Pathologic Classification of Focal Segmental Glomerulosclerosis

By Vivette D'Agati

Focal segmental glomerulosclerosis (FSGS) is defined as a clinical-pathologic syndrome manifesting proteinuria and focal and segmental glomerular sclerosis with foot process effacement. The pathologic approach to the classification of FSGS is complicated by the existence of primary (idiopathic) forms and multiple subcategories with etiologic associations, including human immunodeficiency virus (HIV)-associated nephropathy, heroin nephropathy, familial forms, drug toxicities, and a large group of secondary FSGS mediated by structural-functional adaptations to glomerular hyperfiltration. A number of morphologic variants of primary and secondary focal sclerosis are now recognized, including FSGS not otherwise specified (NOS), perihilar, cellular, tip, and collapsing variants. The defining features of these morphologic variants and of the major subcategories of FSGS are discussed with emphasis on distinguishing light microscopic patterns and clinical-pathologic correlations.

THE FIRST IMAGE of focal segmental glomerulosclerosis (FSGS) was published in 1925 in a remarkably accurate drawing by Fahr[1] from an atlas of human pathology. Even at that early time, Fahr[1] recognized the relatedness of this novel lesion to minimal change disease when he aptly entitled it *lipoid nephrosis with degeneration*. It would be another 32 years before Rich[2] provided a more detailed pathologic description of focal sclerosis in autopsy specimens of children dying with nephrotic syndrome caused by apparent lipoid nephrosis. Rich[2] was the first to observe the preferential distribution of the segmental sclerosing lesions in juxtamedullary glomeruli early in the disease, indicating the focality of the sclerosing process. He postulated that the development of sclerosis probably accounted for the progression to renal failure seen in a subset of children with idiopathic nephrotic syndrome. However, it was not until the 1970s, in a report by the International Study of Kidney Diseases in Children, that focal segmental glomerulosclerosis emerged as a separate clinical-pathologic entity that was distinguished from minimal change disease by its greater steroid resistance and progression to renal failure.[3]

Over the past 30 years, concepts of FSGS have been refined in more detailed clinical-pathologic studies from many centers. FSGS is defined as a clinical-pathologic syndrome manifesting proteinuria, usually of nephrotic range, associated with lesions of focal and segmental glomerular sclerosis and foot process effacement.[4,5] Although hyaline insudation is common, the condition lacks glomerular immune complex deposits. Early in the disease process, the pattern of glomerular sclerosis is focal, involving a subset of glomeruli, and segmental, involving a portion of the glomerular tuft. As the disease progresses, a more diffuse and global pattern of sclerosis evolves. Alterations of the podocyte cytoarchitecture constitute the major ultrastructural findings.

The approach to a diagnosis of FSGS is problematic because the morphologic features are nonspecific and can occur in a variety of other conditions or superimposed on other glomerular processes.[6] In addition, because the defining glomerular lesion is focal, it may not be adequately sampled in small needle biopsies.

The diagnosis of FSGS is further complicated by the existence of a primary (or idiopathic) form and many secondary forms (Table 1).[6,7] Before a diagnosis of primary FSGS can be reached, secondary forms must be carefully excluded. Idiopathic FSGS must be distinguished from human immunodeficiency virus (HIV)-associated nephropathy and heroin nephropathy, as well as the large group of secondary FSGS caused by structural-functional adaptations mediated by intrarenal vasodilatation and by increased glomerular capillary pressures and plasma flow rates.[7] Such maladaptive glomerular hemodynamic alterations can arise through: (1) a reduction in the number of functioning nephrons (such as after unilateral renal agenesis, surgical ablation, oligomeganephronia, or any advanced primary renal disease), or (2) mechanisms that place hemodynamic stress on an initially normal nephron population (as in morbid obesity, cyanotic congenital heart disease, and sickle cell

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Table 1. Etiologic Classification of FSGS

Primary (idiopathic) FSGS
C1q nephropathy
HIV-associated nephropathy
Heroin nephropathy
Familial FSGS
Mutations in α-actinin 4 (autosomal dominant)
Mutations in podocin (autosomal recessive)
Mitochondrial cytopathies
Drug toxicity
Pamidronate
Lithium
Interferon-α
Secondary FSGS (adaptive structural-functional response likely mediated by glomerular hypertrophy/hyperfiltration)
Reduced renal mass
Oligomeganephronia
Unilateral renal agenesis
Renal dysplasia
Reflux nephropathy
Sequela to cortical necrosis
Surgical renal ablation
Any advanced renal disease with reduction in functioning nephrons
Chronic allograft nephropathy
Initially normal renal mass
Diabetes mellitus
Hypertension
Obesity
Cyanotic congenital heart disease
Sickle cell anemia
Nonspecific pattern of FSGS caused by renal scarring
Focal proliferative glomerulonephritis (IgA nephropathy, lupus nephritis, pauci-immune focal necrotizing and crescentic glomerulonephritis)
Hereditary nephritis
Diabetic nephropathy
Hypertensive arterionephrosclerosis
Membranous glomerulopathy
Thrombotic microangiopathies

anemia). Finally, primary and secondary FSGS also must be differentiated from the nonspecific pattern of focal and segmental glomerular scarring that can follow a variety of inflammatory, proliferative, thrombotic, and hereditary conditions.

FSGS comprises a number of morphologic subtypes that may have different prognostic and therapeutic implications. These morphologic variants were defined at a recent consensus conference of renal pathologists in New York City (Table 2). The categorization outlined in Table 2 encompasses the spectrum of primary FSGS, as well as some secondary forms. This schema presumes prior exclusion of secondary FSGS caused by glomerular scarring in the course of other primary glomerular diseases (such as chronic glomerulonephritis, diabetic glomerulosclerosis, membranous glomerulopathy, hereditary nephritis, and so forth). Five main light microscopic patterns of FSGS have been defined, including FSGS (not otherwise specified [NOS]), perihilar variant, cellular variant, tip variant, and collapsing variant. Although the appearance of the glomerular tuft differs in these forms, all share the common feature of podocyte alterations at the ultrastructural level. At the present time, it is unclear if these morphologic variants reflect pathogenetic differences or whether they are the consequence of different severities of podocyte injury or tempos of histopathologic evolution. Future studies are needed to address these questions. The pathologic features and major clinical correlates of each of these morphologic variants are discussed.

FSGS (NOS)

FSGS (NOS) constitutes the generic lesion of FSGS. The synonyms *classic FSGS* or *FSGS of the usual type* often are applied. This category requires that other morphologic categories (perihilar, cellular, tip, and collapsing) be excluded. FSGS (NOS) is the most common morphologic pattern of FSGS. Evidence from repeat biopsy examinations suggests that other variants may evolve into this pattern in the course of disease progression and increasing chronicity.

Pathologic Features

FSGS (NOS) is defined as a discrete segmental consolidation of the glomerular tuft by increased extracellular matrix, causing obliteration of the glomerular capillary lumen/lumina (Figs 1A–1B). Early in the disease, the segmental lesions have a predilection for the juxtamedullary glomeruli. Lesions of sclerosis can affect the perihilar (ie, vascular pole) region or the periphery of the tuft. In some glomeruli, segmental lesions may affect more than one lobule, involving both the perihilar and peripheral regions. According to one study using serial sections, peripheral lesions tend to be more common in childhood FSGS than the adult disease.[8] Any number of glomeruli can be affected by segmental sclerosis, with or without associated global sclerosis.

Glomerular capillaries are occluded segmentally by relatively acellular matrix material, often asso-

Table 2. Morphologic Variants of FSGS

Variant	Positive Criteria	Negative Criteria
FSGS (NOS)	At least one glomerulus with segmental increase in matrix obliterating the capillary lumina There may be segmental glomerular basement membrane collapse without podocyte hyperplasia	Exclude perihilar, cellular, tip, and collapsing variants
Perihilar variant	Perihilar sclerosis and hyalinosis involving >50% of segmentally sclerotic glomeruli	Exclude cellular, tip, and collapsing variants
Cellular variant	At least one glomerulus with segmental endocapillary hypercellularity occluding lumina, with or without foam cells and karyorrhexis	Exclude tip and collapsing variants
Tip variant	At least one segmental lesion involving the tip domain (outer 25% of tuft next to origin of proximal tubule) The tubular pole must be identified in the defining lesion The lesion must have either an adhesion or confluence of podocytes with parietal or tubular cells at the tubular lumen or neck The tip lesion may be sclerosing or cellular	Exclude collapsing variant Exclude any perihilar sclerosis
Collapsing variant	At least one glomerulus with segmental or global collapse and podocyte hypertrophy/hyperplasia	None

ciated with inframembranous hyalinosis, endocapillary foam cells, and wrinkling of glomerular basement membrane (GBM). Hyalinosis, also known as *plasmatic insudation*, consists of the accumulation beneath the GBM of amorphous glassy material that is eosinophilic, nonargyrophilic, and trichrome-red (Fig 1B). Clear lipid vacuoles may be entrapped in the hyaline material. There often is continuity between the glomerular hyalinosis and hyalinosis involving the contiguous afferent arteriole. There may be segmental GBM collapse without podocyte hypertrophy or hyperplasia. Mesangial hypercellularity and glomerulomegaly may be present. Mesangial hypercellularity is more prevalent in pediatric FSGS, especially early in the disease course.[9-11]

Adhesions or synechiae to Bowman's capsule are common. The overlying visceral epithelial cells often appear swollen and can form a cellular cap over the sclerosing segment (Fig 1B). Detachment of podocytes from the sclerosing segment with intervening accumulation of newly formed matrix material may produce an apparent halo of weakly periodic-acid Schiff (PAS)-positive or weakly trichrome blue-positive matrix between the sclerosed segment and the detached podocytes (Fig 1B). There is no restriction on the degree of podocyte hypertrophy and hyperplasia seen in FSGS (NOS) provided that these podocyte alterations do not affect collapsed capillaries.

