecdote, retrospect, and expert opinion. The most common approach used for cFSGS in non-HIV positive patients is in analogous to that used for noncollapsing FSGS, i.e., use of steroids or immunosuppressive agents (39-41). Although, the drugs, dosages, duration, and the definition of response vary among the studies, leading to variable results in different studies, the overall results are poor. A complete remission of 9.6% and a partial remission of 15.2% have been reported (2). A second approach involves the use of highly active anti-retroviral therapy (HAART) in cases of cFSGS in HIV-1 positive patients. This has been shown in a retrospective analysis to slow down the rate of progression of the disease to ESRD by 38% (2).

Given the lack of effective therapeutic agents and the uniformly poor prognosis of the condition, there is an urgent need for the development of highly effective and specific agents, based on the knowledge of the pathogenetic pathways of cFSGS. Among these, the use of small molecule inhibitors of cyclin dependent kinases (CDKs) in preclinical studies in small animals have been shown to prevent the development, and retard the progression, of experimental lesions of cFSGS. Similarly, the use of differentiating agents such as retinoic acid derivatives, to inhibit the proliferation of podocytes and induce their differentiation to a mature, quiescent phenotype, has also been shown to ameliorate the experimental cFSGS. Promising results have also been obtained in improving renal function in experimental forms of cFSGS by the use of small molecule inhibitors of inflammatory pathways controlled by NF-κB and cyclooxygenase-2. These findings underscore the multifactorial basis for the proliferative phenotype of VECs in cFSGS, and indicate that rational approaches to therapy for cFSGS based on the knowledge of pathogenesis may be available very soon (2).

8. Prognosis

Up till now, the prognosis of cFSGS has been uniformly poor. Only occasional cases of spontaneous remission are recorded, the response to empirical therapy is poor, and the rapid progression to ESRD is universal (1, 2). With further research into the pathogenesis of this disease, it is hoped that specific treatments will be available in near future.

9. Conclusions

Many advances have been made in understanding the etiology and pathogenesis of cFSGS. These advancements are opening up new avenues for research into the rational therapy of this disease. The success of preclinical testing of new treatment strategies based on the knowledge of pathogenetic pathways obtained from studies in humans and animal models holds promise that the currently bleak prognosis of cFSGS is set to change in the near future.

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Conflict of interest

None declared.

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