The number of glomeruli affected by segmental lesions depends on the severity of the disease process and the number of serial sections examined. As the lesions evolve globally, there is progression to complete glomerular obsolescence. Lobules unaffected by the segmental sclerosis usually appear normal by light microscopy but for mild swelling of the podocytes.

There is typically patchy tubular atrophy and interstitial fibrosis commensurate with the severity and distribution of the glomerular sclerosis. Proximal tubules frequently contain intracellular lipid and protein resorption droplets (Fig 1C). Interstitial foam cells may be identified, either as isolated cells or aggregates.

In some cases, there is disproportionately severe tubulointerstitial damage relative to the degree of glomerular sclerosis. In such cases, the tubules may display degenerative and regenerative changes including epithelial simplification, enlarged hyperchromatic nuclei, and nucleoli. Such damage tends to be more common in cases with severe unremitting nephrotic syndrome in which long-standing heavy proteinuria itself is likely to mediate the progressive tubulointerstitial damage. Evidence from human and animal studies indicates that increased protein trafficking through tubular reabsorption of filtered protein promotes progressive tubulointerstitial damage.[12,13] Protein overload of tubular cells leads to increased tubular

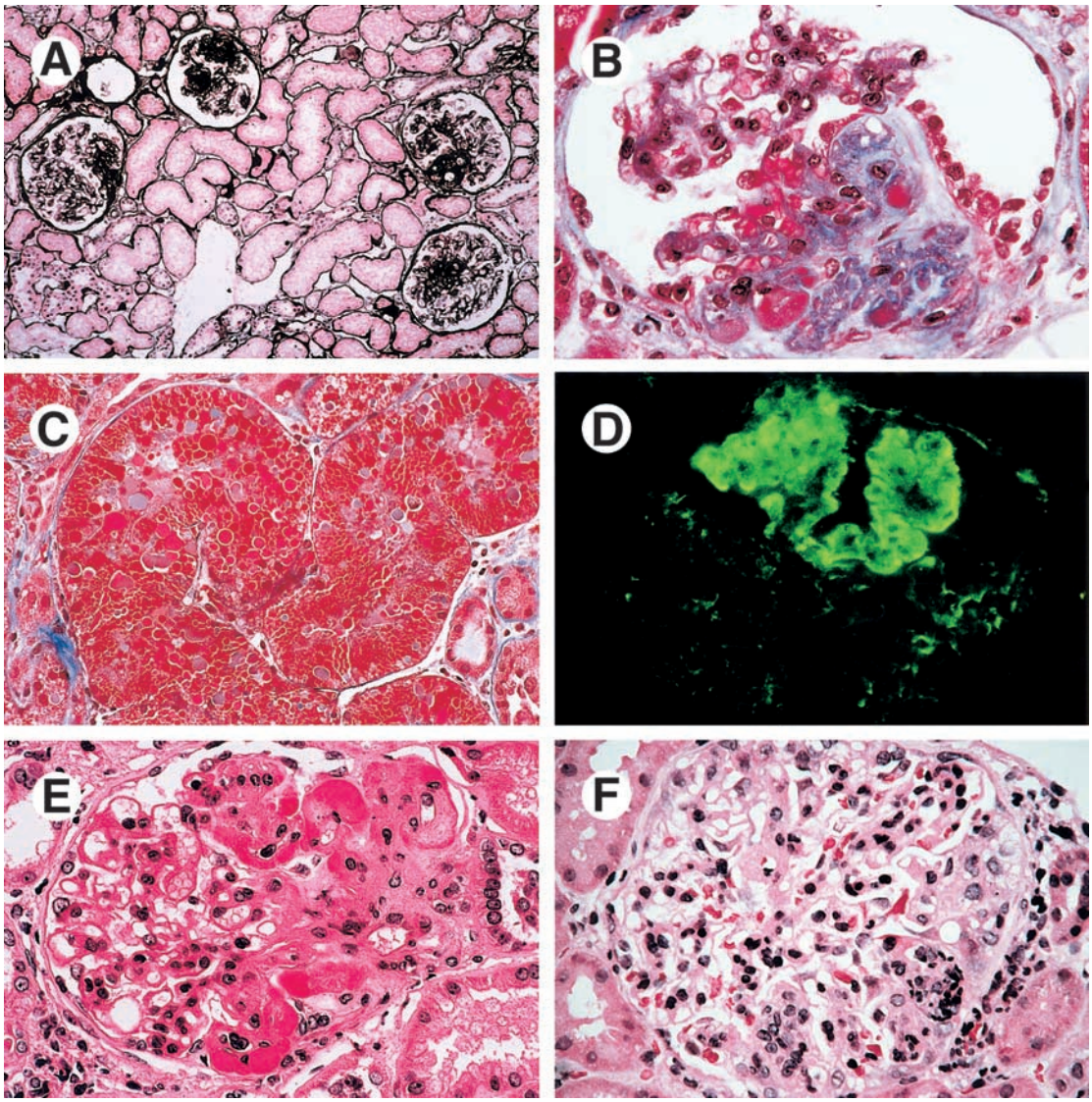

Fig 1. Light and fluorescence microscopic findings in FSGS (NOS), FSGS, perihilar variant and FSGS, cellular variant. (A) FSGS (NOS): Low power view showing segmental sclerosis involving many glomeruli. The lesions of segmental sclerosis are discrete and readily distinguished from the adjacent preserved portions of the tuft. In this example, there is no evidence of tubular atrophy. (Jones methenamine silver; JMS). (B) FSGS (NOS): Trichrome stain helps to distinguish the wrinkled and retracted glomerular basement membranes, shown in blue, from the red-staining hyaline insudation. There is detachment and capping of the overlying podocytes, with a halo-like zone of pale neomembrane overlying the site of detachment. (C) FSGS (NOS): The tubules contain abundant intracytoplasmic protein resorption droplets that stain red and blue with the trichrome stain. (D) FSGS (NOS): By immunofluorescence, there is segmental staining for IgM involving the sclerotic portion of the tuft, with weaker mesangial positivity involving the adjacent nonsclerotic segments. (E) FSGS, perihilar variant: The lesion of segmental sclerosis and hyalinosis is located at the glomerular vascular pole, or hilus, which is identified by the presence of the juxtaglomerular apparatus with macula densa. The hyalinosis appears glassy and eosinophilic. There is no podocyte reactivity. (Hematoxylin and eosin; H&E). (F) FSGS, cellular variant: The glomerular capillary lumina are segmentally obliterated by endocapillary hypercellularity including numerous infiltrating leukocytes, resembling a proliferative glomerulonephritis. There is hypertrophy of the overlying podocytes. (H&E).

expression of chemokines such as monocyte chemoattractant protein-1 and osteopontin that in turn attract inflammatory cells to the interstitium and lead to enhanced expression of fibrogenic cytokines that promote interstitial fibrosis. Tubular synthesis of endothelin-1 also may contribute to interstitial fibrosis by local vasoconstrictive effects and resultant ischemic injury.[13]

By immunofluorescence, there is typically focal and segmental granular deposition of immunoglobulin (Ig)M, C3, and, more variably, C1 in the distribution of the segmental glomerular sclerosis and hyalinosis (Fig 1D). More generalized weak (<2+) mesangial deposition of IgM also may be present (Fig 1D). Staining for albumin and some immunoglobulins (particularly IgA as well as IgG) may be found within the podocytes, corresponding to intracytoplasmic protein resorption droplets. One should be careful to distinguish this intracellular staining from immune deposits within the glomerular tuft itself. Similarly, intracytoplasmic deposits of albumin, immunoglobulins, and sometimes C3 may be found involving proximal tubules that are engaged in active protein resorption.

By electron microscopy, the lesions of segmental sclerosis display wrinkling and retraction of GBM and accumulation of inframembranous hyaline, with resulting narrowing or occlusion of the glomerular capillary lumina (Fig 4A). The electron dense hyaline material is usually more waxy in appearance than true immune complex deposits and tends to pool beneath the GBM, conforming to the contours of the delimiting membrane. Hyaline deposits frequently contain curvilinear membranous particles or entrapped electron lucent lipid globules. Endocapillary foam cells appear as large intracapillary cells containing abundant electron lucent vacuoles (Fig 4A).

Directly overlying the lesions of segmental sclerosis there usually is complete effacement of foot processes, accompanied by podocyte alterations that include hypertrophy, increased organellar content, and focal microvillous transformation. This microvillous appearance is caused by the formation of slender cellular projections resembling villi along the surface of the podocytes facing the urinary space. The hypertrophied podocytes display rounded cell bodies that adhere smoothly to the GBM, with frequent loss of primary processes.

There may be detachment of podocytes from the sclerosing segment (Fig 4B), as well as from nonsclerotic segments (Fig 4C). In these areas, intervening accumulation of lamellated neomembrane material commonly is observed between the naked GBM and the retracted podocyte cell body (Fig 4C). These foci of detachment correspond to the halos observed by light microscopy surrounding the sclerosing segments.

The major ultrastructural finding involving nonsclerotic glomerular capillaries is foot process effacement. The degree of foot process fusion observed overlying these open capillaries varies from mild to severe, but usually involves greater than 50% of the total glomerular capillary surface area. In general, the degree of fusion correlates roughly with the severity of the proteinuria, such that patients with subnephrotic proteinuria tend to have less foot process fusion than those who are fully nephrotic. In the areas of foot process effacement, there usually is loss of recognizable slit diaphragms and mat-like condensations of cytoskeletal filaments oriented parallel to the direction of the GBM itself. Thus, although the lesions of FSGS are focal at the light microscopic level, the podocyte alterations are relatively diffuse at the electron microscopic level.

Clinical-Pathologic Correlations

The most prognostically significant clinical features in FSGS are serum creatinine and the severity of proteinuria at presentation.[14] The presence of nephrotic proteinuria (>3.0–3.5 g/d) has been associated with a worse outcome in primary FSGS, with mean time course to end-stage renal disease of 6 to 8 years.[14] This is compared with over 80% 10-year renal survival in patients with nonnephrotic proteinuria. Not surprisingly, severe proteinuria of over 10 g/d is associated with an even more rapid course to renal failure (<3 y).[15,16] Prognosis is better in those who undergo a remission of nephrotic syndrome than those with persistent nephrotic syndrome. Most studies agree that the best pathologic predictor of poor outcome is the degree of interstitial fibrosis.[17-20] Interestingly, the percentage of glomeruli with segmental scars or global sclerosis has not been found to be independently predictive of outcome.

FSGS (NOS) accompanied by mesangial hypercellularity is most common in the pediatric age group. Studies by Yoshikawa et al[9] and by the Southwest Pediatric Nephrology Study Group[10] in 57 and 75 patients, respectively, did not show

prognostic import of diffuse mesangial hypercellularity occurring in idiopathic FSGS. The only correlation reported by the Southwest Pediatric Nephrology Study Group study was a shorter time course from clinical presentation to biopsy examination in the patients with FSGS and diffuse mesangial hypercellularity compared with FSGS without mesangial hypercellularity.[10] Thus, similar to cellular FSGS, the presence of diffuse mesangial hypercellularity in FSGS (NOS) appears to represent an early stage in the development of FSGS but does not correlate with outcome. Therefore, the consensus conference concluded that the presence of diffuse mesangial hypercellularity in FSGS did not warrant a separate morphologic classification.

FSGS, PERIHILAR VARIANT

This category requires that the cellular variant, tip variant, and collapsing variant be excluded. It is defined by the presence of perihilar sclerosis and hyalinosis involving greater than 50% of segmentally sclerotic glomeruli (Fig 1E). Glomerulomegaly and adhesions are common. There often is arteriolar hyalinosis, sometimes in continuity with hyalinosis in the perihilar segment. Foam cells may be entrapped in the sclerotic lesions. Podocyte hypertrophy and hyperplasia may be present but typically are less frequent than in the other variants. Other glomeruli may show lesions of segmental and/or global glomerulosclerosis, as described for FSGS (NOS) earlier. Immunofluorescence and ultrastructural findings are similar to those described in the section on FSGS (NOS).

Clinical-Pathologic Correlations

This variant of FSGS may occur in primary FSGS. However, when accompanied by glomerulomegaly, it is particularly common in patients with secondary forms of FSGS mediated by an adaptive response to increased glomerular capillary pressures and flow rates (as in association with obesity, cyanotic congenital heart disease, reflux nephropathy, renal agenesis, dysplasia, oligomeganephronia, or any advanced renal disease with a reduced number of functioning nephrons; see discussion of secondary forms of FSGS later).

FSGS, CELLULAR VARIANT

The cellular variant of FSGS was first described by Schwartz and Lewis[21] in 1985. A diagnosis of cellular FSGS requires that tip and collapsing variant be excluded.

Pathologic Features

The cellular variant is defined by the presence of at least one glomerulus with segmental endocapillary hypercellularity involving at least 25% of the tuft and causing occlusion of the capillary lumen/lumina (Fig 1F). Any segment (perihilar or peripheral) may be affected. When numerous glomeruli are affected, the process may mimic focal proliferative glomerulonephritis.[6] The lesions of endocapillary hypercellularity typically are expansile, causing engorgement of the glomerular capillaries. The endocapillary cells may include endothelial cells, foam cells, and infiltrating leukocytes, including monocyte/macrophages (Fig 1F). Other leukocytes, including lymphocytes and neutrophils, also may be present. Some of these lesions are accompanied by foamy hyaline material, fibrin, and karyorrhexis, resembling segmental necrotizing lesions, but without rupture of GBM.

Although the cellular variant is defined by the presence of segmental endocapillary hypercellularity, it also frequently displays extracapillary hypercellularity owing to hyperplasia of the podocytes. Podocytes may appear swollen and crowded, sometimes forming pseudocrescents. These pseudocrescents usually can be distinguished from true crescents by their lack of attachment to Bowman's capsule or continuity with the parietal epithelial cells. Moreover, the extracapillary cells tend to be plump, rounded, and poorly cohesive, with frequent intracellular protein resorption droplets. These extracapillary cells lack the spindled morphology or pericellular matrix typically observed in true crescents. Another distinguishing feature is that Bowman's capsule itself is intact, without the ruptures typical of cellular crescents of the inflammatory type.

In some cases, cellular lesions are identified in all affected glomeruli, whereas in others they affect a minority of glomeruli, possibly reflecting different stages in the evolution of sclerosis. Other glomeruli may contain lesions of segmental or global glomerulosclerosis of the usual type, as described for FSGS (NOS).

By immunofluorescence there is focal and segmental glomerular positivity for IgM and C3. At the ultrastructural level, the cellular variant usually displays severe foot process effacement, correlat-

ing with the generally high levels of proteinuria (Fig 4D). Cellular lesions consist of segmental occlusion of glomerular capillaries by endocapillary hypercellularity including foam cells and monocytes (Figs 4E and 4F). The GBM is intact, without evidence of rupture.

Clinical-Pathologic Correlations

Compared with FSGS (NOS), the cellular variant is characterized by more severe proteinuria and a shorter time course from clinical onset of renal disease to biopsy examination, suggesting an early phase in the evolution of the segmental sclerosis.[21] Schwartz and Lewis[21] found a shorter interval between onset of proteinuria (3.4 versus 71.9 mo) in patients with cellular versus classic FSGS. Moreover, 90% of patients in the cellular group had urine protein levels greater than 3 g/d, compared with 49% of those without cellular lesions. Similarly, the incidence of full nephrotic syndrome at presentation was significantly higher (70% versus 23%). Indeed, patients with cellular FSGS often have a very abrupt onset of severe nephrotic syndrome resembling the presentation of minimal change disease (personal observations). Repeat biopsy examinations in some cases have shown evolution to more typical segmental scars, supporting the concept that the hypercellularity is an early stage in the development of the segmental sclerosis. A similar evolution from cellular to more sclerosing lesions has been documented by repeat biopsy examination in recurrent FSGS in the transplant.[22]

The cellular variant may be responsive to immunosuppressive therapy.[23] This favorable treatment response probably relates to the early and relatively active stage of glomerular injury in the cellular variant.

FSGS, TIP VARIANT

The tip variant of FSGS is defined by the presence of at least one glomerulus with a segmental lesion involving the tip domain (ie, the peripheral 25% of the glomerular tuft next to the origin of the proximal tubule). There must be either adhesion between the tuft and Bowman's capsule at the tubular lumen or neck, or confluence of podocytes with parietal epithelial or tubular epithelial cells at the tubular pole or neck (Figs 2A–2B). The proximal tubular pole must be identified in the defining glomerulus. The designation of tip lesion requires that the collapsing variant be excluded.

Pathologic Features

As defined originally by Howie and Brewer,[24] the early lesion is characterized by confluence of swollen, hypertrophied visceral epithelial cells with parietal or tubular epithelial cells at the tubular pole. The affected lobule may display endocapillary hypercellularity with endocapillary foam cells and hyalinosis. In some cases, the affected segment appears to herniate into the tubular lumen (Fig 2B). As the lesion evolves, there is adhesion of the glomerular tuft to Bowman's capsule at the point of transition to the proximal tubular basement membrane (Fig 2A).[24] Later lesions may form segmental scars.

Other glomeruli may show segmental sclerosis or endocapillary hypercellularity in the periphery but not involving the tip, or in a portion of the tuft that cannot be identified as tip or perihilar. However, the presence of segmental sclerosis or endocapillary hypercellularity in a perihilar location rules out the tip variant of FSGS. Global sclerosis may be present.

The segmental lesions usually stain for IgM and C3 by immunofluorescence. But for their location at the tubular pole, the lesions often resemble those of cellular FSGS at the ultrastructural level.

Differential Diagnosis

Tip lesions are not specific, but may occur in the setting of a variety of glomerular diseases including membranous glomerulopathy, IgA nephropathy, diabetic glomerulosclerosis, and others.[25] Thus, the designation of glomerular tip lesion should be applied only to those cases with glomeruli that look otherwise like minimal change disease or focal segmental glomerulosclerosis, and in which other glomerular conditions have been excluded.

Clinical-Pathologic Correlations

It is uncertain how the pathogenesis of tip lesion may differ, if at all, from that of the more classic lesions of FSGS. A study of autopsy kidneys from children dying with minimal change disease in the presteroid era revealed focal tip lesions in a small percentage of glomeruli.[26] This study concluded that tip lesions may arise as a nonspecific response of the peritubular segment of the glomerular tuft to fluxes of protein-rich filtrate in the setting of nephrotic syndrome.

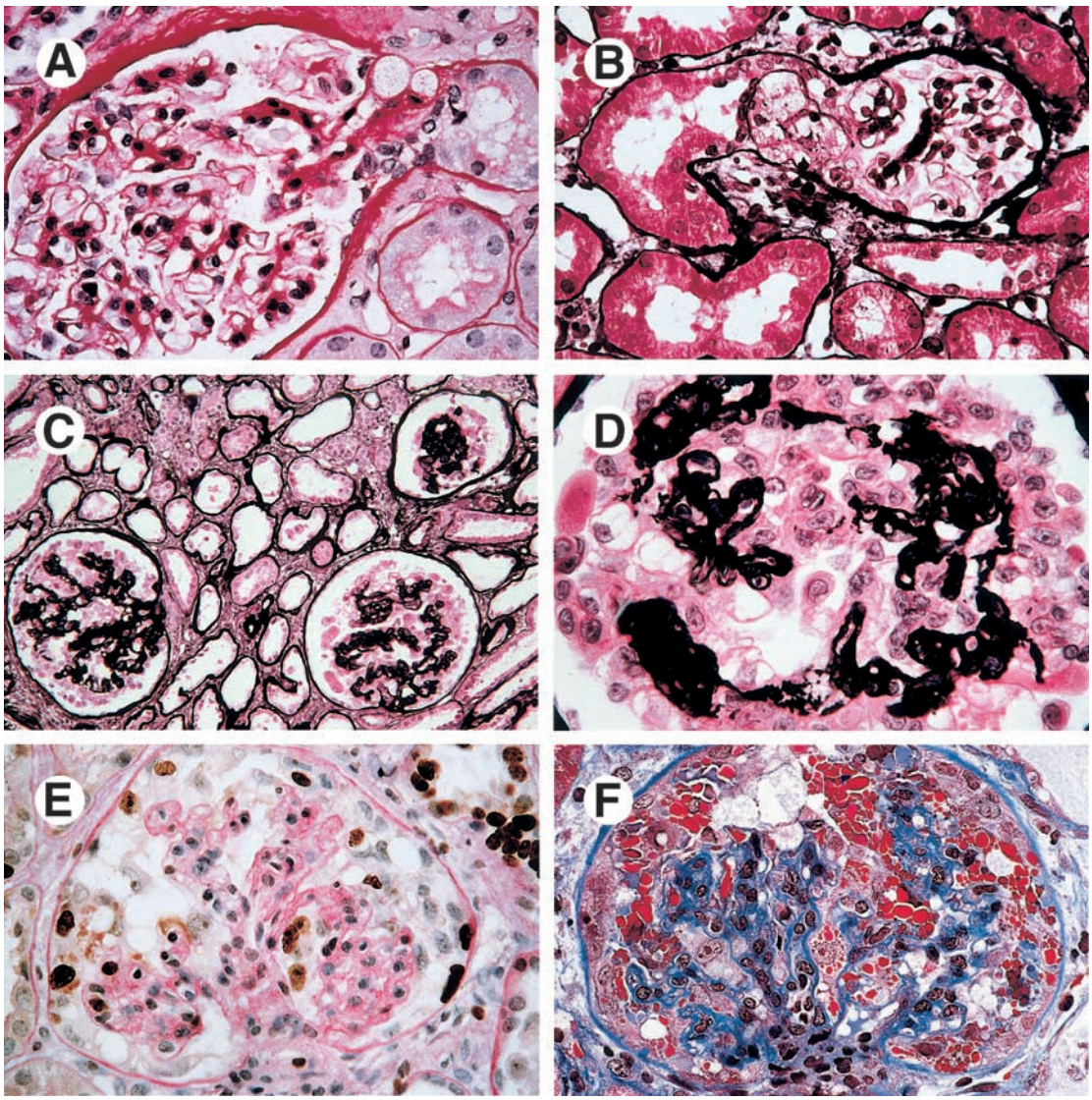

Fig 2. Light microscopic findings in FSGS, tip variant and FSGS, collapsing variant. (A) FSGS, tip variant: There is a segmental lesion with endocapillary foam cells that forms an adhesion to Bowman's capsule at the origin of the tubular pole. The podocytes are capped over this segment and merge with the tubular epithelial cells. (Periodic-acid Schiff, PAS). (B) FSGS, tip variant: A segmental lesion herniates into the tubular pole. The tip zone is engorged with endocapillary foam cells and forms an adhesion to Bowman's capsule at the tubular origin. There is confluence of the podocytes and the tubular epithelial cells surrounding the tip lesion. (Jones methenamine silver, JMS). (C) FSGS, collapsing variant: The glomerular collapse is diffuse and global in distribution, with associated severe tubular degenerative changes, (JMS). (D) FSGS, collapsing variant: In the collapsed tuft, the glomerular basement membranes are imploded, without appreciable increase in matrix material. The podocytes overlying the collapsed tuft are marked hyperplastic with enlarged vesicular nuclei, focal binucleated forms, and crowding of the urinary space. At the periphery, some of the podocytes appear to be falling off into the urinary space (JMS). (E) FSGS, collapsing variant: Immunostaining for proliferation marker Ki-67 (MIB1) shows many cycling cells in the urinary space, including visceral and parietal cells, as well as adjacent tubular epithelial cells, (Immunoperoxidase). (F) FSGS, collapsing variant: Trichrome stain delineates the collapsed blue-staining tuft and the abundant hyperplastic podocytes forming a pseudocrescent containing many intracytoplasmic fuchsinophilic protein resorption droplets. The podocyte hyperplasia lacks the spindled cellular morphology and pericellular matrix seen in true crescents of parietal cell origin.

The relationship of tip lesion to minimal change disease and FSGS has been hotly debated. Whereas some groups have reported a greater likelihood of steroid responsivity and excellent long-term prognosis resembling that of minimal change disease, others have described an evolution toward more typical FSGS.[27] Indeed, repeat biopsy examinations in some of these patients have shown progression to focal segmental and global glomerulosclerosis with development of renal failure.

Recently, Hogan-Moulton et al[28] described 80% steroid responsivity in glomerular tip lesion compared with 33% in FSGS, but with similar long-term renal survival (87% at 4 years in both groups). Clearly, evaluation of larger series of patients will be required to determine the significance of this lesion.

FSGS, COLLAPSING VARIANT

The designation of collapsing variant (also known as *collapsing glomerulopathy*) is applied to cases of FSGS in which at least one glomerulus displays segmental or global obliteration of the glomerular capillary lumina by wrinkling and collapse of GBMs associated with podocyte hypertrophy and hyperplasia. Collapse involving a single glomerulus is considered significant, such that the presence of any glomerular collapse pre-empts the other morphologic categories of FSGS.

The term *glomerular collapse* was first introduced by Weiss et al[29] in 1986 to describe an unusual clinicopathologic complex of severe nephrotic syndrome, rapidly progressive renal failure, and glomerular collapse occurring in 6 black patients. Two patients required dialysis within 10 weeks of clinical presentation and 5 had an ill-defined febrile illness. Although the clinical and pathologic findings suggested possible HIV-associated nephropathy, only one of these patients subsequently developed acquired immune deficiency syndrome. Two subsequent series have reported a similar malignant course to renal failure in patients with collapsing FSGS who lack HIV infection.[30,31] The incidence of the collapsing variant is increasing. Collapsing FSGS 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.[31,32]

Pathologic Features

Collapsing FSGS presents a dramatic pattern of injury. Glomerular capillary lumina are occluded by an implosive wrinkling and collapse of the GBMs that is more often global than segmental, without predilection for the perihilar segments (Figs 2C–2D). This GBM collapse is best delineated with the use of the PAS or the Jones methenamine silver stains (Figs 2C and 2D). The acute nature of the glomerular injury is evidenced by the lack of appreciable increase in intracapillary or mesangial matrix.

The glomerular collapse must be accompanied by striking hypertrophy and hyperplasia of the overlying podocytes, which have enlarged, open vesicular nuclei with frequent nucleoli, occasional binucleated forms, and rare mitotic figures (Fig 2D). Proliferation marker Ki-67 (MIB1) is frequently positive in the distribution of the podocytes, indicating that they are cell-cycle engaged (Fig 2E).[33] Podocytes may be so crowded as to fill the urinary space, forming pseudocrescents, and often contain prominent intracytoplasmic protein resorption droplets (Fig 2F).

In collapsing FSGS, the podocyte displays a dysregulated phenotype with increased rates of proliferation and apoptosis.[33] Podocytes normally are endowed with high levels of constitutive expression of cyclin kinase inhibitors to safeguard against easy entry into the cell cycle that might jeopardize the cell's ability to maintain its highly differentiated cytoarchitecture. However, in collapsing FSGS, this system is perturbed, leading to structural deterioration. The injured podocytes exhibit reduced expression of cyclin kinase inhibitors p27 and p57, promoting permissive cellular proliferation.[34,35] As the cells enter the cell cycle they lose their mature podocyte markers (such as synaptopodin, WT-1, GLEPP-1, C3b receptor, and CALLA).[33] Transdifferentiation of podocytes to macrophage/monocytes also has been described.[36,37] The podocytes become less cohesive, round up, and may actually detach and shed into the urinary space.[37] Thus, in collapsing FSGS podocytes appear to lose their highly differentiated cytoarchitecture through activation of a genetic program that involves re-entry into the cell cycle, disruption of the cytoskeleton, and cellular dedifferentiation.

Collapsing FSGS is distinguished from the cellular form by the absence of endocapillary hypercellularity. In fact, there is often an apparent reduction in the number of glomerular endothelial cells in collapsed lobules. Unlike FSGS (NOS), glomeruli with collapsing sclerosis usually lack hyalinosis, endocapillary foam cells, and adhesions to Bowman's capsule. Mesangial hypercellularity, glomerulomegaly, and arteriolar hyalinosis are uncommon.

Tubulointerstitial disease is an important component of this condition and often appears out of proportion to the degree of glomerular sclerosis. In addition to tubular atrophy, interstitial fibrosis, edema, and inflammation, there are widespread tubular degenerative and regenerative changes.[31] These include tubular epithelial simplification with enlarged hyperchromatic nuclei, nucleoli, mitotic figures, and focal apoptosis (Fig 2C). About 40% of cases may have tubular microcysts that contain loose proteinaceous casts.[31]

By immunofluorescence there are segmental to global deposits of IgM, C3, and, less commonly, C1 in collapsing segments. Visceral epithelial protein resorption droplets often stain for IgG, IgA, and albumin, with similar staining in the tubular epithelial protein droplets.

At the ultrastructural level, the collapsed lobules display wrinkling and little or no thickening of GBMs (Fig 5A). The overlying podocytes are markedly hypertrophied with severe foot process effacement, focal detachment, and increased numbers of organelles including electron dense protein resorption droplets, electron lucent transport vesicles, and rough endoplasmic reticulum. The actin cytoskeleton usually appears disrupted, giving the cells a relatively open appearing cytoplasm (Fig 5A). Noncollapsed capillaries also display severe foot process effacement. No electron dense deposits are observed, with the exception of rare small paramesangial electron densities corresponding to the mesangial deposits of IgM. In contrast to HIV-associated nephropathy, no tubuloreticular inclusions are identified in idiopathic collapsing FSGS.

Collapsing glomerulopathy may be confused with forms of crescentic glomerulonephritis. The proliferating podocytes in collapsing FSGS lack the spindled morphology and pericellular matrix seen surrounding the proliferating parietal cells of true crescents. Crescentic glomerulonephritis also is distinguished by the usual presence of necrotizing lesions in the underlying tuft and breaks in the GBM.

Clinical-Pathologic Correlations

Once a diagnosis of collapsing FSGS has been reached, the possibility of HIV-associated nephropathy must be ruled out. Exclusion of HIV-associated nephropathy is based on the demonstration of negative HIV serologies, and is supported by the absence of endothelial tubuloreticular inclusions.

When compared with patients with FSGS (NOS) or classic FSGS, patients with idiopathic collapsing FSGS are more likely to be black and to present with more severe markers of nephrotic syndrome, including more severe proteinuria, hypoalbuminemia, and hypercholesterolemia. Moreover, these patients have a higher presenting serum creatinine level (3.5 versus 1.3 mg/dL and 4.2 versus 2.0 mg/dL) despite a shorter time course from clinical onset to biopsy examination.[30,31]

Primary FSGS with collapsing features typically has a rapid course to renal failure and is often unresponsive to steroid therapy.[30-31,38] One group found a median renal survival of 13.0 months compared with 62.5 months for controls with classic FSGS.[31] Thus, this variant has been considered the morphologic counterpart of the malignant FSGS proposed years earlier by Brown et al[16] and Cameron et al.[39]

Recently, some cases of FSGS with collapsing features have been identified as a form of drug nephrotoxicity in older patients treated with pamidronate, an osteoclast inhibitor that reduces bone resorption, for myeloma, or carcinoma metastatic to bone.[40] Collapsing FSGS has been reported to occur in some patients with viral infections owing to parvovirus B19[41] or SV40,[42] suggesting a role for direct viral infection of the kidney.

A collapsing pattern of FSGS may also occur de novo or as a recurrent disease in the allograft.[43-45] In this setting, the de novo disease often is unaccompanied by nephrotic syndrome and appears to be a less specific morphologic lesion that does not necessarily represent primary FSGS. Nadasdy et al[45] has reported a zonal distribution of collapsing FSGS in some allografts with transplant arteriopathy, suggesting a role for ischemic injury. These findings are reminiscent of the collapsing or cellular pattern of focal sclerosis observed in some native kidney specimens with ischemia and pro-

teinuria on the basis of renovascular hypertension or cholesterol embolization.[46,47]

OTHER FORMS OF FSGS

Among the entities listed in Table 1, only C1q nephropathy, HIV-associated nephropathy, and secondary FSGS mediated by structural-functional adaptations will be discussed in any depth owing to space constraints.

C1q NEPHROPATHY

This controversial entity was first described by Jennette and Hipp[48] in 1985. It is defined as a form of idiopathic nephrotic syndrome caused by a glomerulopathy with dominant paramesangial deposits of C1q (of at least 2+ intensity on a scale of 0–4+).

Pathologic Features

The pattern by light microscopy is usually one of FSGS with variable mesangial hypercellularity (Fig 3A). Although early reports emphasized the mesangial proliferative features,[48] subsequent reports have stressed the resemblance to FSGS.[49]

By immunofluorescence, in addition to staining for C1q (of at least 2+ intensity), most cases have codeposits of IgG (90%) of mean 1.6 intensity, or IgM (94%) of mean 1.1 intensity, and C3 (90%) of mean 1.1 intensity on a scale of 0 to 4+.[50] Deposits of IgA are less common and were observed in 56% of biopsy examinations with mean intensity 0.7. The mesangial deposits are often comma shaped because of their paramesangial location and conformation to the overlying GBM reflection (Fig 3B).

Electron dense deposits are primarily or exclusively located in the mesangium. In over 90% of cases, electron microscopy reveals prominent paramesangial electron dense deposits located subjacent to the GBM reflection (Fig 5B). In a minority of cases, rare subendothelial and subepithelial deposits also may be seen. There is prominent but variable foot process effacement.

Clinical-Pathologic Features

Many investigators believe that C1q nephropathy represents a morphologic variant of primary FSGS with similar pathogenesis and outcome.[48-50] Most patients present with idiopathic nephrotic syndrome and renal insufficiency (with mean urine protein levels of 5.9 g and mean serum creatinine levels of 1.5 mg/dL).[50] Edema and hypertension are observed in almost half of the cases.[50] Serologies for lupus and HIV are negative, serum complement levels are normal, and there is no clinical evidence of systemic disease. Most cases are steroid resistant, although some have achieved full remissions.[50] Three-year renal survival was reported at 84% in a cohort of 79 patients.[50]

HIV-ASSOCIATED NEPHROPATHY

Pathologic Features

HIV-associated nephropathy (HIV-AN) is defined as a form of focal segmental glomerulosclerosis occurring in HIV-infected patients. The light microscopic findings in HIV-associated nephropathy are qualitatively similar to those described earlier in collapsing glomerulopathy.[51,52] The characteristic lesion is a collapsing sclerosis with prominent podocyte alterations. As the lesions progress, the glomerular tuft may be reduced to an acellular sclerotic ball with crowning of the overlying podocytes and relative dilatation of the urinary space (Fig 3C). A proteinaceous filtrate frequently is identified within the enlarged urinary space (Fig 3C).

Tubular microcysts are common, affecting approximately 30% to 40% of cases[51] (Fig 3C). Some patients with advanced disease at autopsy have almost complete replacement of the cortical parenchyma by massive microcyst formation. This microcystic transformation likely contributes to the enlarged kidneys and increased echogenicity by ultrasound observed even in patients with end-stage renal failure.

The immunofluorescence findings are similar to those of primary FSGS with collapsing features. Differences between HIV-associated nephropathy and idiopathic collapsing glomerulopathy are seen only at the ultrastructural level (Figs 5C-5E). The major distinguishing feature is the abundance of tubuloreticular inclusions in the glomerular endothelial cells of HIV-associated nephropathy (Fig 5D).[51] Tubuloreticular inclusions, also known as *interferon footprints* consist of 24-nm interanastamosing tubular structures located within dilated cisternae of endoplasmic reticulum. They may be large and multiple per cell. Although they are identified most readily in the glomerular endothelium, they also occur in arterial or interstitial capillary endothelial cells as well as infiltrating leukocytes. Tubuloreticular inclusions were noted with

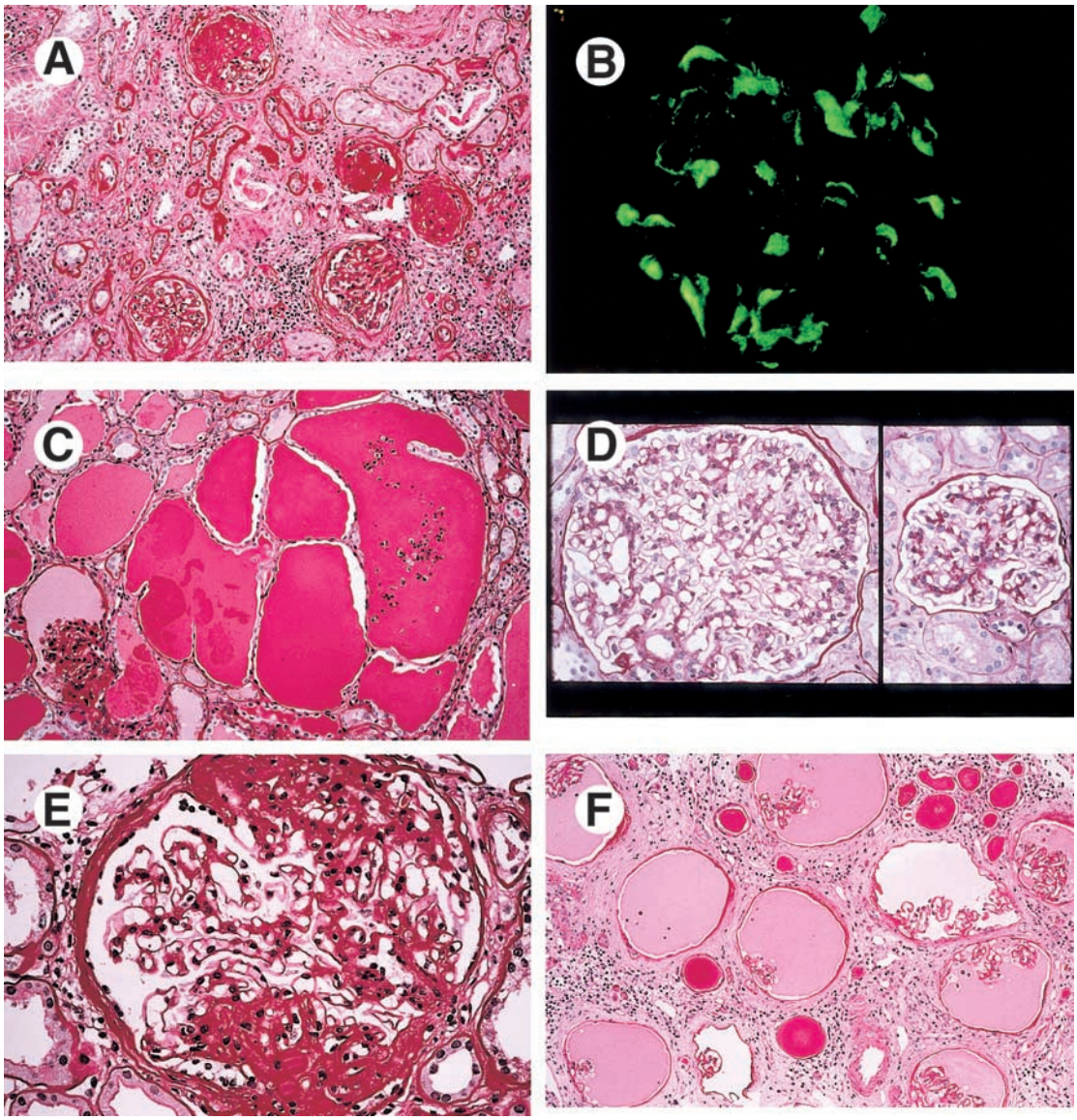

Fig 3. Light and fluorescence microscopic findings in C1q nephropathy, HIV-AN, and secondary FSGS. (A) C1q nephropathy. Low-power view showing a characteristic field of focal segmental and global glomerulosclerosis with patchy tubular atrophy and interstitial fibrosis (PAS). (B) C1q nephropathy. There are global comma-shaped deposits of C1q outlining the paramesangial regions (immunofluorescence). (C) HIV-associated nephropathy. There is collapse of the glomerular tuft with dilatation of the urinary space. The tubules are markedly dilated forming microcysts with voluminous proteinaceous casts (PAS). (D) Secondary FSGS caused by obesity. The glomerulus on the left from an obese patient shows marked glomerulomegaly compared with that of an age- and sex-matched nonobese control on the right. (E) Secondary FSGS caused by obesity. There are 2 discrete lesions of segmental sclerosis, one arising from the vascular pole, and the other involving the periphery of the tuft. Note the absence of podocyte reactivity (PAS). (F) Secondary FSGS caused by hypertensive nephrosclerosis. In the subcapsular area there are numerous atubular glomeruli forming glomerular microcysts with shrunken and simplified tuft, dilatation of the urinary space, and proteinaceous filtrate. The adjacent tubules are severely atrophied (PAS).

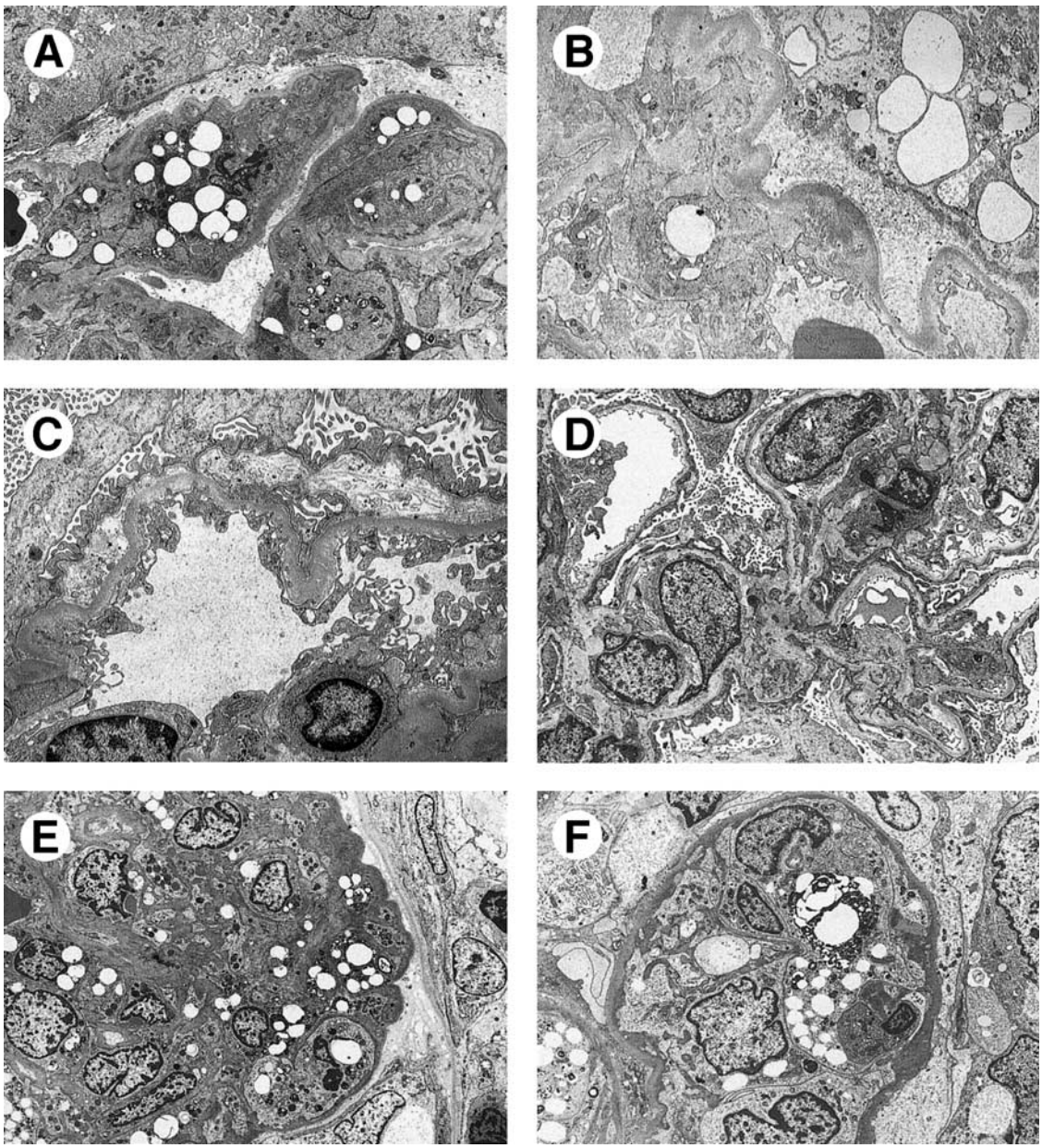

Fig 4. Electron microscopic findings in FSGS (NOS) and FSGS, cellular variant. (A) FSGS (NOS). A lesion of segmental sclerosis with inframembranous hyalinosis, endocapillary foam cells, and podocyte detachment with complete effacement of foot processes. (B) FSGS (NOS). Overlying the segmental lesion there is podocyte detachment with large intracytoplasmic electron lucent transport vesicles. The GBM are wrinkled and the glomerular capillaries are obliterated by matrix material. (C) FSGS (NOS). A nonsclerotic segment showing detachment of podocytes with lamellation of neomembrane material. The podocytes are hypertrophied with microvillous transformation of their cytoplasm. (D) FSGS, cellular variant. Nonsclerotic capillaries display complete foot process effacement with extensive microvillous transformation. (E) FSGS, cellular variant. The glomerular capillary lumen is obliterated by endocapillary hypercellularity including many foamy cells with clear lipid vacuoles. The overlying podocytes are detached with neomembrane formation. (F) FSGS, cellular variant. The glomerular capillary lumen is engorged with cells, including infiltrating monocytes and foam cells, admixed with inframembranous hyaline. There is marked hypertrophy and hyperplasia of the overlying podocytes.

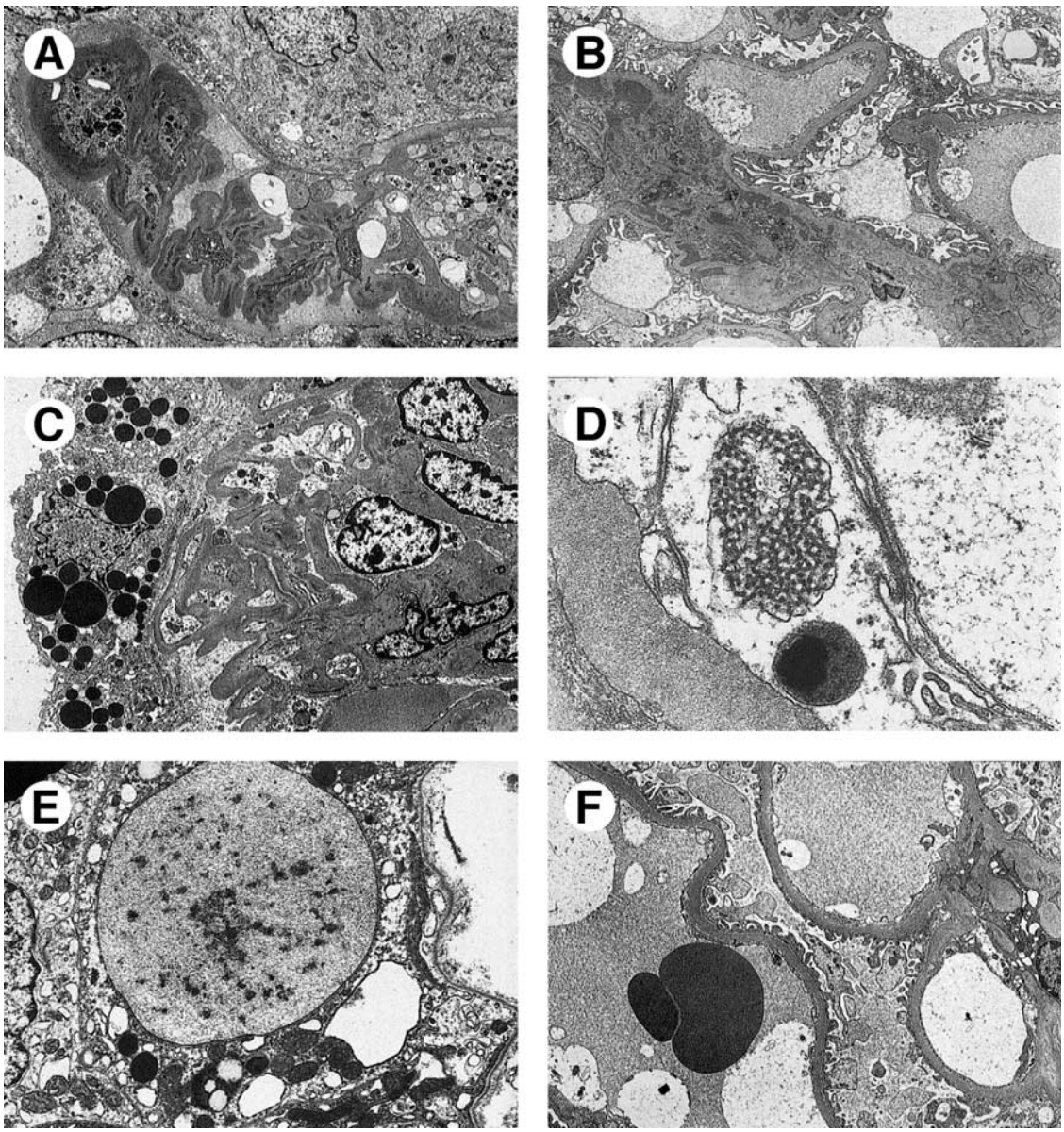

Fig 5. Electron microscopic findings in FSGS, collapsing variant, C1q nephropathy, HIV-AN, and secondary FSGS caused by obesity. (A) FSGS, collapsing variant. There is tight collapse of the GBMs causing luminal obliteration. Note the marked hypertrophy and hyperplasia of the overlying podocytes with loss of primary processes, complete effacement of foot processes, and podocyte detachment. (B) C1q nephropathy. Electron dense deposits are present in the mesangium. The deposits tend to pool in the paramesangial regions, subjacent to the GBM reflection over the mesangium. There is mild focal foot process effacement. (C) HIV-AN. The GBMs are collapsed with secondary luminal narrowing. The overlying podocytes form a cellular cap with marked hypertrophy and numerous intracytoplasmic protein resorption droplets. (D) HIV-AN. A glomerular endothelial cell contains a large tubuloreticular inclusion located within a cistern of endoplasmic reticulum. (E) HIV-AN. A tubular epithelial cell displays granular degeneration of its nuclear chromatin. (F) Secondary FSGS caused by obesity. The foot processes show minimal effacement involving less than 20% of the glomerular capillary surface area, despite the presence of nephrotic-range proteinuria.

frequency in renal biopsy examinations of HIV-infected patients in the 1980s. However, they may be far less frequent in the modern era of highly active antiretroviral therapy, probably owing to reduced viral burden (personal observations).

Other characteristic but relatively less frequent ultrastructural findings include nuclear bodies within tubular and interstitial cells, granular-fibrillar transformation of the tubular nuclei, and confronting cylindrical cisternae (Fig 5E).[51]

Differential Diagnosis

The major differential diagnosis is from primary FSGS with collapsing features. HIV serologies are required for definitive distinction between these entities.

Included within the spectrum of HIV-associated nephropathies are diffuse mesangial hypercellularity and minimal change disease, which are more common in HIV-infected children than adults. These milder variants usually present with nephrotic syndrome and normal renal function, without the rapid course to renal failure that characterizes the collapsing form of HIV-associated nephropathy.

HIV-associated nephropathy must be differentiated from a variety of other glomerular and tubulointerstitial diseases that occur in HIV-infected patients.[52] One of the most common immune complex–mediated glomerular lesions is membranoproliferative glomerulonephritis, particularly in HIV-infected intravenous drug abusers with hepatitis C virus coinfection. Another common glomerular disease in the HIV population is IgA nephropathy, which may be associated with IgA-containing cryoglobulins. IgA nephropathy has been reported in both HIV-infected blacks and whites. Glomerular immune deposits eluted from the glomeruli of some of these patients have shown specificity for HIV envelope or core proteins. Other glomerular lesions occurring in HIV-infected patients include membranous glomerulopathy, lupus-like glomerulonephritis, acute postinfectious glomerulonephritis, and thrombotic microangiopathies.

Clinical-Pathologic Correlations

The incidence of heroin nephropathy has decreased reciprocally with the advent of HIV-AN in the early 1980s.[32] In 1984, a distinctive form of FSGS occurring in HIV-infected patients was first described at Downstate Medical Center in New York City.[53] HIV-AN is predominantly a disease of blacks (90%). Although it can occur in both sexes and with any HIV risk factor, it is most common in male intravenous drug abusers.

Presenting features include proteinuria, usually in the nephrotic range, and renal insufficiency. Despite the high frequency of nephrotic-range proteinuria and hypoalbuminemia, hypercholesterolemia and edema are relatively uncommon. The absence of hypercholesterolemia likely reflects the reduced hepatic synthesis of lipoproteins in acquired immune deficiency syndrome. Hypertension is relatively uncommon.[54] By ultrasound, the kidneys usually are large and echogenic.

Early reports of HIV-AN described a rapid course to renal failure, with mean time to dialysis of less than 2 months.[53] However, in the modern era of highly active antiretroviral therapy, reduced viral load and improved renal survival have been achieved. After highly active antiretroviral therapy there may be dramatic improvement in the renal biopsy findings, with reversal of tubular microcysts.[55] A more detailed description of this entity can be found in the article by Herman and Klotman in this issue.

SECONDARY FSGS

Secondary FSGS denotes the pattern of focal and segmental glomerulosclerosis that develops in the course of a number of renal diseases in which there is reduced number of functioning nephrons or hemodynamic stress on an initially normal nephron population (see Table 1).[6,7] Secondary FSGS is most common in the setting of obesity, hypertensive nephrosclerosis, sickle cell anemia, and any advanced renal process with significant loss of functioning nephrons.

Pathologic Features

Glomerular hypertrophy is a relatively constant finding (Fig 3D). Although actual measurements of glomerular diameter are not performed routinely in clinical practice, an experienced renal pathologist can recognize hypertrophied glomeruli readily by routine light microscopy. As a simple rule of thumb, hypertrophied glomeruli usually fill a 40× high-dry microscopic field. Because the glomerular tuft is a sphere, glomerular hypertrophy is best assessed in a plane of section that transects the hilus of the glomerulus, at the epicenter of the glomerular tuft. The largest glomerular volumes

recorded are seen in oligomeganephronia, a congenital disorder with markedly reduced nephron number from birth.

In forms of secondary FSGS resulting from loss of renal mass, FSGS usually is seen in a background of extensive global glomerulosclerosis with corresponding tubular atrophy and interstitial fibrosis.

Most forms of secondary FSGS have discrete segmental scars, often involving the perihilar regions of hypertrophied glomeruli (Fig 3E). Podocyte hypertrophy and hyperplasia are less frequent than in primary FSGS (Fig 3E). In secondary FSGS, the degree of foot process fusion is generally mild, affecting less than 50% of the total glomerular capillary surface area (Fig 5F). Because of its variability, however, the percentage of foot process fusion cannot be used as an absolute or specific criterion by which to distinguish primary from secondary FSGS.

In secondary FSGS caused by hypertensive nephrosclerosis, there is prominent arteriolosclerosis, arteriolar hyalinosis, and arteriosclerosis. Predilection for glomerular sclerosis to occur in the outer cortex with formation of subcapsular scars is appreciated readily in biopsy specimens in which the renal capsule has been sampled. There is invariably prominent chronic tubulointerstitial disease and glomerular hypertrophy. Lesions of segmental sclerosis and hyalinosis are often perihilar and develop in glomeruli that also are hypertrophied. Most lesions of segmental sclerosis are of the classic type, with solidification of the tuft by increased matrix. However, in some cases there also are cellular or collapsing features that may mimic idiopathic FSGS. This is especially the case in patients with secondary FSGS in the setting of cholesterol embolization or renovascular hypertension.[46,47] A common feature of secondary FSGS owing to hypertensive nephrosclerosis is the development of atubular glomeruli with cystic dilatation of Bowman's space (Fig 3F).[56] The tuft is shrunken and partially resorbed into Bowman's capsule. Atubular glomeruli are most abundant in areas of subcapsular scarring with severe tubular atrophy (Fig 3F).

In obesity-associated FSGS, there is prominent glomerular hypertrophy and the lesions of focal sclerosis typically affect a minority of hypertrophied glomeruli.[57,58] Lesions are characteristically perihilar with associated hyalinosis. There is little, if any, podocyte reactivity (Fig 3E). FSGS usually develops in the absence of significant background tubulointerstitial disease. Mild mesangial sclerosis may be seen, resembling the changes of early diabetic glomerulosclerosis.[57]

Pathogenesis

Secondary FSGS is often mediated by increased glomerular capillary pressures and flow rates that occur as an adaptive response to a reduced number of functioning nephrons.[7] Increased wall tension causes mechanical stress on the podocyte foot process-GBM connection. This in turn leads to local dilatation of capillaries and strain on the podocytes.[59-61] If the tension on the podocyte is severe and prolonged, there is progressive cell body attenuation, pseudocyst formation, and, ultimately, detachment from the GBM.[61] Overload of the lysosomal system with protein resorption droplets may promote cell autoinjury.

Podocyte detachment is the first committed lesion to segmental sclerosis, leaving bare patches of GBM. The concept of relative podocyte insufficiency proposed by Kriz explains how these denuded segments of GBM come into contact with parietal epithelial cells, promoting synechiae to Bowman's capsule.[61] If patent capillaries remain caught in the adhesion, a route of filtration into the periglomerular interstitium toward the tubular pole can lead to obliteration of the tubular pole and formation of atubular glomeruli with microcystic dilatation of Bowman's capsule.[56]

Clinical-Pathologic Correlations

Knowledge of the presenting clinical features and associated medical conditions is essential to differentiate primary FSGS from secondary FSGS caused by structural-functional adaptations.[7] Typically, patients with secondary FSGS manifest nephrotic range or subnephrotic proteinuria without full nephrotic syndrome. Thus, they may have proteinuria levels greater than 3.0 g/d, but they usually lack hypoalbuminemia, hypercholesterolemia, and edema. Because the development of FSGS is often a response to a loss of functioning nephrons, most patients have a history of renal insufficiency for months or years preceding the development of nephrotic proteinuria. An exception is FSGS secondary to morbid obesity, in which patients often have an initially supernormal glomerular filtration rate, reflecting a hyperfiltration state imposed by an

increased ratio of body mass to renal mass.[57] The resulting glomerular overwork is associated with increased renal plasma flow rates, as well as an elevated glomerular filtration rate. Hypoxia caused by sleep apnea may play a role in this process by stimulating the renin-angiotensin system through sympathetic activation.

The therapeutic approach to secondary FSGS depends on the underlying condition. Correction of the underlying process, such as surgical repair of reflux or congenital heart disease, should be sought where appropriate. In patients with hyperfiltration caused by reduced renal mass (such as after vesicoureteral reflux, hypertensive nephrosclerosis, renal agenesis, and so forth), maneuvers to reduce glomerular capillary pressures, such as angiotensin converting enzyme inhibition or angiotensin II receptor blockade are generally offered. Steroids are uniformly ineffective in secondary FSGS and may even promote weight gain and progressive sclerosis in patients with obesity and latent diabetes. The course of obesity-related glomerulopathy is generally indolent and few patients progress to end-stage renal disease. In this condition, reductions of proteinuria can be achieved with weight loss, sleep apnea therapy, and angiotensin receptor blockade or angiotensin converting enzyme inhibitors.[57]

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